Session A: Early and Advanced Breast Cancer

A1 A REGIMEN OF MULTIPLE HIGH-DOSE CHEMOTHERAPY (HDC) WITH DOCETAXEL (T), EPIRUBICIN (E) AND CYCLOPHOSPHAMIDE (C), (HD-TEC) FOR HIGH RISK BREAST CANCER (HRBC) PATIENTS. PRELIMINARY CLINICAL RESULTS OF A PHASE II STUDY

Saverio Cinieri, Emilia Cocorocchio, Pierfrancesco Ferrucci, Liliana Calabrese, Giulio Giordano, Francesco Bertolini, Fedro Peccatori, Alberto Luini, Giuseppe Viale, Aron Goldhirsch, Giovanni Martinelli
European Institute of Oncology, Milan, Italy

IBCSG (International Breast Cancer Study Group) 15/95 trial preliminary results seem to indicate a trend in favor of multiple high-dose chemotherapy (HDCT) according to EC regimen in high risk breast cancer (HRBC) patients in terms of DFS. No data are available on use of docetaxel (T) in adjuvant HDCT regimen. We assessed the toxicity and clinical activity of the addition of T to high-dose epirubicin–cyclophosphamide (HD-EC) in adjuvant setting for HRBC patients. From 6/1998 to 12/2000, 110 pts [median age 44 (24–65), median number of involved axillary nodes 12 (2–63), ER-positive 70/110, premenopausal 70/110] were enrolled. Twenty-five patients received at least two courses of primary CT with no anthracycline or taxanes. At least 6×10^6/kg $CD34^+$ (mobilized with filgrastim, 5 μg/kg twice daily for 5 days) were collected before starting the HDCT program and stored in three fractions. Treatment consisted of three courses of T: 85 mg/m^2 and E: 200 mg/m^2 administered on day 1, and C: 4 g/m^2 on day 2. On day 5, at least 2×10^6 of $CD34^+$ were reinfused at each course. The toxicity profile for 110 pts (328 cycles) was evaluated. Median duration of hospitalization was 16 days (12–26); 95% of patients experienced mucositis which was grade 3–4 in about 13% of them, not requiring parenteral nutrition. No significant cardiac toxicity was observed during and at the end of the program. Eight months after the end of HD-TEC, one patient developed an ALL proB. After the end of chemotherapy, 36 (31.8%) pts relapsed (median time to relapse: 15 months, range 2.7–49.5 months) and 74 (67.2%) are alive and disease-free (median follow-up: 48-month). Multiple HD-TEC is a safe and feasible regimen, and the addition of T (85 mg/m^2) to HD-EC does not prolong time to hematological recovery; the major non-hematological toxicity observed is oral mucositis. Considering the clinical results observed with HD-TEC, we suggest such a combination is suitable for randomized trial, especially if subsequent analysis of 15/95 will demonstrate a significant statistical advantage for women treated with HDCT.

A2 MULTIDISCIPLINARY BREAST CANCER (BC) CLINIC CAN IMPROVE DISEASE MANAGEMENT

Paola Poletti[1], Privato Fenaroli[1], Anna Bettini[1], Ermenegildo Arnoldi[1], Miriam Valentini[2], Maurizio Belfiglio[2], Alberto Personeni[1], Roberto Labianca[1], Carlo Tondini[1]
[1]Ospedali Riuniti di Bergamo, Bergamo; [2]Istituto Ricerche Farmacologiche Mario Negri Sud, Milan, Italy

Multidisciplinary management of breast cancer (BC) and the institution of specialised Breast Cancer Units (BCU) have been proposed to increase the quality of care for BC patients. At Ospedali Riuniti in Bergamo, a regular multidisciplinary collaboration of all involved specialists has been running since January 2000, with weekly clinical rounds both in the pre-surgical evaluation of all new cases of BC and post-surgical planning of adjuvant treatment. All data are collected on a specific database of the Outcomes Research in Oncology Project, with the aim to evaluate the efficiency and effectiveness of BC management. Between January 2000 and May 2003, a total of 769 pts with newly diagnosed BC were evaluated. Of these, 542 (72%) were diagnosed and treated in our specialised BCU, whereas 213 were referred from a General Surgery Unit (GSU). The purpose of this analysis is to evaluate the characteristics of these unselected cases of consecutive patients and to analyse several aspects involved with BC management. Median age was 60 years (27–89), with 2/3 of women being postmenopausal. Most women (61%) sought medical attention for self-detection of a breast lump. Only 12% of cases were identified from the screening programme. Most patients (70%) presented T1 lumps, and 1/3 of patients had lesions greater than 2 cm. In 15% of patients, clinically palpable nodes were present. Diagnostic and surgical performance between our BCU and GSU patients was compared. Overall, 96% of BCU patients had a pre-operative FNA or core-biopsy diagnosis, while 48% of GSU patients underwent either surgical biopsy or frozen section analysis during surgery. Breast conserving surgery (BCS) was carried out in 72% versus 62% ($P < 0.01$) and effective sentinel node biopsy in 68% versus 14% ($P < 0.0001$) of BCU and GSU patients, respectively. AD was avoided in 47% versus 13% of BCU and GSU patients, respectively. Pre-operative treatment was considered for all patients with T2 lesions. Only 13 of 37 pts chose upfront chemotherapy (CT) in an attempt to undergo BCS. All cases were discussed before postoperative adjuvant treatment planning. All specialists had formulated a treatment proposal. This proposal was adjusted after thorough discussion in about 15% of cases. St. Gallen clinical recommendations were systematically applied. Radiotherapy was carried out in 50% of patients, 36% of patients underwent CT and 57% hormonal treatment. In the final report, we will present treatment characteristics as well as short-term outcome analysis.

A3 THE ROLE OF GENETIC POLYMORPHISMS AS PREDICTIVE FACTORS OF TOXICITY AND RESPONSE TO ADJUVANT TREATMENT OF EARLY BREAST CANCER

V. Ludovini[1], S. Gori[1], L. Pistola[1], A. Rulli[2], A.M. Mosconi[1], I. Floriani[3], G. Nocentini[4], S. Piattoni[5], M. Colozza[1], Z. Mhyailova[1], F.R. Tofanetti[1], C. Basurto[1], P. Anastasi[1], C. Bisacci[2], M. Montedoro[1], C. Riccardi[4], M. Tonato[1]
[1]Medical Oncology Azienda Ospedaliera, Perugia; [2]Breast Unit Azienda Ospedaliera, Perugia; [3]Biometry Unit Oncology, Istituto Mario Negri, Milan; [4]Pharmacology Department, University of Perugia, Perugia; [5]Internal Medicine, University of Perugia, Perugia, Italy

Background: Drug resistance and toxicity are often limiting factors in successful chemotherapy. Identifying the genetic reasons behind either the occurrence of toxicity or lack of tumor response will reduce the unpredictability of cancer treatment. Several polymorphism genes that codify enzymes which are involved in drug metabolism could affect toxicity, disease-free survival (DFS) and overall survival (OS) of patients (pts) with resected breast cancer, treated with adjuvant chemotherapy. CMF, FEC or FAC are still the regimens of adjuvant chemotherapy most commonly used for early breast cancer; therefore, the study of polymorphic genes such as GSTT1, GSTM1, TS, MTHFR and RFC1, involved in the transport and metabolism of these chemotherapy drugs, will allow evaluation of their predictive role for toxicity and treatment effectiveness. The purpose of this study was to evaluate in patients with early breast cancer treated with adjuvant chemotherapy (CMF, FEC, FAC): (i) the relationship between five polymorphic metabolic genotypes and clinical-pathological parameters, (ii) their impact on toxicity, DFS and OS.

Methods: Genomic DNA extracted from peripheral blood was used by multiplex-PCR assay to simultaneously amplify the GSTT1 and GSTM1 genes; PCR-restriction fragment-length polymorphism analysis was used to determine the RFCI and MTHFR genes, whereas PCR assay was used for the TS gene.

Results: From June 2000 to June 2003, 121 pts were enrolled. Mean age was 51.9 years (31–75.7), the prevalent histology was ductal infiltrant (87.6%), stage I/II/III 40.5/38/21.5. The frequency of the five polymorphic genes are as follows: GSTT1 –/+ 20/80, GSTM1 –/+ 52/48, RFC1 AA/AG/GG 25/52/23, MTHFR CC/CT/TT 31/40/28, TS 2/2-2/3-3/3 29/44/27. Analysis of preliminary results shows that the omozigote CC genotype of MTHFR is associated with lymph node negative status (N– 40% versus N+ 22.9%, $P = 0.04$) and with stage I ($P = 0.012$). Other polymorphic genes analyzed do not show any statistically significant correlation with age, menopausal status, lymph nodes and stage.

Conclusion: These preliminary findings, based on the description of the sample and the relationship between polymorphisms and patients and disease characteristics, could suggest a potential prognostic role of these factors to be confirmed in the final analysis. That will also include an evaluation of their impact on toxicity and prognosis. This is an ongoing study and mature results will be presented at the meeting.

Research project CNR-MIUR

A4 FEATURES AND PROGNOSIS OF SCREEN-DETECTED BREAST CANCERS DIAGNOSED IN THE PROVINCE OF MODENA FROM 1996 TO 2000

Vincenzo Emanuele Chiuri[1], Claudia Cirilli[1], Barbara Braghiroli[1], Laura Cortesi[1], Ivan Rashid[1], Rossella Negri[2], Ennio Gallo[2], Silvia Ruscelli[1], Maria Elisa Artioli[1], Massimo Federico[1]
[1]Oncologia Medica, Università di Modena e Reggio Emilia, Modena, Italy; [2]Modena Mammography Screening Program

Background: The purpose of this study was to evaluate the outcome of breast cancers diagnosed within the Mammography Screening Program (MSP) in the Province of Modena.

Patients and methods: In total, 1058 new cases of breast cancer diagnosed between 1996 and 2000 in women aged 50–69 years (587 screen-detected and 471 not) were reviewed. Information on disease extension, initial therapy and outcome was obtained in almost all cases. Information on pathologic features was available in 84–93% of cases, depending on the specific parameter. Survival curves were constructed by the Kaplan–Meier method and compared using the log rank test. The analysis was carried out using the SPSS statistical package.

Results: Mean age was 59 years in both screen-detected (SD) and not-screen-detected (NSD) groups. Ductal carcinoma *in situ* (DCIS) represented 18% and 9% of SD and NSD cases, respectively. Infiltrating ductal carcinoma was the most common histologic type in both groups (77% and 79%, respectively). The mean diameter were 13 and 19 mm in the SD and NSD groups. Among SD cancers, 77% were classified as stage I, 81% were N- and 86% hormone-sensitive; in the NSD group, 46% were classified as stage I, 60% were N- and 79% hormone-responsive. Seventy-five per cent of SD and 48% of NSD cases underwent conservative surgery; 40% and 56% received adjuvant chemotherapy, and 64% and 68% hormonal therapy. After a mean follow-up of 52 months, the 5-year estimated OS was 94% for patients with SD and 84% for those with NSD cancers, respectively ($P = 0.0000$; LR = 18.59). The 5-year RFS was 93% and 88% ($P = 0.0076$; LR = 7.68) and the 5-year EFS 89% and 75% ($P = 0.0001$; LR = 19.99).

Conclusion: Our data confirm that SD cancers have more favourable presentation pattern and better survival rates. Since the effect of screening on breast cancer mortality will only become evident in the long term, monitoring the early outcomes in terms of 5-year OS, RFS and EFS may be of relevance in estimating the potential gain of the screening program.

A5 ITALIAN NETWORK FOR HEREDITARY-FAMILIAL BREAST/OVARIAN CANCER: AN ONCOLOGIST-BASED MODEL OF CANCER GENETIC COUNSELLING

Alma Contegiacomo[1], Matilde Pensabene[1], Ida Capuano[1], Massimo Federico[2], Daniela Turchetti[2], Laura Cortesi[2], Paolo Marchetti[4], Enrico Ricevuto[3], Giovanni Cianci[3], Salvatore Venuta[4], Vito Barbieri[4], Vittorio Silingardi[2]
On behalf of the Italian Network on Hereditary Breast Cancer.
[1]Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II', Naples; [2]Department of Medical Oncological Research, University of Modena and Reggio Emilia, Modena; [3]Department of Experimental Medicine, University of L'Aquila; [4]Department of Clinical and Experimental Medicine 'G. Salvatore', University of Catanzaro 'Magna Graecia', Italy

Background: Advances in the molecular genetics of breast cancer have led to the development of genetic counselling in the oncological setting. We have devised a multistep model of cancer genetic counselling that has been validated within the context of the Italian Network for Hereditary and Familial Breast/Ovarian Cancer. Here we report consent data for each counselling step.

Methods: Counselling was addressed to cancer-affected subjects with a personal history suggesting genetic risk or with a family history of cancer, and to disease-free subjects belonging to families clustering cancers. The model was designed to promote awareness using a multistep approach in order to allow users to assimilate fully the information given, and to become fully aware of their condition and all its implications. Step T0 of the model entails information giving; this is followed by pedigree analysis and risk assessment (T1), risk communication and genetic testing (T2) and genetic test result communication (T3). User consent was required to proceed from one step to the next. Preventive measures are proposed to at-risk users.

Results: Of the 940 subjects who requested counselling, consent data for each counselling step were available for 905. Consent was high at T0 (905/940 cases; 96.27%), T1 (893/894 cases; 99.80%) and T2 (885/892 cases; 99.20%). Consent decreased at the crucial points of counselling: T2 (genetic testing) in 312/383 cases (81.40%), T3 (genetic test results communication) in 312/322 cases (96.80%) and T3 (extension of counselling and genetic testing to relatives) in 48/78 cases (61.50%).

Conclusions: The model fosters the user's knowledge about cancer and favours identification of at-risk subjects. Furthermore, by promoting awareness about genetic testing and surveillance measures, the algorithm enables users to make a fully informed choice of actions in the case of predisposing or familial cancer risk.

Supported by MIUR–COFIN 2001 and COFIN 2003

A6 PHASE II STUDY OF HIGH-DOSE DENSE CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK STAGE II–IIIA BREAST CANCER

Luca Frassineti[1], Ugo De Giorgi[2], Giovanni Rosti[1], Emanuela Flamini[2], Noemi Giovannini[2], Gabriele Ciucci[1], Luciano Spinolo[1], Federica Zumaglini[1], Manuela Montanari[1], Dino Amadori[2], Maurizio Marangolo[1]
[1]Pierantoni Hospital, Forlì; [2]Santa Maria delle Croci Hospital, Ravenna, Italy

Chemotherapy combination with epirubicin and paclitaxel is one of the most active regimens for patients (pts) with breast cancer. Recent studies showed clinical evidence that the treatment efficacy is related to the chemotherapeutic dose-intensity in pts with breast cancer. Fifty-three consecutive pts with stage II–IIIA breast cancer and nine or more involved nodes (first 25 pts) or four or more (next 28 pts) received a mobilizing course consisting of epirubicin 150 mg/m^2, preceded by dexrazoxane (day 1), paclitaxel 175 mg/m^2 (day 2), plus filgrastim; followed by three courses of epirubicin 150 mg/m^2, preceded by dexrazoxane (day 1), paclitaxel 400 mg/m^2 (day 2), with peripheral blood progenitor cell support (PBPCS) and filgrastim, every 16–19 days. Paclitaxel 400 mg/m^2 was given as a 6 h infusion in the first 25 pts (P6h pts), and as 24 h infusion in the next 28 pts (P24h pts) in order to reduce neurotoxicity. No toxic death occurred. Three patients went off study due to a severe hypersensitivity reaction to paclitaxe l (1 P6h/2 P24h pts). Five patients interrupted the treatment due to prolonged grade 3 peripheral neurotoxicity (3 P6h/2 P24h pts). In all cases, neurotoxicity was reversible. Prospective evaluation of cardiotoxicity is ongoing; none of the pts developed clinically apparent congestive heart failure. In P6h pts, the disease-free and overall survival rates at 48-month follow-up were 54% and 71%, respectively. It is too early for results in P24h pts. The high-dose dense chemotherapy regimen appears a feasible and safe approach in patients with high-risk stage II–IIIA breast cancer. Updated results will be presented at the Meeting.

This work was supported by the Italian National Research Council (Project n°31412), and by a grant from Istituto Oncologico Romagnolo

A7 RADIATION SCHEDULES AFTER BREAST CONSERVING SURGERY (BCS). HISTORICAL COMPARISON BETWEEN CONVENTIONAL FRACTIONATION (CF) AND SHORT FRACTIONATION (SF): COSMETIC AND LOCAL CONTROL OUTCOME ON 685 WOMEN

Marco Di Lieto, Marco Stefanacci, Enola Vezzani, Andrea Chiavacci
U.O. Radioterapia Oncologica, ASL 3, Pistoia, Italy

Radiation therapy (aiming at a better local control) has become accepted as standard treatment after breast conserving surgery (BCS) for women with stage I or II cancer. Many authors have recently proposed shorter regimens, employing a higher dose per fraction or even hyperfractionation.

From January 1994 to May 2001, at the Radiotherapy Department of Pistoia, 935 women have undergone postoperative radiotherapy after BCS for early breast cancer (ductal or lobular carcinoma). From December 1997, considering the new data on fractionation for breast cancer after BCS, we decided to deliver (initially to patients not submitted to chemotherapy) a dose of 44 Gy, in 16 fractions, with a short fractionation (SF) of 2.75 Gy × 5 fractions/week to 507 patients. We have evaluated 685 women, 75% pT1, 13% pT2, 6% pTis, 254 treated with CF and 431 with SF, with 2 years minimum follow-up for cosmetic results and local control. Qualitative evaluation of cosmesis has been carried out by two radiotherapists separately (one of which was a woman) in accordance with a four-point score (modified EORTC method): 1, excellent: no visible sequelae; good: visible, but no disturbing sequelae; 3, fair: marked sequelae; 4, poor: unacceptable sequelae.

The following table shows cosmetic results and local failure:

Fractionation	No. pts	Median follow-up	% lob./duct. carcinoma	% chemoth. sequential	% hormon.	% cosmetic results (*four-point score)				% local failure
						1	2	3	4	
CF	254	59	12 (30/254)	40.5 (102/254); 58 anthra	30 (76/254)	85	10	5	–	2.5
SF	431	46	11.6 (50/431)	25.2 (107/431); 44 anthra	35.7 (150/431)	87	9	4	–	0.6

duct., ductal; chemoth., chemotherapy; hormon., hormonotherapy.

Also if this comparison is historical and not randomised, and has different median follow-up, these data indicate that the shorter course of radiation may be an acceptable alternative to conventional fractionation. This schedule is more attractive for patients and radiotherapists, because it is less resource-intensive for the facility.

A8 HOW OFTEN IS ADJUVANT CHEMOTHERAPY ADMINISTERED TO ELDERLY WOMEN (≥70 YEARS) WITH EARLY BREAST CANCER?

U. Basso[1], A. Brunello[1], C. Pogliani[1], F. Lumachi[2], S. Monfardini[1]
[1]Departments of Medical Oncology and [2]Endocrine Surgery, Azienda Ospedale-Università, Padua, Italy

Background: No randomized trials on adjuvant treatment of operable breast cancer (BC) in elderly women are available. We thus carried out a retrospective study of chemotherapy administration in women ≥70 years.

Material and methods: We reviewed tumor stage and treatment of all elderly BC patients referred from 1999 to 2003 to our institution. Major risk factors and therefore potential indication for chemotherapy were: T≥2 cm, Grade 3, N positive and estrogen receptor (ER) negative status.

Results: In total, 260 elderly consecutive patients were eligible (diagnosis of pT1–pT3, non-metastatic BC). Median age was 76 years (70–97). Fifty-five per cent underwent conservative surgery; 84.6% nodal dissection and 5.8% sentinel node biopsy. Tumor characteristics were as follows:

Tumor size	pT1 142 pts *54.6%*	pT2 111 pts *42.7%*	pT3 7 pts *2.7%*		Total 260 pts *100%*
Nodal state	Positive 94 pts *40.3%*	Negative 139 pts *59.7%*			Total 233 pts *100%*	n.a. 27 pts
ER	Positive 208 pts *82.5%*	Negative 44 pts *17.5%*			Total 252 pts *100%*	n.a. 8 pts
Tumor grade	G1 5 pts *23.8%*	G2 105 pts *45.5%*	G3 71 pts *30.7%*		Total 231 pts *100%*	n.a. 29 pts
c-erbB2	+++28 pts *20.3%*	++– 28 pts *20.3%*	+– 50 pts *36.2%*	— 32 pts *23.2%*	Total 138 pts *100%*	n.a. 122 pts
Vascular invasion	Present 73 pts *43.7%*	Absent 94 pts *56.3%*			Total 167 pts *100%*	n.a. 93 pts

n.a., not available.

Adjuvant chemotherapy was proposed for 96 of 186 high risk patients. Thirteen refused, while chemotherapy was started in 83 patients: 84.4% CMF, 9.6% 3M (mitoxantrone, methotrexate, mitomycin), 6.0% anthracycline-based regimens. Chemotherapy was interrupted in 21 patients, completed in 56 with dose reduction ≥25% in 16.1% of cases. Therapy is still ongoing in five patients.

Conclusions: Adjuvant chemotherapy was not proposed for 48.4% of elderly patients with high recurrence risk BC, probably due to age associated conditions (comorbidities, cognitive status, family support). Prospective studies are needed to determine tumor characteristics and geriatric conditions that should guide the choice for adjuvant chemotherapy in elderly patients and to define the role of biological parameters such as c-erbB2 overexpression.

A9 EARLY INVASIVE BREAST CANCER (BC): WHAT IS THE IMPACT OF AGE ON TUMOUR CHARACTERISTICS? ANALYSIS OF 2917 CONSECUTIVE PATIENTS (PTS)

Monica Giovannini[1], Rebecca Pedersini[1], Michela Frisinghelli[1], Michele Pavarana[1], Marta Mandarà[1], Alessandra Auriemma[1], Elena Fiorio[1], Rocco Micciolo[2], Gian Luigi Cetto[1], Annamaria Molino[1]
[1]Oncologia Medica, Università di Verona, Verona; [2]Dipartimento di Statistica, Università di Trento, Trento, Italy

Introduction: Age is one of the major factors affecting the risk of developing BC. We compared systematically early invasive BC (T1, T2, T3) of pts diagnosed before and after 65 years in terms of pathological, biological, clinical and physiological characteristics.

Materials and methods: In this study of 2917 pts, we verified the differences between 1899 BC diagnosed before and 1018 diagnosed after the age of 65 years in terms of T (T1 versus T2 and T3); nodal involvement; estrogen/progesterone receptor (ER/PgR) status; Ki-67 levels (low 0–15%, intermediate 16–25%, high 26–100%); grading; c-erbB2; p53, p21, BCL2 levels; vascular invasion and multifocality; type of diagnosis (asymptomatic versus symptomatic); family history (FH); age at menarche (<12, 13–15, <16 years); number of pregnancies (0, 1, 2, >3); age at first pregnancy and menopause.

Results: The tumours of pts aged <65 years were more frequently smaller (T1: 70.1% versus 64.6%; $P<0.01$), N+(39.8% versus 33.5%; $P<0.01$), ER− (19.9% versus 13.4%; $P<0.01$), higher grade (G3: 32.4% versus 25.4%; $P<0.01$), c-erbB2+(43.9% versus 36.5%; $P<0.01$), vascularly invasive (37.9% versus 26.3%; $P<0.01$), diagnosed asymptomatically (40.9% versus 28.2%; $P<0.01$); the patients were also more likely to have a FH (33.3% versus 25.4%; $P<0.01$). There were no differences in terms of PgR, Ki-67, p53, p21, BCL2 and multifocality, but the younger patients experienced menarche earlier (<12 years: 47.1% versus 38.8%; 13–15 years: 49.2% versus 53%; >16 years: 3.8% versus 8.2%; $P<0.01$) and less frequently reported a high number of pregnancies (>3: 25.7% versus 36.1%; $P<0.01$). Linear correlation analysis between age at diagnosis and first pregnancy revealed that they had their first pregnancy earlier ($P<0.01$). There were no significant between-group differences in age at menopause.

Conclusions: A younger age seems to correlate with negative factors (N+, ER−, higher grading, c-erbB2+ and vascular invasion); the greater frequency of smaller tumours may be due to mammographic screening. An earlier age at menarche and fewer pregnancies indicate greater exposure to the mitogenic effects of estrogens.

A10 ROLE OF SENTINEL LYMPH NODE MAPPING IN HUMAN BREAST CANCER AFTER PRIMARY CHEMOTHERAPY

M.P. Brizzi[1], A. Bottini[2], G. Allevi[2], S. Aguggini[2], S. Bonardi[2], D. Generali[2], F.M. Fringuelli[2], A. Bersiga[2], B. Iacona[2], M. Milani[2], G. F. Lima[2], A. Berruti[1], L. Dogliotti[1]
[1]Oncologia Medica, ASO S. Luigi, Orbassano; [2]Breast Unit, A. Istituti Ospitalieri, Cremona, Italy

Background: Sentinel lymph node (SLN) biopsy is a widely recognized reliable method for early breast cancer (BC) staging offering an alternative to complete axillary dissection. The role of this procedure after primary chemotherapy still remains controversial.

Patients and methods: From August 2000 to November 2003, 102 patients bearing T2–4, N0, M0 BC, were treated with epirubicin-based primary chemotherapy. Lymphoscintigraphy with technetium-99 labeled nanocolloidal albumin was carried out after chemotherapy before definitive surgery. Injection was carried out around the primary tumor, between the tumor and the axilla. All patients underwent complete axillary lymph node dissection. No additional immunohistochemical staining was carried out in SLN biopsy specimens.

Results: The SLN was identified in 99 cases (96.0%). Thirty-one (31.6%) had metastatic involvement, and in 15 of them (53.6%), the SLN was the only positive node. Nine patients had false-negative SLN biopsy; that is, the sentinel node was negative, but at least one nonsentinel node contained metastases. The SLN biopsy revealed a sensitivity of 77.5%, specificity 100%, and a predictive negative value of 86.6%.

Conclusion: In the present experience, SLN biopsy was not sensitive enough to predict axillary status in breast cancer patients undergoing primary chemotherapy. Whether immunohistochemical evaluation could improve the diagnostic accuracy of SLN is currently under investigation.

Supported by a grant from Consiglio Nazionale Ricerche (CNR), Rome

A11 CORRELATION BETWEEN BRCAPRO RISK ESTIMATE AND INCIDENCE OF BRCA1–BRCA2 MUTATION IN 178 PATIENTS WITH FAMILIAL BREAST AND/OR OVARIAN CANCER FROM CENTRAL ITALY

S. Rosati[1], F. Bianchi[1], L. Belvedersi[1], C. Loretelli[1], R. Catalano[1], D. Gagliardini[1], R. Bracci[1], A. Piga[1], R. Cellerino[1], E. Porfiri[2]
[1]Oncologia Medica, Università Politecnica delle Marche, Ancona, Italy; [2]CR-UK Institute for Cancer Studies, Birmingham, UK

Background: We studied the ability of BRCAPRO to identify patients (Pts) at high risk for BRCA1 or BRCA2 mutations among individuals with familial breast cancer (BC) or ovarian cancer (OC) from central Italy.

Patients and methods: Selection criteria were: Family History of BC (FH BC): Pts with BC and at lest one first degree relative with BC. Family History of OC (FH OC): Pts with OC or BC and least one first degree relative with OC. Pts diagnosed with BC or OC before the age of 40 (Early onset BC-OC). Male Pts with BC (MBC). Patients with BC and OC (BOC). Carrier probability was assessed using BRCAPRO version 3.3.2.b. BRCA1 and BRCA2 analysis was carried out using single-strand conformation polymorphism (SSCP), protein truncation test (PTT) and direct sequencing.

Results: Mutation analysis has been completed in 162 of the 178 patients in the study and is summarised in the table. A 60% correction factor was used to account for the low sensitivity of PTT and SSCP. 13 mutations were found among the 26 Pts with a mutation risk >75% whereas three mutations were found among the 100 Pts with a risk ≤ 10%.

Patient group	Patient no.	Average carrier probability	Mutations expected	Mutations expected using SSCP-PTT	BRCA1–BRCA2 mutations detected
FH BC	88	0.199	17.5	10.5	8
FH OC	24	0.56	13.4	8	8
MBC	9	0.55	4.95	2.9	2
Early onset BC-OC	39	0.04	1.6	1	1
BOC	2	0.29	0.58	0.35	1
Total	162		38	22.75	20

Conclusions: BRCAPRO has been demonstrated to be useful in identifying subjects with high carrier probability in a patient population from central Italy. Our data confirm the unsatisfactory sensitivity of PTT-SSCP. A low incidence of mutations (3%) was found in patients with low carrier probability; we believe that these patients should not be excluded from testing and that cost effective screening strategies should be defined for them.

A12 BRCA1 AND BRCA2 ANALYSIS IN SARDINIAN BREAST CANCER FAMILIES

G. Palomba[1], A. Cossu[2], M.F. Dedola[2], M.G. Giuseppina[2], A. Farris[2], A. Contu[3], M.P. Satta[1], M.C. Sini[1], P.P. Demuro[1], C. Rozzo[1], M. Casula[1], M. Colombino[1], A. Manca[1], P. Baldinu[1], A.A. Carboni[2], F. Tanda[2], G. Palmieri[1], M. Pisano[1]
[1]ICB-CNR, Alghero (SS); [2]Università degli Studi di Sassari, Sassari; [3]Ospedale Civile ASL1, Sassari, Italy

The genetically homogeneous Sardinian population can be useful in defining the molecular basis of cancer. To evaluate the incidence of disease-causing mutations in breast cancer (BC) families from Sardinia, we screened the two major BC susceptibility genes, BRCA1 and BRCA2, and correlated the presence of mutations with clinicopathological features. Families were selected having at least three BC cases, two generations involved, and one bilateral-BC or male-BC or prostate or ovarian cancer. Using a combination of techniques such as single-strand conformation polymorphism (SSCP), denaturing high-performance liquid chromatography (DHPLC) and sequence analysis, 101 Sardinian families were analyzed for germline mutations in BRCA1 and BRCA2 genes.

Two BRCA1/2 germline sequence variations were identified: BRCA2-8765delAG and BRCA1-Lys505ter. They are two deleterious mutations (due to their predicted effects on protein truncation), and were found in 19 families (19%).

BRCA2-8765delAG was found in 17/19 (90%) BRCA1/2-positive families, showing a founder effect, but only in 26/691 (4%) unselected and consecutively collected BC patients. In fact, the prevalence of this mutation was significantly correlated with the total number of female BCs ($P<0.01$), increased by the presence of (i) at least one case of ovarian or male BC, or (ii) three generations affected, or (iii) bilateral BC. The BRCA1-Lys505ter mutation was found in only 2/101 (2%) families, suggesting that BRCA2 gene could be more involved in developing breast cancer in Sardinian population.

Identification of such features should address BC patients and their families to genetic counseling and BRCA1/2 mutational analysis. In addition, this is the first report of a detailed BRCA1/2 mutation screening in Sardinia, having immediate implications for the clinical management of BC families.

A13 ONCOGENETIC COUNSELLING FOR HEREDITARY AND FAMILIAL BREAST AND/OR OVARIAN CANCER: DATA FROM NAPLES

Matilde Pensabene, Ida Capuano, Ilaria Spagnoletti, Caterina Condello, Alma Contegiacomo
Department of Molecular and Clinical Endocrinology and Oncology, Area Funzionale 'Screening and Follow-up for Hereditary and Familial Tumours', University of Naples 'Federico II', Naples, Italy

Introduction: The discovery of the BRCA1 and BRCA2 susceptibility genes increased the demand for identification of the hereditary and familial risk for breast

cancer (BC), which in turn led to the development of *ad hoc* medical services, including cancer genetic counselling.

Aim: Here we report our counselling experience in the oncological setting. Counselling entailed risk identification, risk definition and risk management of families on the basis of the multistep model devised by our unit and validated in the context of the Italian Network for hereditary and familial breast cancer.

Subjects and methods: We assessed familial and hereditary risk for affected and disease-free subjects who requested counselling. We also defined the personal risk for disease-free subjects, and offered genetic testing to subjects at hereditary risk. Surveillance measures were offered to probands and their relatives at hereditary or familial risk.

Results: Between 1999 and 2003, 129 affected and 29 disease-free probands were referred to our unit. We acquired and analysed 158 pedigrees from which we identified 79 cases at hereditary risk: 68 at familial risk and 11 sporadic BC. Genetic testing was carried out in 42/79 subjects at hereditary risk. In 18 families, genetic testing was not possible because the affected members refused blood sampling, had died or were psychologically challenged. We identified eight mutation carriers (six BRCA1 and two BRCA2). Genetic testing was extended to first-degree relatives, and revealed 12 positive cases (seven BRCA1 and five BRCA2). At a 3-year follow-up of 99 subjects, we diagnosed one BC, one ovarian cancer and one case of colon hyperplasic polyps in BRCA1 mutation carriers from three different families. We also diagnosed two contralateral BCs, one malignant melanoma, two endometrial cancers and two atypical breast ductal hyperplasias in subjects without BRCA mutations in families clustering BC.

Conclusion: Our counselling model provides a global approach, from risk identification to risk management for patients and their relatives affected by hereditary or familial breast cancer.

Supported by MIUR–COFIN 2001

A14 CHANGING PATTERNS IN THE PRESENTATION OF BREAST CANCER OVER THE LAST TEN YEARS: A SINGLE INSTITUTION EXPERIENCE

B. Vivorio, P. Morselli, F. Adami, R. Cengarle, G. Cavazzini, C. Rabbi, F. Pari, E. Aitini
Medical Oncology and Hematology Department, 'C. Poma' Hospital, Mantova, Italy

This study reports the distribution by stage at diagnosis in breast cancer in our department from 1993 to 2003. All histologically proven incident cases of breast cancer were identified in the study period above and classified for tumor site and nodal involvement according to the phatological TNM (tumour–node–metastasis) criteria.

The data from 2065 breast cancer patients demonstrate a chronologically based change in all stages of disease at presentation over the 10 years except Tis and T3; for the period 1993–2003, percentages of patients' disease stage were as follows: Tis (8.0%), T1 (50.9%), T2 (30.2%), T3 (2.6%), T4 (8.3%). Specifically, there was an increase in the proportion of patients with T1 tumors: 44.3% (1993) versus 56.1% (2003) and a decrease in T2 tumors (33.8% versus 27.0%) as shown in Figure 1. T3 tumors showed no difference and T4 showed a significant decrease (7.2% versus 5.4%). In our experience, we did not observe a percentage increase in Tis incidence as reported in other studies (Figure 1).

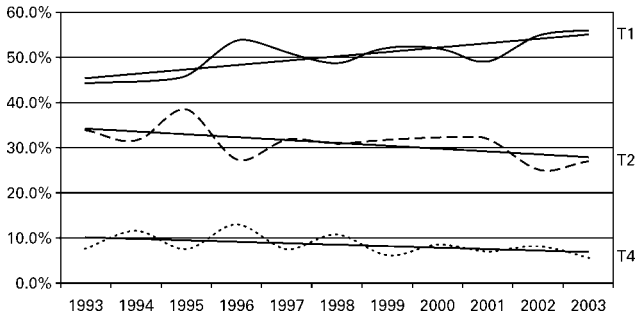

Figure 1. Percent of patients' disease stage from 1993 to 2003 T1, —; T2,- - -; T4, · · ·.

In our opinion, it is very important, in the next years, to improve the quality of this study in order to verify changing patterns in the presentation of breast cancer, specifically in Tis incidence.

In fact, the cancer register should be encouraged to report data on stage distribution in breast cancer in order to provide an essential contribution to studies on screening programs and quality of diagnosis.

A15 BIOLOGICAL FEATURES OF BREAST CANCER DIAGNOSED DURING PREGNANCY OR LACTATION

Fedro Peccatori[1], Oreste Gentilini[2], Nicole Rotmensz[3], Sara De Dosso[1], Michele Masullo[4], Serife Simsek[2], Giovanni Mazzarol[4], Paolo Veronesi[2], Giovanni Martinelli[1]
Departments of [1]Hematoncology [2]Senology [3]Epidemiology/Biostatistics and [4]Pathology, European Institute of Oncology, Via Ripamonti 435, 20141, Milan, Italy

Breast cancer presenting during pregnancy and lactation (BCdP/L) is a rare, but difficult clinical situation. The question whether cancer is influenced by the endocrinologic milieu of pregnancy/lactation or is just a concomitant event, is still open. Here we report clinical and pathological features of a consecutive series of patients referred to a single institution, in order to identify specific biological peculiarities. Between November 1996 and September 2003, 35 patients with BCdP/L were observed. Family history for breast cancer, ovarian cancer, previous parity, histological tumor type, primary tumor size, nodal status, grading (G), proliferation index (expression of Ki-67), estrogen (ER) and progesterone receptor (PgR) status, HER2/neu overexpression, occurrence of peritumoral vascular invasion (PVI), were recorded for all patients. Median age was 35 years (range 28–43). A family history of breast cancer was present in 40% of patients (first-degree relative with breast cancer in 17.1%). Nineteen patients were diagnosed during pregnancy and 16 patients within 1 year from delivery, during lactation. Median tumor size was 2.9 cm (range 0.19–12 cm). Axillary lymph nodes were positive in 60% of the patients. Both ER and PgR were not expressed in 42.8%; 93.1% had moderately or poorly differentiated cancer, and the Ki-67 labeling index was above 20% in 84.9% of the tumors. HER2/neu was overexpressed in 25.7% and PVI was identified in 40% of breast carcinomas. Despite the observation of BCdP/L presenting as a more aggressive form of breast cancer, with features correlated to poor prognosis, it should be acknowledged that a large proportion of these patients are diagnosed with node negative or with a potentially endocrine responsive disease. These data will be compared with an age and prognostic factor-matched group of breast cancer patients, in order to verify the possible specific influence of pregnancy and lactation on biologic features. A registry of all pregnancy-associated tumors will be developed in the near future.

A16 GENETIC COUNSELLING AND SURVEILLANCE IN B/O CANCER FAMILIAL RISK: A TWO YEARS EXPERIENCE AT REGINA ELENA CANCER INSTITUTE

S. Gasparro[1], A. Savarese[1], G. Maggi[1], F.M. Sega[1], A. Caruso[1], F. Ferranti[1], E. Cossu[2], G. Simonetti[2], M. Crecco[1], F. Cognetti[1]
[1]Istituto Nazionale Tumori 'Regina Elena', [2]Dip. Diagnostica per Immagini, Policlinico Tor Vergata, Rome, Italy

Background: Increasing education and surveillance among high-risk individuals is crucial for cancer control. Information processing and acceptance of screening programs in these subjects are however still under investigation.

Patients and methods: Cancer patients or suspected high-risk subjects referred to the Regina Elena Cancer Institute in Rome from April 2002 to February 2004 were addressed to genetic counselling. Breast/Ovarian Cancer Syndrome (HBOC) risk was assessed following the Criteria of Modena in order to offer a clinical and psychological intensive surveillance program (performed in collaboration with the University of Rome Tor Vergata) and BRCA1/2 mutation analysis.

Results: In total, 208 subjects (204 female, four males, median age 50 years) belonging to 154 families with a history of breast/ovarian (B/O) cancer were recruited. They were addressed to counselling because of their familial risk perception (30%), prevention opportunity (25%) or anxiety and fear (3%). The remaining 42% had no risk perception, and accepted the counselling following the clinician's indications. Among these families, 54 (35%) met the criteria for suspected HBOC and cancer patients in 50 families (92%) underwent mutation analysis. A surveillance program with annual mammography and breast MRI, 6-month breast and pelvic US scan and physical examination was accepted by 50% of the individuals. In two cases, early breast cancer lesions were identified by MRI. Psychological evaluation showed a higher reactive anxiety in 45% of subjects, with affected emotional adjustment. Moreover, one-fifth of the sample reported clinically significant levels of depression.

Conclusions: In our experience, people largely accept being investigated for familial risk, although only 60% of subjects have a perception of risk and 35% meet the risk criteria. Intensive screening is not widely accepted (50% of eligible sample) before knowing the result of the mutation test. Additional evaluation and recruitment are ongoing.

Partially supported by Ministero della Salute–Italia, and Lega Italiana Tumori

A17 NON PALPABLE BREAST LESIONS DIAGNOSED BY VACUUM-ASSISTED CORE BIOPSY: EXPERIENCE OF AN ONCOLOGY PREVENTION UNIT

Lucia Bedei[1], Paola Angela Sanna[1], Donata Casadei Giunchi[1], Maria Paola Innocenti[1], Patrizia Vignutelli[1], Roberta Maltoni[2], Fabio Falcini[1]
[1]Oncology Prevention Unit and [2]Department of Medical Oncology, Pierantoni Hospital, Forlì, Italy

This study aimed to investigate the frequency of histological underestimation of breast carcinoma following diagnosis of atypical ductal hyperplasia (ADH) or ductal carcinoma *in situ* (DCIS) using vacuum-assisted large-core needle biopsy. From June 1999 to November 2003, 1639 vacuum-assisted biopsies of non-palpable breast lesions were performed in 1478 women. Median age was 51 years (range 22–86 years). Biopsy had been requested for the following radiological lesions: 1269 microcalcifications, 263 opacities and 100 parenchymal distortions. In eight cases, the biopsy was performed next to the clip located at the end of a previous biopsy that had been considered unsatisfactory. The median lesion size was 0.8 cm

(range 0.2–5.5 cm) and the median number of specimens removed was 12 (range 1–87). A histological diagnosis of ADH was made in 50 biopsies (3%) taken from 46 microcalcifications, one opacity, one distortion, two clips, and of DCIS in 194 biopsies (12%) taken from 185 microcalcifications, six opacities and three distortions. Underestimation of DCIS was defined when a lesion diagnosed as ADH at percutaneous biopsy was diagnosed as ductal carcinoma *in situ* or invasive breast carcinoma at surgical biopsy, and underestimation of invasive breast cancer was defined when a lesion diagnosed as DCIS at percutaneous biopsy was diagnosed as invasive cancer at surgical excision. An underestimation of DCIS diagnosis was observed in only 2/50 cases (4%): both radiological lesions were microcalcifications of >2 cm, with a radiologically evident residue of >50% after biopsy. Underestimation of infiltrating cancer was observed in 27/194 biopsies (14%): 26 were carried out on microcalcifications and one on a distortion. Median age of patients was 52 years (range 30–69 years) and median size of the radiological lesion was 1.3 cm (range 0.5–3.2 cm), with radiologically evident residual lesions in 18/27 cases (67%). Twenty-four infiltrating ductal and three infiltrating lobular cancers were histologically confirmed. The underestimation of diagnosis of DCIS often occurred when the radiological lesion is >2 cm, with a residue of >50% after biopsy, whereas the complete excision of a radiologically evident lesion did not exclude the underestimation of infiltrating cancer.

A18 MICROINVASIVE BREAST CANCER: CLINICAL-PATHOLOGICAL CHARACTERISTICS AND TREATMENT. EXPERIENCE FROM TWO INSTITUTIONS

S. Gori[1], A.M. Mosconi[1], P. Anastasi[1], A. Rulli[2], L. Scopece[3], E. Franceschi[3], C. Aristei[1], E. Perrucci[1], F. Mascione[1], C. Basurto[1], A. Cavaliere[4], C. Bisacci[2], G. Cavallo[3], R. DegliEsposti[3], L. Crinò[3], M. Tonato[1]
[1]Medical Oncology-Radiotherapy Department, [2]Breast Unit, Policlinico Hospital, Perugia; [3]Oncology Department, Bellaria Hospital, Bologna; [4]Institute of Pathological Anatomy and Histology, Perugia University, Perugia, Italy

Background: Data on the biological behaviour and treatment of microinvasive (MIC) breast cancer are scarce and discordant due to the rarity and a previous lack of standardized definition. Recently MIC has been defined as having a size limit of 1 mm (Sobin LH, Wittekind Ch. *International Union Against Cancer. TNM classification of malignant tumours*. 5th Edition, John Wiley & Sons, New York, 1997). The surgical management of MIC, particularly of the axilla, is controversial. Widespread use of mammographic screening for breast cancer determined an increase in the detection of DCIS and early stage invasive carcinoma. In this retrospective study, clinical-pathological characteristics of MIC from two different institutions are reported.

Patients and methods: From January 1999 to February 2004, 63 MIC were diagnosed and treated in 2209 pts with early breast cancer (3%). MIC was defined as a microinvasion ≤ 1 mm in its greatest dimension. Pathologic characteristics and treatment (locoregional ± systemic), particularly of axilla management, were evaluated.

Results: Median age of 63 pts was 59 years (range 39–83); 52 (83%) pts were postmenopausal. Sixty (95%) MIC were associated with ductal carcinoma *in situ* (DCIS) and three (5%) with lobular carcinoma *in situ* (LCIS). Thirty-one (49%) patients received mastectomy; 31 pts (49%) breast conservative breast surgery (BCS) and radiotherapy; one patient refused radiotherapy after BCS. Axillary lymph node (LN) dissection was carried out in 32 pts (51%) and all LN were negative for metastases. Sentinel lymph node biopsy (SLN) was carried out in 14 pts (22%) and was negative in all cases. In 17 pts (27%), axillary status was not evaluated. Adjuvant endocrine therapy was administered to 35 pts (55%) and anthracycline-based chemotherapy to three patients with overexpressed HER2 (3+). After a median follow-up of 16 months (range 1–65), one patient was lost to follow-up and two patients died due to stroke. All remaining patients are alive and disease-free.

Conclusions: In our experience, MIC is not associated with axillary metastases and appears to be associated with an excellent prognosis.

A19 A PHASE II STUDY OF TEMPORARY OVARIAN SUPPRESSION WITH GOSERELIN FOR PREVENTION OF CHEMOTHERAPY-INDUCED EARLY MENOPAUSE IN EARLY BREAST CANCER PATIENTS

T. Catzeddu[1], L. Del Mastro[1], C. Bighin[1], E. Maggi[1], C. Bell[1], S. Pastorino[1], S. Mammoliti[1], D. Testa[2], M.R. Sertoli[3], L. Boni[4], R. Rosso[1], M. Venturini[1]
[1]Oncologia Medica A, Istituto Nazionale per la Ricerca sul Cancro, Genoa; [2]Dipartimento di Ginecologia e Ostetricia, Azienda Ospedaliera S. Martino e Cliniche Convenzionate, Genoa; [3]Oncologia Medica B, Istituto Nazionale per la Ricerca sul Cancro, Genoa; [4]Centro Trias, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

Early menopause is a frequent irreversible side-effect induced by chemotherapy (CT) in young patients and no standard methods for its prevention are available. Preclinical data and some phase II trials suggested that LHRH analogs given during CT can decrease gonado-toxicity induced by CT. The aim of the present trial was to investigate the ability of Goserelin (G) to prevent CT-induced menopause by a two-step phase II study. Treatment with G was considered clinically interesting if it was active to prevent menopause in 80% of patients (pts) whilst the accrual was stopped with a <50% success rate. The planned sample size was 29 patients (pts). End point of the study was resumption of menstrual activity or a FSH value <40 within 12 months after the last cycle of CT. G 3.6 mg was administered at least 1 week before CT and then every 4 weeks until CT completion. From October 2001 to June 2003, a total of 30 pts were enrolled. Median age was 39 (29–47); 11 (37%) pts had no previous pregnancy. All but one patient (96%) received FEC regimen; median number of CT cycles: 6 (5–8), median number of G doses: 5 (2–6). All patients had hot flushes, sweating and headache during CT and G administration. After CT, all ER + and/or PgR + pts received tamoxifen. Among 28 pts evaluable for activity until now, 21 (70%) pts resumed menstrual activity and 26 (93%) pts have a FSH value <40. A total of 19 pts completed CT from at least 12 months, among them only three (16%) pts did not resume menstrual activity indicating a failure of treatment. Median time to menstrual resumption was 5 months (1–12). **Conclusion:** Our data indicate that G administered before and during CT is active to prevent menopause induced by CT in young early breast cancer patients.

A20 COMPARISON OF DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING (DCE-MRI) AND SONOGRAPHY (US) IN PATIENTS RECEIVING PRIMARY CHEMOTHERAPY (PCT) FOR LOCALLY ADVANCED BREAST CANCER (LABC)

Laura Martincich, Filippo Montemurro, Giovanni De Rosa, Stefano Cirillo, Vincenzo Marra, Riccardo Roagna, Marco Gatti, Piero Sismondi, Daniele Regge, Massimo Aglietta
Istituto per la Ricerca e la Cura del Cancro, Candiolo, Italy

Background: The purpose of this study was to compare DCE-MRI and US in monitoring tumor size in patients with LABC undergoing PCT.

Patients and methods: 20 patients with LABC, underwent four cycles of PCT with paclitaxel 175 mg/m^2 and doxorubicin 50 mg/m^2 every 3 weeks, followed by surgery. DCE-MRI and US breast examinations were carried out and interpreted by two different radiologists who were blinded to each other's results. Tumor size was defined as the product of the two major tumor diameters. The correlation between DCE-MRI and US measurements was calculated at baseline, after two cycles of PCT and after four cycles of PCT. The largest tumor diameter measured by the two techniques after four cycles of PCT was also correlated with the histopathological major tumor diameter.

Results: Baseline DCE-MRI identified 24 breast lesions (one patient had multicentric disease with five nodes) while US detected 22 lesions, failing to detect the two smallest foci of the multicentric tumor. The correlation between baseline DCE-MRI and US measurements was 0.47 ($P = 0.02$). Seventeen of the 22 lesions identified by both techniques were larger when measured by DCE-MRI than by US. After two and four cycles of PCT, the correlation between measurements improved (0.620, $P = 0.002$, and 0.867, $P < 0.001$, respectively). The correlation between post-treatment measurements and histopathological diameter was 0.871 ($P < 0.001$) and 0.800 ($P < 0.001$) for DCE-MRI and US, respectively. The four cases achieving a pathological complete response were correctly identified by DCE-MRI, but not by US.

Conclusions: Accurate estimation of the initial tumor extent and identification of patients achieving a pathologically complete response (pCR) after PCT support the hypothesis that DCE-MRI may be the preferred imaging tool in the management of LABC patients undergoing PCT followed by surgery.

A21 IMMUNOHISTOCHEMICAL PREDICTORS OF PATHOLOGICAL RESPONSE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER (LABC) UNDERGOING PACLITAXEL-BASED NEOADJUVANT CHEMOTHERAPY (NCT)

G. De Rosa, F. Montemurro, S. Redana, R. Ponzone, L. Martincich, M. Gatti, I. Sarotto, N. Biglia, M. Risio, P. Sismondi, M. Aglietta
Institute for Cancer Research and Treatment Candiolo, Turin, Italy

Introduction: We studied factors predictive for the achievement of a major pathological response (MPR) in patients (pts) with locally advanced breast cancer (LABC) undergoing neo-adjuvant chemotherapy (NCT).

Patients and methods: Thirty-nine patients with T > 3 cm or stage III A/B breast cancer, received NCT followed by surgery. NCT consisted of paclitaxel (P) 175 mg/m^2 + doxorubicin (A) 50 mg/m^2 q3 weeks for four cycles in 35 pts, six cycles of PA in 2 pts, and four cycles of P alone in 2 pts. Seven patients had inflammatory breast cancer. The mean tumor diameter for non-inflammatory cancers was 5.3 cm. Pathological response was scored using a five-point scheme: score 4 (small cluster of dispersed residual cancer cells) and score 5 (no residual viable cancer cell) were defined as MPR. Baseline 18-Gauge needle tumor biopsies were used to determine by immunohistochemistry the following factors predictive for MPR: estrogen and progesterone receptor status (ER, PgR), proliferative activity (Ki-67), and HER2.

Results: Clinical response rate was 87% (complete in seven and partial in 27 pts, Table 1). Twelve patients achieved a MPR (31%, 6 score 5 and 6 score 4). Ki-67 > 20%, and estrogen receptor negativity (ER–) were predictive for MPR at univariate analysis. At multivariate analysis, only ER– retained statistical significance (Odds Ratio 5.100, $P = 0.036$, 95% CI 1.113–23.372).

Conclusions: Although patients with ER– tumors derived the highest benefit in terms of MPR from P-based NCT, clinical tumor regression, which at the present time is the main aim of NCT, occurred in 87% of the patients (75% in pts with ER + tumors, table). Thus, despite a negative association with MPR, ER-positivity should not be considered an exclusion criterion for NCT in this clinical setting.

Table 1. Tumor response according to receptor status

	Clinical, *n* (%)			Pathological, *n* (%)			No. patients
	CR	PR	SD	Score 1–3	Score 4	Score 5	
ER+	3 (15)	12 (60)	5 (25)	17 (85)	2 (10)	1 (5)	20
ER–	4 (21)	15 (79)	0 (0)	10 (53)	4 (21)	5 (26)	19
	$P = 0.07$*			$P = 0.023$*			

*Univariate P values (χ^2).

A22 INCIDENCE OF LIPID AND BONE METABOLISM IMBALANCE IN POSTMENOPAUSAL WOMEN TREATED WITH 5 YEARS TAMOXIFEN (TAM) OR AROMATASE INHIBITOR (A.I.) AFTER TAMOXIFENE WITHDRAWAL

D. Coletta, M. Di Seri, M.S. Rosati, C. Proietti, A. Ranuncoli, F. Petricola, A. Oliveti, R. Maglio, R. Grande, L. Frati
Department of Experimental Medicine and Pathology, University of Rome 'La Sapienza', Rome, Italy

Background: The purpose of this study was to compare the incidence of cholesterol levels and mineral bone density (MBD) modification in women with a physiologic, surgical or drug-induced menopausal status treated for early stage breast cancer (stage I, IIA) with tamoxifen (TAM) or aromatase inhibitors (A.I.) after TAM withdrawal due to uterine bleeding, endometrial hyperplasia or high risk of thromboembolic events.

Materials and methods: We investigated 86 patients (pts): 29 pts with hormone-receptor positive tumors treated with TAM for 5 years; 31 pts who received A.I. after TAM withdrawal (TAM → A.I.); 26 pts with hormone-receptor negative tumors not treated with anti-estrogenic therapy (control group). In order to evaluate if the physiologic age-related modification of lipidic metabolism and calcium remodeling could interfere with our results, we stratified pts as shown below:

Age	TAM	TAM → A.I.	Control
30–50 postmenopausal women	12	16	13
>50 postmenopausal women	17	15	13
Total	29	31	26

Results: No differences in MBD are seen in the TAM group or in the TAM → A.I. group compared to the control group. Incidence of osteoporosis is, respectively, 2.1%, 2.25% and 1.7% in the 30–50 years old pts and 4.25%, 3.6% and 4.9% in the older women. We found a relevant difference in median cholesterol levels at the end of 5 years of treatment between TAM and TAM → A.I. groups compared to controls. The incidence of hyperlipemic status is higher in the TAM → A.I. group: in the 30–50 year old women, we found, respectively, 189.2, 227.2 and 190.1 mg/dl. In the older women subgroup, cholesterol levels are, respectively, 205.3, 241.0 and 201.0 mg/dl.

Conclusion: Our study suggests that TAM → A.I. therapy increases the incidence of hyperlipemic status, mostly in 30–50 year old postmenopausal women.

A23 PREVALENCE OF INHERITED AND ACQUIRED RISK FACTORS FOR VENOUS THROMBOEMBOLIC (VTE) DISEASE AMONG WOMEN WITH BREAST CANCER TAKING ADJUVANT TAMOXIFEN (TAM)

Stefano Molica[1], Caterina Battaglia[1], Rita Santoro[2], Rosanna Mirabelli[1], Roberto Squillace[1], Piergiorgio Iannaccaro[2], Bonaventura Lazzaro[1], Gaetano Muleo[2]
[1]U.O. Oncologia Medica, [2]Servizio Emostasi e Trombosi, Azienda Ospedaliera 'Pugliese-Ciaccio', Catanzaro, Italy

Information dealing with the association between tamoxifen (TAM) and the risk of developing venous thromboembolism (VTE) mainly rely on women included in clinical trials of chemoprevention or adjuvant breast cancer therapy. However, the prevalence of inherited risk factors for VTE and their correlation with acquired ones was never evaluated in detail in women receiving adjuvant TAM in the setting of clinical practice. Before starting TAM therapy, we evaluated the prevalence of either acquired (i.e. hypertension, diabetes, hyperlidemia, previous angina and smoking status) or inherited (i.e. VTE familial history, factor V Leiden and prothrombin G20210A mutations) risk factors for VTE in 48 consecutive operable and estrogen (ER) and/or progesterone (PR) receptor-positive breast cancer women. Median age was 55 years (range, 29–77) and 29 (60.4%) were in postmenopausa. TAM was the sole therapy in 11 out of 48 (22.9%) while it was given after adjuvant chemotherapy consisting of CMF or anthracycline-based regimen to the remaining 37 (77.0%). The factor V Leiden mutation was detected in three out of 48 (6.2%) women and the prothrombin G20210A mutation in four (8.3%), while no homozygote was observed. When comparison was carried out with 181 age- and sex-matched healthy control women used for statistical comparison, no difference in the prevalence of either V Leiden ($P = 0.374$) or prothrombin G20210A ($P = 0.107$) mutation was found. Patients carrying V Leiden or prothrombin mutations displayed a trend towards an increase in VTE episodes among first-degree family members ($P = 0.07$), but the same did not apply for the patient's thrombotic history ($P = 0.316$). We looked for the excess of VTE risk due to the concomitant presence of inherited and acquired factors in the same subsets of patients. No association was found between V Leiden or prothrombin mutations and the presence of diabetes ($P = 0.206$), hypertension ($P = 0.560$), hyperlipidemia ($P = 0.280$) and smoking status ($P = 0.652$). In conclusion, before starting with TAM, screening for inherited VTE risk factors should be offered to women with personal or familial thrombotic history. Also asymptomatic patients with heterozygous factor V Leiden or prothrombin mutations should be shifted to aromatase inhibitors.

A24 THE ECONOMIC IMPACT OF SENTINEL LYMPH NODE (SN) APPROACH TO BREAST CANCER

S. Severi[1], A. Pellegrini[2], G. Raulli[3], L. Amaducci[4], F. Matteucci[1], G. Petrone[5], P. Mingolla[6], G. Gaddoni[7], A. Gambi[4], D. B. Poddie[7], C. Corbelli[1], G. Giugni[8]
[1]Nuclear Medicine Department, [2]Surgical Department, [3]Phatology Department, [4]Oncology Department, [5]Health Management, [6]Surgical Department, Imola; [7]Surgical Department, Ravenna; [8]Dept. Epidemiological, Faenza Hospital

Introduction: Started as a research procedure and with the severe scrutiny of the scientific community, SN has now become a standardised and accepted technique that is nowadays required by patients (pt). After years of SN procedure application, it is time to make a complete analysis of the results. Certainly the main goal is reduction of surgical invasivity but we also had an important change in the economic impact of definitive surgical treatment.

Materials and methods: We operated on 500 patients with proved breast cancer (diameter less than 2.5 cm) from four different surgical departments. The DRGs applied for this pathology are differentiated for negative and positive axillary nodes, with an economic value of €1150.18 and 1782.78, respectively. The three possible approaches are: (A) tumour excision associated with axillary dissection under general anaesthesia, (B) tumour excision and SN procedure under general anaesthesia with axillary dissection only for positive cases, (C) tumour excision and SN procedure under local anaesthesia in day surgery, and delayed axillary dissection for SN positive cases. In (C) (we operated on more than 100 pts with this modality), there is an additional DRG for the delayed dissection that is €2438.48 for the negative axilla result and €5196.4 for the positive result.

Results: Our surgical result showed a 30% SN positivity, and 17% of SN as the only positive. To treat all 500 pts with A modality, the overall DRG reimbursement would have been €669 980, with B modality it would have been €669 980 (with the addition of 500 SN and frozen section procedures and 350 axillary dissections avoided) whereas with C modality, it would have been €1 081 020 (with the addition of 500 SN procedures and 350 axillary dissections avoided).

Conclusion: In breast cancer, the SN technique can reduce surgical invasivity avoiding 70% of unnecessary and expensive axillary dissections. By treating the patient in day surgery, there is a significant mean additional reimbursement.

A25 BRCA-1 STATUS, MOLECULAR MARKERS AND CLINICAL VARIABLES IN BREAST CANCER (BC) PATIENTS WITH HIGH PROBABILITY OF HAVING AN INHERITED, CANCER-PREDISPOSING GENETIC MUTATION

Nadia Naldi[1], Antonino Musolino[1], Maria Michiara[1], Maria Angela Bella[1], Vittorio Franciosi[1], Paola Zanelli[2], Beatrice Bortesi[2], Marzia Capelletti[2], Roberta Camisa[1], Nelda Bandini[1], Mario Savi[2], Tauro Maria Neri[2], Andrea Ardizzoni[1], Stefano Cascinu[3]
[1]Medical Oncology Unit [2]Medical Genetics Service, University Hospital, Parma; [3]Medical Oncology Unit, Le Torrette Hospital, Ancona, Italy

Background: The purpose of this study was to evaluate the clinical features and outcomes of BC patients with genetic susceptibility to this disease and the contribution of BRCA1 mutation to the phenotype of these tumors.

Patients and methods: We reviewed the clinical and pathological records of 144 women with suspicion of breast (+/– ovarian) cancer inheritance. All women underwent full genetic counseling. In total, 101 selected patients with high risk of harboring a germline mutation were tested for BRCA-1 mutation analysis. Exon 11 was screened using Protein Truncation Test; detected mutations were confirmed by Direct Sequencing (DS). All the other exons were analyzed by DS.

Results: The two different risk groups had similar clinical outcomes. Of the 62 patients with completed mutation analysis, 48 (77.4%) patients had wild-type BRCA-1, seven (11.3%) had variants of unclear significance, seven (11.3%) had deleterious mutations. With regard to entry criteria for genetic testing, mutations were detected in 18.7%, 11.7%, 21.4% and 0% of women with family history, early-onset BC (< 40 years), breast-ovarian cancer and bilateral BC. BRCA1 Associated Breast Cancers (BABC) were significantly less likely to present with stage I disease than cases in women without mutations (14% versus 51%; $P = 0.045$). Individuals with mutations were more likely to have histological grade 3 and a high proliferation rate (100% versus 14%, $P \leq 0.001$; 100% versus 24%, $P \leq 0.001$). BABC were significantly more likely to be estrogen and progesterone receptor-negative (86% versus 13%, $P \leq 0.001$; 71.4% versus 23%, $P = 0.004$). Though not statistically significant,

all evaluable tumors with BRCA-1 mutations were HER-2/neu negative. There were no differences between BABC and non-BABC in 20-year relapse-free- (71% versus 64%, P = NS), 20-year contralateral breast cancer-free- (67% versus 70% P = NS), 20-year event-free- (0% versus 41%, P = NS), or 20-year overall-survival.
Conclusion: BABC seem to present with adverse molecular and histopathologic features. However, the prognosis of BABC appears to be similar to that of non-BABC.

A26 FEASIBILITY AND SAFETY OF BREAST CONSERVATION SURGERY AFTER TUMOR DOWNSTAGING BY PRIMARY CHEMOTHERAPY IN LOCALLY ADVANCED STAGE III B BREAST CANCER (LABC) PATIENTS

M.T. Ionta[1], A. Scanu[1], A.M. Carta[1], V. Pusceddu[1], A. Farris[2], A. Contu, V. Lorusso[3], S. Palmeri[4], L. Minerba, B. Massidda[1]
[1]Departments of Medical Oncology and Biostatistics of Cagliari [2] Sassari [3]Bari and [4]Palermo, Italy

Background: In the past, many LABC patients (pts) have been considered to be inoperable because of early metastatic disease; over the last decade, primary chemotherapy, as part of multimodality treatment, has become the standard therapy to increase DFS and OS, making some pts eligible for breast conservation treatment (BCT) in place of mastectomy (MRM). The aim of our study was to verify the feasibility and safety of BCT in stage III B breast cancer pts who responded to primary chemotherapy.
Methods: From 1998 to 2001, 48 stage III BT4 pts, 25% inflammatory, 88% clinical axillary nodes positive, median age 51 (22–70); 48% premenopausal; 37% ERneg; 67% PgRneg; 54% Ki-67pos; 44% G3, received six cycles of primary PEV regimen (cisplatin 50 mg/m^2, epirubicin 100 mg/m^2, vinorelbine 25 mg/m^2) every 14–21 days followed by surgery, RT and adjuvant CMF.
Results: Overall clinical response rate was 81% with 17% cCR and 64% cPR. No patients progressed during the treatment. At surgery, 36% of pts had no residual or minimal microscopic residual tumor and 64% had gross residual disease in breast; 50% had axillary nodes negative. Using the strict eligibility criteria for breast conservation, nine of 36 T4abc pts (25%) had BCT. Inflammatory cancer pts (T4d) were never considered candidates for BCT regardless of clinical response. Overall, 39 of 48 pts (81%) had MRM. All pts, except five, had RT. At a median follow-up of 48 months (22–60), no patients in the BCT group relapsed or died; 12 pts (31%) in the MRM group relapsed: just two local, three local and distant (all five pts had declined RT); seven distant metastases; 7 pts (18%) died. Overall 4-year DFS and OS rates were 75% and 85%, respectively: 100% and 100% in BCT group and 69% and 82% in MRM group, respectively. In conclusion, the multimodality approach with initial chemotherapy is the best treatment of LABC pts to attempt a successful BCT in a selected group of pts allowing for less disfigurement, and improving locoregional control as well as distant micrometastatic disease.

A27 BREAST CANCER UNDER 35 YEARS OF AGE: FEATURES OF THE DISEASE IN 82 PATIENTS

C. Ghiotto, M. Beda, E. D'Andrea, A. Favaretto, S. Monfardini
Medical Oncology Department, Azienda Ospedaliera, Padua, Italy

Background: Breast cancer is a rare event in young women less than 35 years old. In this age group, cancer is usually considered more aggressive.
Material and methods: The aim of this study is to retrospectively evaluate the biological, genetic and clinical features of 82 premenopausal breast cancer patients younger than 35 years treated at our institution from 1998 to 2003. Estrogen receptor (ER) and progesterone receptor (PgR), histologic type, grading (G), Her2/neu test detection, pathological stage according to the TNM staging system (pTNM), number of involved axillary lymph nodes, type of surgery, anthracycline-based therapy and BRCA1/2 mutation status were evaluated.
Results: The mean age of the patients was 32 (range 22–35). The ER or PgR status was positive in 67% of the patients. Most of the tumors were invasive ductal carcinoma (83%) and the most common grade was G2–G3 (96%). According to the TNM classification 20%, 46%, 22% and 6% were stage I, II, III and IV, respectively. Her2/neu was carried out in 35 patients (43%) and in 10 was 2+ or 3+. Modified radical mastectomy was carried out in 51% of the patients and axillary lymph node involvement was present in 51% of the patients. In total, 53 out of 82 patients received anthracycline-based chemotherapy. All ER/PgR positive patients received LH-RH analogues for 2 years and tamoxifen for 5 years. During the follow-up, 22 patients relapsed and two died due to disease. BRCA1/2 mutational analysis was carried out in 17 patients, and three mutations (two BRCA1 and one BRCA2) were found in probands of very high risk families.
Conclusions: This retrospective analysis of patients less than 35 years old showed a higher percentage of less differentiated disease (96% grade 2 or 3) than in older patients. A high rate of estrogen (ER) or progesterone (PgR) positive tumors (67%) was observed, higher than that reported in literature (30–50%) for these patients. BRCA mutational analysis was more likely informative in patients with early onset breast cancer when a positive family history for breast/ovarian cancer existed.

A28 DIFFERENT EXPRESSION OF BRCA1 STATUS AND CLINICAL VARIABLES IN A SAMPLE OF ITALIAN WOMEN WITH EARLY ONSET BREAST CANCER (EOBC)

Maria Angela Bella[1], Maria Michiara[1], Antonino Musolino[1], Nadia Naldi[1], Paola Zanelli[2], Beatrice Bortesi[2], Marzia Capelletti[2], Tauro Maria Neri[2], Mario Savi[2], Nelda Bandini[1], Vittorio Franciosi[1], Vincenzo De Lisi[3], Paolo Sgargi[3], Andrea Ardizzoni[1], Stefano Cascinu[4]
[1]Medical Oncology Unit, [2]Medical Genetic Service, University Hospital, [3]Parma Cancer Registry, Parma; [4]Medical Oncology Unit, Le Torrette Hospital, Ancona, Italy

Background: To estimate genetic alterations, family history (FH) and clinical variables in a EOBC population, diagnosed before 41 years, consecutively seen at the Genetic Oncology Service of Parma from 1999 to 2003, and to investigate the contribution of BRCA1/2 mutations to the phenotype of these tumors. We analyzed clinical and pathological characteristics of 60 EOBC pts. In total, 52 (86%) were tested for BRCA1/2 mutation analysis while eight (14%) refused it. Exon 11 was screened for BRCA1 mutations using the protein truncation test (PTT); mutations detected were confirmed by direct sequencing (DS). Remaining exons were analyzed by DS. BRCA2 was screened using Denaturing High-Performance Liquid Chromatography (DHPLC). Samples showing a heterozygous DHPLC elution profile were analyzed by DS. In total, 33 (55%) and 10 (16%) out of the 60 pts had breast and ovarian cancer (OC) FH, respectively. Median age of BC diagnosis was 34 years (range: 23–41); 7 pts (13%) had Bilateral BC (BBC). Two pts had similar history of sarcoma at 11–12 years and EOBC at 31–32 years and one patient had EOBC + OC + Melanoma. Of the 19 pts with completed mutation analysis, 14 (74%) had wild-type BRCA1 (WT) (including 3 pts with EOBC + other tumors), three (16%) had variants of unclear significance, two (10%) had deleterious mutations in BRCA1. Breast FH was similarly distributed in the five mutation carriers (MC) and in WT (60% versus 78%), while ovarian FH was more frequent in MC (60% versus 21%). One of five MC had BBC (age 28 for the first BC and age 42 for the second BC) and one had no FH. Stage II–III (80% versus 36%), grade 3 (75% versus 33%), lack of estrogen (50% versus 20%) and progesterone receptor (67% versus 20%), and high proliferation rate (75% versus 43%) were more common in MC than in WT. BRCA2 analysis is ongoing. Until now, a deleterious mutation in BRCA2 was detected in two pts. Our data confirm that in EOBC adverse histopathologic features and ovarian FH are predictive of being MC.

A29 RISK OF BREAST CANCER AND FAMILIARITY OF FIRST AND SECOND GRADE: A CASE CONTROL STUDY

O. Aronadio, F. Tomao, G. La Ferla, C.G. Rispoli, S. Tomao
Center for Preventive Oncology, National Cancer Institute 'Regina Elena', Rome, Italy

Familiarity constitutes the main risk factor for breast cancer in women without a history of ductal carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS), or atypical hyperplasia. In the era of molecular and genetic epidemiology, the study of risk factors for breast cancer from an analytical point of view is still full of interest because it gives the possibility to plan selective genetic testing in a high risk population and to assess the role of other cofactors involved in the risk of breast cancer. According to these concepts, a case–control study was carried out utilizing the data collected at the University of Messina, Service of Senology from January 1998 to October 2003 in order to evaluate the role of first and second grade familiarity in the risk of breast cancer. Among the 6609 women enrolled in a breast surveillance program, 84 cases with breast cancer and 335 controls were selected. The characteristics of the cases (a) and controls (b) were: median age: 58.0 (a), 59.6 (b); early menarcal age: 41% (a), 44% (b); late menopause 56% (a), 53% (b); late first birth: 34.9% (a), 42.9 (b); oral contraceptives: 4.5% (a), 6% (b); HRT: 4.8% (a), 0% (b). With reference to the familiar variable, the odds ratio was 1.19 for grade I and 0.69 for grade II. The results of the study suggest that the risk of breast cancer seems to be related to the familiarity for breast cancer in relatives of first grade. Moreover, in our study, there is evidence that this risk increases with the age until 69 years (OR 2.17) and then it decreases after 70 years (OR 0.51).

A30 COGNITIVE IMPAIRMENT IN BREAST CANCER PATIENTS SUBMITTED TO ADJUVANT CHEMOTHERAPY

M.R. Barulli[1], V. Lorusso[1], C. Stangalino[2], L. Mariani[2], A. Caraceni[2], V. Lepore[3], E. Paternello[1], G. Gallus[2], M. De Lena[1]
[1]Oncology Institute, Bari; [2]National Cancer Institute, Milan; [3]Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy

Background: There is increasing evidence that adjuvant chemotherapy may induce an impairment of cognitive function in long-term survivors. However, some studies support the hypothesis that cognitive deficits may become evident very early, even during treatment, whereas other studies suggest that cognitive problems may arise many years after treatment.
Methods: In this longitudinal cohort study, we examined 124 patients (53 treated plus 71 controls) affected by early breast cancer. The 53 treated patients received chemotherapy with CMF (n = 24), ADM (n = 4), CMF + ADM (n = 25) plus (n = 37)

or minus ($n = 16$) tamoxifen. The 71 patients in the control group were affected by the same disease, but they did not need any treatment. The only prerequisites for entering the study were age >60 years and ≥5 years from the last surgical intervention. A second examination, after 1 year, is planned for all patients in order to monitor cognitive function in time. All patients were assessed using the following neuropsychological assessment: two cognitive deterioration-screening tests (MODA and MMSE); 12 analytic tests (Prose Memory test, Word List Learning test, Digit Cancellation test, Trail Making test, Verbal span, Raven Coloured Progressive Matrices, Elithorn's Perceptual Maze test, Token test, Verbal Phonemic Fluency, Verbal Semantic Fluency, Street's Completion test, Figure Copying test).

Results: The two groups did not show any difference with regard to MMSE (treated group 29.6 ± 0.9; control group 29.7 ± 0.8) and MODA (treated group 94.4 ± 3.3; control group 95.2 ± 2.6) scores, respectively. Conversely, the performance score of the treated group was significantly worse with regard to Prose Memory test (Wilcoxon Test, $P = 0.03$) and Verbal Phonemic Fluency scores (Wilcoxon Test, $P = 0.01$).

Conclusions: These results, although preliminary, show the presence of a statistically significant difference on episodic memory and phonemic lexical access ability between the groups suggesting an impairment of cognitive function for patients treated with adjuvant chemotherapy. However, longer follow-up and larger series are needed to draw definitive conclusions. Nevertheless, we agree with those authors claiming that all patients over 55 years undergoing adjuvant cancer treatment should be submitted to a neuropsychological assessment before therapy.

This study was supported by a grant from the Health Ministry, PRF Conv. N.ICS 160/RA00.72

A31 BIOLOGICAL CHARACTERIZATION OF SMALL (<1 CM) BREAST CANCER TUMORS AND ITS POTENTIAL PROGNOSTIC VALUE

Alessia Ferrari, Antonio Frassoldati, Michela Maur, Massimiliano Nicolini, Roberto Sabbatini, Claudia Mucciarini, Pier Franco Conte
Division of Medical Oncology, University of Modena and Reggio Emilia, Modena, Italy

Background: The purpose of this study was to evaluate the prognostic value of biological parameters in small breast tumors (< 1 cm), usually considered as 'good prognosis'.

Patients and methods: We retrospectively evaluated 28 women with breast cancer tumors ≤ 1 cm in size. Women were stratified into two groups in respect to relapse, age, menopausal status, and classical biological parameters (ER, PgR, MibI). The two groups were compared for the expression of p53, HER2 and cyclin E. The expression of these parameters has been correlated with outcome.

Results: Mean age was 55 years (range 35–73); 93.1% were menopausal. Mean size of tumors was 8 mm (range 1–10 mm); histologic subtype was infiltrating ductal in 66.7%, infiltrating lobular in 20%, and other varieties in 13.3%. In total, 65.2% and 34.8% of tumors were histologic grade I and II, respectively. Tumors were hormone-sensitive in 67.9% of the cases. Mib-1 >20% was observed in 10.7% of the tumors. Tumors positive for p53 were 37.5%; for cyclin E (>2%) 17.9% and for erbB-2 (3+) 10.7%. An inverse correlation between ER, Mib-1, erbB-2 and tumor size was observed. A relapse occurred in 26.7% of the women, after a mean interval of 38.8 months (range 17–64) (ipsilateral 25%, contralateral 12.5%, local and distant 50%, distant only 12.5%). We observed a significant correlation between erbB-2 overexpression and relapse ($P = 0.019$), while a similar relationship was lacking for cyclin E ($P = 0.325$) and for p53 ($P = 0.061$). Patients with overexpression of erbB-2 also had a significantly poorer disease free survival ($P = 0.0001$).

Conclusions: Small breast cancers, normally considered as good prognosis, comprise tumors with substantial risk of relapse. The classical biological parameters have little chance to separate groups with different prognosis. In our experience, only erbB-2 expression was associated with a worse outcome, and, even if not included in the classical panel of parameters, it should be considered to define the risk and need for adjuvant treatment in this subset of patients.

A32 TAMOXIFEN (T) AND EXEMESTANE (E) IN EARLY BREAST CANCER PATIENTS: ENDOMETRIAL EFFECTS. A RANDOMIZED PHASE III TRIAL

Ornella Garrone, Bruno Favilla, Marcella Occelli, Ernesto Principe, Silvia Giubergia, Marco Merlano
Medical Oncology, Gynecology S. Croce General Hospital, Cuneo, Italy

Background: Tamoxifen (T) represents the treatment of choice in hormonal receptor positive early breast cancer patients (EBCP). It is known that patients under T are considered at higher risk of endometrial carcinoma. During the last few years, several trials have been conducted to evaluate endometrial changes under T. Many of them revealed an increase in endometrial thickness (ET) in most patients detected by transvaginal ultrasound (TVUS) or hysterosonography. These abnormalities are due to stromal hypertrophy and cystic proliferations. Although such changes are correlated with a minimum increase in risk of uterine cancer, the fear of it induces some women to discontinue the treatment. The availability of aromatase inhibitors (AI), and their lack of uterine toxicity, make them interesting in long-term treatment such as in EBCP. However, a direct comparison between T and E induced uterine effects is still lacking. In order to compare the endometrial changes in EBCP receiving either T or E, we started a phase III trial.

Patients and methods: Postmenopausal hormonal receptor positive patients were randomly assigned to receive T or E. A baseline TVUS was carried out and repeated after 6 and 12 months. The primary end point (endometrial thickness) is evaluated with Student's *t*-test.

Results: To date, 50 of 114 planned patients have been enrolled. Patients' characteristics are well balanced in each arm. Preliminary results at the end of the evaluation (12 months) of the first 32 patients (16 pts in T arm and 16 in E arm) are summarized in the

	ET (median); baseline	ET (median); after 12 months	*P* value	$P = 0.07$
Tamoxifen	2.89 mm	6.1 mm	0.0003	
Exemestane	3 mm	3.03 mm	n.s	

A33 NEO-ADJUVANT CHEMOTHERAPY IN BREAST CANCER. A REVIEW OF DAILY CLINICAL PRACTICE

Cristiano Oliva, Paola Bergnolo, Antonella Boglione, Simona Chiadò Cutin, Orietta Dal Canton, Paolo Pochettino, Ferdinando Garetto, Annalisa Pigoni, Emanuela Biscardi, Alessandro Comandone
Medical Oncology Department, Gradenigo Hospital, Turin, Italy

Neo-adjuvant chemotherapy (CT) is a common approach in locally advanced breast cancer (LABC). Anthracycline-based is the usual schedule with a 70% response rate and 10% Complete Responses.

In our clinical practice, since 1998, we have used the combination of epirubicin and docetaxel following the classic schedule of 75 mg/m^2 for each drug q 3 weeks. Three courses were planned for all patients before surgical intervention. We reported the results recorded in our experience. In total, 15 women aged 28–68 (median age 44) years were treated following the above mentioned protocol. Clinical stage was T2 for four patients (pts), T3 for 6 pts and T4 for 5 pts. Clinical N + was detected in 10 pts (66.7%). Three pts had an inflammatory tumour. We administered 55 courses of chemotherapy in neo-adjuvant setting (range 3–6, median three courses). Main toxic effects were: nausea and vomiting: G2 for 18 episodes, G3 in five episodes; G2 mucositis in 12 episodes; G3 neutropenia was described in six cases and G4 febrile neutropenia in only one patient. Only in this patient did we decide to reduce drugs doses by 25%.

We reached two Complete Responses, eight Partial Responses and five Stable Disease for an overall response rate of 66.7%. Surgery was possible for all 15 patients: 12 pts had a radical Madden's mastectomy and 3 pts underwent conservative surgery. Histology was ductal carcinoma in nine women and lobular carcinoma in four; 2 pts were classified as pT0, 3 pT1, 4 pT2, 4 pT3, 2 pT4. In two cases, we had a pathological Complete Response. Pathological nodal involvement was: pN0 5 pts, pN1 4 pts, pN2 6 pts. Tumours were G3 in 8 pts and G2 in 5 pts. In total, 13 patients had an additional three or six courses of adjuvant chemotherapy. At this moment, eight patients are disease free. Median Disease Free Survival was 40 months; 5 pts died from evolution of breast carcinoma; Median Overall Survival has not yet been reached; the 59th percentile was 36 months.

Conclusions: Epirubicin + docetaxel can be considered a very active, safe and easy to administer cycle in neo-adjuvant CT for locally advanced breast cancer (LABC). We can confirm that this combination can be routinely used in breast carcinoma even in small institutions as a daily clinical practice.

A34 LOCAL RECURRENCE AFTER NEO-ADJUVANT CHEMOTHERAPY AND BREAST CONSERVING SURGERY

Antonio Frassoldati, Michela Maur, Federico Piacentini, Roberto Sabbatini, Massimiliano Nicolini, Guido Ficarra, PierFranco Conte
Oncology and Haematology Department of Modena, Study University of Modena and Reggio Emilia, Modena, Italy

Primary systemic therapy (PST) may avoid mastectomy in the majority of operable breast cancer patients. We studied the pattern of locoregional relapse after PST and surgery.

In total, 47 pts were treated (1991–2004) with PST followed by surgery (27 anthracycline; 20 anthra-taxane). At diagnosis, median tumor size was 4.2 cm (range 1.5–12 cm), clinical pathologic lymph node involvement was present in 37% of pts (18); tumors were ER/PgR positive in 75/52% of pts, respectively; 31% of tumors were high grade. Median number of cycles was four (range 3–6). After PST: objective response was observed in 58% of pts [2 clinically complete response (cCR)]. Breast conserving surgery (BCS) was carried out in 10/40 pts so far operated (25%). Median tumor size after PST was 2.9 cm (0–7 cm). After surgery we observed: negative margin status in 31/36 pts, positive in 5/36 pts; one pathologically complete response (pCR), pathologic node involvement in 54% of pts. Thirteen pts underwent postoperative radiation (10 after quadrantectomy; three post-mastectomy; 13 pts 50 Gy; 6 pts, 60 Gy). The overall local recurrence rate is 14% (7/48, see Table 1)

T-pre (cm)	OR	Margins	Surgery	Grading	Ki-67/Mib-1	RT/boost
4.0	PR	Negative	Mastectomy	2	High	No
2.5	NR	Positive	Mastectomy	3	Low	No
3.0	NR	Positive	Mastectomy	2	High	No
8.5	PR	Negative	Mastectomy	2	High	No
4.0	PR	Negative	Quadrantectomy	2	High	Yes/yes
4.0	NR	Negative	Mastectomy	2	High	Yes/yes
4.5	PR	Negative	Quadrantectomy	3	Low	Yes/yes

To date, 4 pts died because of metastatic disease, 44 pts are alive (nine with disease).

Radiotherapy after BCS results in low rates of local recurrences in patients treated after PST. Probably pathological tumor size, high proliferative rate and high grade at diagnosis are the most important factors in predicting local recurrence although our study is underpowered to demonstrate these issues.

A35 BREAST CANCER (BC) IN THE ADJUVANT SETTING: THE FERRARA EXPERIENCE REVISITED BY THE ONCOLOGICAL GUIDELINES

Yasmina Modena, Monica Indelli, Benedetta Urbini, Serena Cataldo, Stefania Guarino, Giorgio Lelli
Clinica Oncology Unit, Azienda Ospedaliera Universitaria, Ferrara, Italy

In this study, we carried out a retrospective analysis of 258 breast cancer patients that underwent adjuvant treatment at our institution from January 2000 to December 2002. Median age + SD was 62 + 12 years; 39 (15%) were pre-menopausal patients, 189 (73%) were physiological postmenopausal patients and 30 (12%) were surgical or chemical postmenopausal patients. In total, 178 (69%) were T1 and 70 (27%) were T2, while only 10 (4%) were T3–T4 BC; lymph node involvement was found in 106 (41%) patients (61/106: 1 to 3 positive lymph nodes, 45/106: >3 positive lymph nodes); 171 (66%) were ER+/PR+, 38 (15%) were ER+/PR−, 2 (1%) were ER−/PR+and 39 (15%) were ER−/PR−; 53 (20%) were G1, 126 (49%) were G2 and 79 (31%) were G3 BC.

We divided the patients in two groups depending on age <65 (149, 58%) or >65 (109, 42%) years and evaluated whether there were differences in the distribution of demographic characteristics, biopathological and clinical variables such as tumor-related bio-pathological factors, number of comorbidities, adherence to standard treatments, status in life and relapse. We also considered if one of these variables could affect adherence to guidelines in the two groups of patients. We did not find any significant difference in the distribution of these variables except for the number of comorbidities that were significantly higher in the group aged >65 years ($P = 0.004$). As number of comorbidities represents a major factor influencing physicians treatment choice, we analyzed if it affected adherence to treatment. Adherence to guidelines decreased with increase in number of comorbidities even if the statistical significance is borderline ($P = 0.076$).

We can conclude that majority of patients accepted the suggested therapies. Only nine patients did not receive any treatment, a few because of the physician's decision and the majority because of fear of side-effects.

A36 EFFECT OF ADJUVANT THERAPY ON COGNITIVE FUNCTIONS IN ELDERLY BREAST CANCER PATIENTS

Antonio Gambardella, Luigi Chianese, Paolo Tirelli, Antonia Silvestri, Emma Comitale, Sossio Serra, Laura Pesce, Michele Varricchio
Department of Gerontology, Geriatrics and Metabolic Disease, Second University of Naples, Naples, Italy

Introduction: There is increasing evidence that potentially curative systemic adjuvant chemotherapy in patients with early stage breast cancer may result in cognitive impairment. Such studies suggest an adverse effect of adjuvant chemotherapy in elderly patients. However, information regarding such impact on cognitive functioning over longitudinal studies is lacking. The aim of this longitudinal study was to examine the neuropsychological functions in elderly women with breast cancer, who had been treated with CMF adjuvant chemotherapy or not, followed by tamoxifen over a 5-year period.

Patients and methods: Thirty-two breast carcinoma old patents (71 ± 4.6 years) who had been treated with CMF (six courses) followed by 5 years of tamoxifen 20 mg daily. We have evaluated elderly cancer patients with Digit Span (forward and backward), Digit Symbol, and Rey 15-Item Memory Test for the evaluation of concentration, attention and short- and long-term verbal memory, respectively. The control group consisted of 34 age-matched patients with stage I breast carcinoma who received the same surgical, radiation and hormonal therapy but no CMF adjuvant chemotherapy.

Results: After 5 years of the entire follow-up period, 23 of 32 CMF-patients were evaluable and they had no significant decline in concentration/attention (25% versus 19%; P = n.s.), and memory function (24% versus 16%; P = n.s.) compared with control patients.

Conclusion: Our final results showed that CMF therapy produced significant cognitive deficits in elderly cancer survivors in the first year after the beginning of chemotherapy. However, in our study, the 5 year trend shows no significant decrease in concentration/attention, memory and cognitive function in the CMF-group compared with the control group and a partial recovery of cognition is achieved. Previous studies had demonstrated that tamoxifen could have neuroprotective effects in elderly patients. So the partial recovery of cognitive functions could be due to using tamoxifen or ending of CMF neurotoxicity. Further studies are required to clarify this finding and for the evaluation of chemo- and hormonal-therapy effects on cognitive functions in younger patients.

A37 A DOSE-FINDING AND TOXICITY STUDY OF TARCEVA GIVEN SEQUENTIALLY TO CAPECITABINE AND VINORELBINE AS FIRST-SECOND-LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER

M. Clavarezza[1], T. Catzeddu[1], C. Bighin[1], E. Maggi[1], S. Pastorino[1], G. Lunardi[1], A. Lambiase[2], L. Del Mastro[1], M. Venturini[1]
[1]Istituto Nazionale per la Ricerca sul Cancro, Genoa; [2]Roche S.p.A., Monza, Italy

Background: The combination of capecitabine (C) and vinorelbine (V) is an active and safe chemotherapy (CT) regimen in the treatment of metastatic breast cancer (MBC) patients (pts). Tarceva (T), an orally active inhibitor of EGFR tyrosine kinases, is well tolerated and has antitumor activity in several types of cancer over-expressing EGFR. The purpose of this study was to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of T given sequentially to fixed doses of CV as first-second line CT in MBC.

Patients and methods: Twelve pts received V 25 mg/mq ev (day 1 and 8) and C 1000 mg/mq orally twice daily (days 1–14), every 3 weeks. Chemotherapy was stopped after six cycles in the case of stable disease (SD) and after eight cycles in the case of complete response or partial response (PR). Subsequently, pts were treated with Tarceva at three dose levels (50–100–150 mg/day) continuously. Before escalating to the next dose-level, 3 pts at each dose level were to be recruited and at least 3 pts should have received no less than 1 month of T monotherapy.

Results: Median age: 56 (40–69). PS: 0–1: 100%. A total of 10/12 pts (83%) had visceral metastases and the same number (83%) had two or more metastatic sites. All pts (100%) had received prior treatment with anthracyclines and eight of them (67%) had also received prior taxanes. Nine patients were evaluable after CV chemotherapy: four PR, three SD and two progressive disease were observed. Three pts started T monotherapy at the first dose level (50 mg daily) with no DLT. The most frequent adverse events related to T were: grade 1 cutaneous rash in 2/3 pts, grade 2 diarrhoea in 1/3 pts. One patient has just started T at the second dose level (100 mg daily) and she is not evaluable. The study is ongoing.

A38 INCIDENCE OF BRAIN METASTATIZATION AS FIRST DISEASE RELAPSE IN METASTATIC BREAST CANCER PATIENTS UNDERGOING FIRST-LINE TREATMENT WITH EPIRUBICIN CONTAINING REGIMENS

Raffaella Bitossi, Paola Sperone, Alfredo Berruti, Alberto Bottini, Maria Giuseppa Sarobba, Saverio Danese, Vito Lorusso, Michela Donadio, Maria Grazia Baù, Antonio Durando, Andrea De Matteis, Federico Castiglione, Luigi Dogliotti
Epirubicin-Lonidamine Group, Orbassano, Turin, Italy

Between 1991 and 2001, three multicenter phase II and III studies were conducted by an Italian Cooperative Group aiming to test the activity of various epirubicin containing regimens as first-line treatment in patients with metastatic breast cancer. A total of 606 consecutive patients were consecutively recruited and followed until disease progression. Brain metastases at baseline was an exclusion criterion in all studies. The aims of the present evaluation were: (i) to determine the frequency of brain metastases as first disease progression, (ii) to identify baseline clinical factors predictive for brain occurrence and (iii) to assess the outcome of brain metastatic patients. To date, 490 patients showed disease progression after first-line chemotherapy, 45 of them recurred in brain (7.4% of the entire population). At baseline, characteristics of patients developing brain recurrence were as follows: median age 58 years (range 34–71); median ECOG performance status (PS) 0 (range 0–2). Thirty-eight patients (84.4%) were postmenopausal; 21 patients (46.7%) were submitted to adjuvant chemotherapy, 14 (31.1%) to adjuvant endocrine therapy and three (6.7%) to first-line endocrine therapy. Baseline metastatic patterns were: lung in 28 patients (62.2%), bone in 20 (44.4%), liver in 17 (37.8%), skin/lymph nodes in 16 (35.5%). Fifteen patients (33.3%) had one metastatic site and 30 (66.7%) two or more. The median number of cycles administered as first-line therapy was six (range 1–8). After first-line treatment, seven (15.5%) patients had obtained complete clinical response, 21 (46.7%) partial response, 10 (22.2%) stable disease and seven (15.5%) patients progressed. Disease free interval (DFI) from diagnosis of breast cancer to first disease relapse was 30 months (range 0–204). Brain metastatization was observed at a median of 7.1 months after the initiation of first-line chemotherapy. Median overall survival from the time of brain progression was 3.6 months. Among the clinical prognostic factors evaluated (age, metastatic pattern, number of sites involved, PS, DFI, adjuvant treatment, response to first-line chemotherapy) none were found to be predictors of brain metastatization.

A39 PHASE II TRIAL WITH RFS2000 IN PATIENTS (PTS) WITH ADVANCED AND/OR METASTATIC BREAST CANCER (MBC)

R. Sorio[1], P. Chollet[2], F. Caponigro[3], G. Carteni[4], S. Scalone[1], D. Crivellari[1], M.D. Magri[1], S.J. Adank[5], A. Veronesi[1]
[1]Medical Oncology, CRO-IRCCS, Aviano, Italy; [2]Centre J Perrin, Clermont Ferrand, France; [3]Ist. Pascale, IRCCS, Naples, Italy; [4]AO Cardarelli, Naples, Italy; [5]NDDO Oncology, Amsterdam, The Netherlands

RFS2000 (Rubitecan or 9-NC) is a new oral topoisomerase I inhibitor. We carried out a phase II study in pts with metastatic breast cancer (MBC) to determine response rate, toxicity and pharmacokinetic-pharmacodynamic (PK-PD) profile of the drug in this setting. Inclusion criteria: locally advanced and/or MBC, at least one measurable lesion (RECIST criteria), PS 0–2, age >18, ANC >1500, Ptl >100 000, creatinine <2 mg/dl, bil $<1.5\times$ upper normal limit (UNL), ASAT/ALAT $<3\times$ UNL (<5 if hepatic metastases), one prior chemotherapy for advanced disease. The starting dose was 1.5 mg/m^2/day $\times$ 5 per week, with dose escalation/reduction (up to 2 mg, down to 0.75 mg). From Jun 2001, 23 pts entered the study: median age 59 years, PS 0–1 in 14–7 pts, 70 courses were administered. Most relevant toxic effects were (total no. pts 20).

Toxicity G 1–2		No. pts
Gastrointestinal	Constipation–diarrhoea	6–8
	Nausea–vomiting	13–9
	Stomatitis–pharingitis–gastritis	7
Infections	Cystitis–urin. tract (G3)	1 (1)
Renal–urinary	Dysuria	3
	Haematuria–proteinuria–leukocyturia	7–9–8
Other	Anorexia (G3)	2 (1)
	Arthralgia	4
	Headache	7
	Alopecia	3

G3–4 haematological toxicity: one episode of anaemia G3 and three of neutropenia G3 (at dose level 0) were observed; no thrombocytopenia; G3 hepatotoxicity: one episode of ALT (dose level + 2) and three of gamma-GT (two at dose level 0, one at + 1). Serious adverse events (SAEs) were reported in four cases; two of them were probably study drug related. Out of 17 evaluable pts, 3 PR and 6 SD were observed. PK and PD data are not yet available. In conclusion (preliminary data): Rubitecan has an acceptable toxicity, good compliance and promising activity (to be confirmed) in pre-treated MBC pts.

A40 LONG-TERM OUTCOME OF METASTATIC BREAST CANCER PATIENTS AFTER TANDEM CYCLES OF HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

Giuseppa Penna[1], Massimo Martino[1], Maria Carmela Zavettieri[2], Rocco Giannicola[2], Mario Nardi[2], Riccardo Mazzitelli[3], Francesco Tropea[2], Bonaventura Lazzaro[4], Stefano Molica[4], Giovanni Cicero[5], Salvatore Palazzo[6], Giuseppe Console[1], Fortunato Morabito[1], Pasquale Iacopino[1]
[1]Centro Trapianti Midollo Osseo, Reggio Calabria; [2]U.O. Oncologia Medica, Reggio Calabria; [3]Chirurgia Generale, Azienda Ospedaliera 'BMM', Reggio Calabria; [4]Oncologia Medica, Azienda Ospedaliera 'Pugliese-Ciaccio', Catanzaro; [5]Oncologia Medica, Azienda Ospedaliera 'Mariano Santo', Cosenza, Italy; [6]Oncologia Medica Ospedale Civico Castrovillari (CS), Italy

The efficacy of high-dose chemotherapy (HDC) followed by autologous peripheral blood stem cell transplantation (APBSCT) for metastatic breast cancer (MBC) patients, constitutes an area of intense controversy among the medical oncology community. In total, 74 patients with MBC, enrolled in three HDC protocols, were stratified according to three risk categories based on the disease-free time interval from primary diagnosis to metastasis, the hormone-receptor status of the tumor and the dominant site of metastasis (Possinger K et al. Cancer Treat Rev 1987 Dec; 14: 263–74). After stratification, 61.3%, 24% and 14.7% of the patients fit into the low, intermediate and high groups, respectively. All patients received at least one APBSCT with HDC after standard chemotherapy, 53.8% received a double and 6.4% a triple course of HDC, so that altogether 125 APBSCT were performed. The objectives of the study were to determine whether the risk categories, which are important for predicting outcome after standard chemotherapy, are also valid after HDC and to evaluate whether the response to HDC changed the relationship between the prognostic score and patient outcome. After the HDC program, the conversion rate to more favourable response was 27.4%. At a median follow-up of 28 months (range 0.3–99), progression free survival (PFS) and overall survival (OS) were 19 + 4% and 31 + 6%, respectively. Patients with low and intermediate risk score had a statistically longer median survival compared with those with a high risk score, while there was no difference between low and intermediate risk groups. The risk groups correlated significantly with the median of PFS (7.1, 12.3, 31.6 months for high, intermediate and low risk, respectively). Patients with CR did significantly better than patients with PR or SD disease in univariate analysis. In multivariate analysis, the attainment of a CR was the predominant predictor for both prolonged PFS and OS. Possinger prognostic risk categories do predict both OS and PFS, but it seems to be less relevant than response to HDC program.

A41 CISPLATIN AND CAPECITABINE IN HEAVILY PRETREATED ADVANCED BREAST CANCER DISEASE: A PHASE II STUDY

Michela Donadio[1], Alessandra Beano[1], Mara Ardine[1], Marinella Mistrangelo[1], Simone Bonardi[2], Federico Castiglione[3], Maria Antonia Polimeni[1], Laura Forti[4], Alberto Bottini[2], Oscar Bertetto[1]
[1]Centro Oncologico ed Ematologico Subalpino, Azienda Ospedaliera San Giovanni Battista, Turin; [2]Breast Unit Azienda Ospedaliera Ospitali Riuniti, Cremona; [3]Oncologia Medica, Ospedale San Lazzaro, Alba; [4]Oncologia Medica, Ospedale Maggiore della Carità, Novara, Italy

There is a general consensus that the efficacy of second and subsequent lines of chemotherapy in metastatic breast cancer is uniformly poor. This issue notwithstanding, women with fairly good performance status can be expected to live for a considerable time and should be offered the chance to benefit from multiple chemotherapy lines. Single agent cisplatin has shown some activity against breast cancer. Cisplatin activity could be increased by the addition of capecitabine.

Entered into the study were 35 consecutive patients. Median age was 52 years, 96% had ECOG PS 0–1. All patients had been previously treated with at least two chemotherapy lines containing either anthracyclines and/or taxanes. Most patients (48%) had visceral disease with prominent hepatic involvement and 54% had more than one metastatic site.

Treatment consisted of cisplatin 20 mg/m^2 on days 1, 8, 15, 22, 29, 36 and capecitabine 2000 mg/m^2/day on days 1–14 and 22–36 every 50 days.

To date, 28 of 35 were assessable for response. Two patients (7%) achieved a complete response and 10 patients (36%) achieved a partial response, yielding a response rate of 43%. Five (18%) patients had stable disease and 11 (39%) progressive disease.

The schedule was well tolerated. Grade 3–4 neutropenia was observed in 20% of patients. Febrile neutropenia was never observed. Gastrointestinal toxicity (45%) and asthenia (22.8%) were the most common non-hematological toxic effects. They were moderate in the great majority of patients. Leukopenia and prolonged epigastralgia were the dose-limiting toxic effects. No patients experienced grade 3–4 alopecia.

To conclude, cisplatin + capecitabine is a manageable and active schedule in heavily pretreated advanced breast cancer patients.

A42 GEMCITABINE, DOXORUBICIN AND PACLITAXEL (GAT) AS FIRST-LINE CHEMOTHERAPY FOR METASTATIC BREAST CANCER: AN EXAMPLE OF TRANSLATIONAL RESEARCH

Alessandro Passardi[1], Anna Tesei[1], Lorenzo Gianni[2], Toni Ibrahim[1], Muller Fabbri[1], Monia Dall'Agata[3], Federica Zumaglini[4], Roberta Maltoni[1], Dino Amadori[1]
[1]Department of Medical Oncology, Forlì; [2]Department of Medical Oncology, Rimini; [3]Istituto Oncologico Romagnolo, Forlì; [4]Department of Medical Oncology, Ravenna Italy;

A phase III clinical trial in patients with metastatic breast cancer (MBC) showed a higher overall response rate and overall survival following treatment with anthracyclines and taxanes than with the fluorouracil–doxorubicin–cyclophosphamide combination. To improve therapeutic results, taking advantage of our experience in the field of pharmacological translational research, we investigated the effect of gemcitabine, doxorubicin and paclitaxel (GAT) and defined the optimal schedule of the three-drug regimen at a preclinical level on *in vitro* breast cancer cell lines. A synergic interaction was observed with the sequence doxorubicin–paclitaxel–gemcitabine [Zoli W et al. Int J Cancer 1999; 80 (3): 413–416]. On the basis of these results, we designed a phase I dose-finding clinical trial in which patients with MBC were treated in cohorts of three individuals with doxorubicin on day 1, paclitaxel on day 2 and gemcitabine on day 6. The maximum tolerated dose was reached at the second level and recommended doses for a phase II trial were doxorubicin 50 mg/m^2, paclitaxel 160 mg/m^2 and gemcitabine 800 mg/m^2 [Ibrahim T et al. J Chemother 2003; 15(5): 488–494]. A phase II multicenter trial is ongoing to verify the activity of the experimentally derived GAT regimen as first-line chemotherapy in patients with stage IIIB–IV breast cancer. According to a two-step Simon design, the treatment scheme will not be considered active if fewer than eight responses are achieved in the first step, comprising 24 patients, and will be considered active and worthy of further study if responses are observed in 25 out of the total series of 63 patients. From January 2002 to March 2004, 22 assessable patients were recruited. The most important toxicity was hematological, with grade III–IV neutropenia observed in 85–90% of patients, requiring the frequent use of G-CSF. Non-hematological toxicity was rare and mild. One patient died due to septic shock during the first treatment cycle. Activity and safety data on the 24 patients included in the first step will be presented.

A43 5-FLUOROURACIL/FOLINIC ACID (LFA) AND VINORELBINE (VNR) IN ADVANCED/METASTATIC BREAST CARCINOMA (MBC): A MULTICENTER EXPERIENCE

Michele Caruso[1], Vittorio Gebbia[2], Francesco Ferraù[3], Paolo Tralongo[4], Nicolò Borsellino[5], Roberto Bordonaro[6], Maurizio Chiarenza[1], Rosanna Aiello[1], Roberto Valenza[7], Mariolina Tirrito[8], Francesco Verderame[9], Biagio Agostara[10]
[1]Centro Oncologico Catanese; [2]Università di Palermo; [3]Ospedale di Taormina; [4]Ospedale Avola; [5]Ospedale Fatebenefratelli di Palermo; [6]Ospedale S. Luigi di Catania; [7]Ospedale di Gela; [8]Casa di Cura Torina; [9]Ospedale Civile di Sciacca; [10]Ospedale Oncologico di Palermo, Italy

Despite impressive tumor shrinking after first-line chemotherapy (CT) with taxanes and/or anthracyclines, all patients with hormone-refractory MBC eventually show disease progression which may require a second- and even a third-line CT. In daily practice, patients with progressive disease (PD) are offered a second-line treatment which should include palliative regimens with a good therapeutic index. VNR and lFA/5FU (FLN) fulfil these requirements. All cases of MBC treated with FLN as second-line treatment in clinical practice were analyzed for efficacy and toxicity. For a total of 301 screened pts, complete records are currently available in 186 cases. Median age was 62 years and median ECOG PS was 1. In total, 178 pts had received surgery, 128 adjuvant radiotherapy, 119 adjuvant hormonotherapy, and 134 adjuvant CT and all first-line CT for MBC (anthracycline). Patients were treated depending on single-center guidelines or patients needs with VNR 25 mg/m^2 given as i.v. bolus on day 1 + 8; 5FU was given as i.v. bolus at the dose of 375 mg/m^2 after lFA 20 mg/m^2 on day 1–3, or 400 mg/m^2 i.v. bolus after lFA 100 mg/m^2 in 2-h infusion followed by 5FU 600 mg/m^2 continuous intravenous infusion according to De Gramont schedule. Overall response rate (ORR) was 41% with 5% pts showing a CR; SD was recorded in 28% of patients. Time to progression (TTP) was 6.4 months (range 2–24). Grade 3–4 hematological toxicity was recorded in 18% of cases. This survey carried out on a large number of patients confirmed that the FLN regimen is well tolerated by most patients and quite active in terms of response rate and symptom palliation as reported by others.

A44 WEEKLY EPIRUBICIN AND DOCETAXEL AS FIRST-LINE CHEMOTHERAPY IN METASTATIC BREAST CANCER

A. D'Ottavio[1], A. Vaccaro[1], F. Belli[1], C. Nunziata[2], L. Meliffi[2], L. Moscetti[3], M. Barduagni[2], I. Sperduti[1], T. Gamucci[1,4]
[1]Department of Medical Oncology ASL Frosinone; [2]Department of Medical Oncology, ASL RomaH; [3]Ospedale Bel Colle Viterbo; [4]Fondazione Ricerca Oncologica FORO Onlus, Italy

Background and objectives: Docetaxel and epirubicin have been shown to be efficacious in first-line chemotherapies for metastatic breast cancer (MBC). At the standard dose of 75 mg/mq for both, this combination carries a significant risk of toxicity consisting of neutropenia, asthenia, mucositis and fluid retention. In recent years, a dose-dense weekly schedule of various antineoplastic agents has been employed to reduce dose-limiting toxicity and to improve therapeutic index. The main objective of this multicentric phase II study is to evaluate the toxicity profile and the activity of a weekly combination of EPI and TXT as first line in MBC.

Treatment plan: patients (pts) with MBC were treated with a weekly regimen of epirubicin and docetaxel, both administered at 25 mg/m^2 × 6 followed by a 2-week rest; additional cycles were planned with 3 week therapy every 5.

Patient data: To date, 33 pts have been enrolled; median age is 58 (range 36–79); WHO PS 0/1 18 pts, WHO PS 2 1 pt; pre/postmenopausal status 9/24 pts; ER positive/negative 17/10 pts. Twenty-four patients had received previous adjuvant chemotherapy. All pts had measurable disease; dominant metastatic site is: visceral in 22 pts; soft tissues in 6 pts, bone in 5 pts.

Results: In total, 29 pts and 96 cycles are evaluable for toxicity and response. Hematological toxicity was very mild with neutropenia G3–G4 in only 1 pt (two cycles); anemia and thrombocytopenia were never observed. Non-hematological toxicity was also very mild with vomiting G3 in 1 pt (one cycle), skin toxicity G3 in 1 pt (one cycle), severe asthenia in 2 pts (two cycles), alopecia G2 in 13 pts, moderate fluid retention syndrome in 2 pts (four cycles), mucositis G2 in 3 pts (four cycles). Reduction < 20% of left ventricular ejection fraction was observed in 1 pt, but within normality range. Treatment was delayed only in one patient due to neutropenia and growth factors were never used.

Response: CR 2 pts (6.9%), PR 16 pts (55.2%) determining an ORR of 62% (95% CI 44.7–79.4); SD 11 pts (37.9%); PD 1 pt.

Conclusion: Preliminary assessment of this weekly combination of epirubicin and docetaxel shows a significant tolerability profile and a good ORR. Accrual of patients is still ongoing and updated results will be notified.

A45 TRASTUZUMAB IN COMBINATION WITH GEMCITABINE AND VINORELBINE (T-GEM-VIN) AS SECOND- OR THIRD-LINE THERAPY FOR HER-2/NEU OVEREXPRESSING METASTATIC BREAST CANCER (MBC)

Alessandro Morabito, Guido Carillio, Paola Bonginelli, Massimo Fanelli, Raffaele Longo, Scolastica Amici, Roberta Sarmiento, Domenico Gattuso, Francesco Torino, Giampietro Gasparini
San Filippo Neri Hospital, Division of Medical Oncology, Rome, Italy

The addition of trastuzumab (T) to taxane-based first-line chemotherapy is associated with a significant improvement in response rate (RR), time to progression (TTP), and overall survival (OS) in HER-2/neu overexpressing MBC. The objective of this study was to evaluate the safety and efficacy of T-gem-vin as second- or third-line therapy for HER-2 overexpressing MBC, pretreated with anthracyclines and/or taxanes + T.

Eligible patients (pts) had HER-2/neu positive disease (IHC 2 + or 3+), PS < 2, normal L-VEF. Pts were treated with weekly T (4 mg/kg on day 1, and then 2 mg/kg), in combination with gem (800 mg/m2) and vin (25 mg/m2) on days 1 and 8, every 21 days. Pts were restaged every three cycles.

Twenty-six patients have been enrolled up to now on to the study, median age 58 years (range 41–74), median ECOG PS = 0 (range 0–2), median number of metastatic sites 3 (range 1–8), prior first-line chemotherapy 90% or second line 10%, prior T treatment (35%). 23 pts are assessable for toxicity and response. Treatment was well tolerated: grade 4 neutropenia in 2 pts, grade 3 thrombocytopenia in 1 pt, grade 3 anemia in 1 pt, and grade 3 asthenia in 2 pts were observed. In total, 9 pts achieved an objective response (one complete and eight partial response; RR = 39.1%). Among the pts with HER-2/neu 3 + or T-naïve the RR was 58.3% and 73.3%, respectively. Noteworthy, four objective responses were observed in pts with brain metastasis. In total, 7 pts had stable disease (30.4%). Median TTP was 6 + months (range 2–15), median OS was 9 + months (range 5–28).

T-gem-vin is a safe and active regimen in this subgroup of pts with poor prognosis. The efficacy of such a schedule is particularly satisfactory in pts with HercepTest 3-plus and in those previously untreated with T. The recruitment is ongoing.

A46 CAPECITABINE (XEL) AND MITOMYCIN-C (MMC) AS SALVAGE THERAPY FOR PATIENTS (PTS) WITH ADVANCED BREAST CANCER (ABC) PRE-TREATED WITH ANTHRACYCLINES AND TAXANES. A PHASE II STUDY

Cristian Massacesi, Annalisa La Cesa, Alberta Pilone, Daniele Santini, Laura Zepponi, Giuseppe Tonini, Maurizio Bonsignori
Department of Oncology and Radiotherapy, Ospedali Riuniti Umberto I–Salesi–Lancisi; Polo Ospedale-Università, Ancona; Medical Oncology Unit, Università Campus Bio-Medico, Rome, Italy

Background: XEL is converted to 5-fluorouracil by thymidine phosphorylase (TP), that is at higher concentration in tumor tissue. MMC determines remarkable up-regulation of TP. The association of XEL and MMC demonstrated activity and good tolerability in advanced colorectal cancer pts. We investigated XELMMC as salvage regimen in heavily pre-treated pts with ABC.

Patients and methods: From September 2002 to January 2004, 36 pts with measurable ABC previously exposed to chemotherapy and endocrine treatment entered the study. The regimen was: MMC 6 mg/m2 day 1, XEL 2000 mg/m2/day for days 1–14, cycles every 28 days.

Results: Pts data: median age 62 years (range 42–77); ECOG PS 0–1/2–3 in 32/4 pts; ER positive/unknown in 29 pts; visceral disease in 30 (83%) pts; disease sites: liver 53%, lung/pleura 44%, nodes/chest wall/skin 44%, bone 67%; >2 metastatic sites: 15 pts. Previous chemotherapy lines: one/two/three/four or more in 2/10/13/11 pts; prior exposure to both anthracyclines and taxanes in 33 (92%) pts. Total and median number of administered cycles was 195 and 5 (range 2–11), respectively. Thirty-four pts were evaluable for response: CR 1/34, PR 9/34, SD 14/34, PD 10/34, for an overall response rate of 29%. At March 2004, 25 and 7 pts progressed and died, respectively. With a median follow-up of 8.2 months, median time to progression (TTP) was 5.5 months. Grade III/IV toxic effects were rare: neutropenia in 8% of pts (one febrile), anemia 3%, thrombocytopenia 3%, mucositis 3%, diarrhea 3%.

Conclusion: In pts with ABC pre-treated with anthracyclines and taxanes, XELMMC as salvage therapy showed good activity and excellent toxicity profile.

A47 WEEKLY DOCETAXEL (WEDO) AS FIRST-LINE THERAPY IN ELDERLY METASTATIC BREAST CANCER (MBC)

Nicola Caristi, Roberto Maisano, Marzia Mare, Giuseppe Chiofalo, Maria Picciotto, Antonio Mafodda, Erika Montalto, Maria Zavettieri, Francesco La Torre
Azienda Ospedaliera Universitaria

Docetaxel (DOC) is burdened with severe toxicity making administration difficult in the elderly. Several trials have shown that WEDO has similar activity and reduced side-effects compared with standard therapy in MBC. Our trial evaluated the activity and safety of a modified WEDO schedule as first-line chemotherapy in the elderly (≥70 years). 21 pts with evaluable MBC, median age 73, hormone-unresponsive received: dexamethasone 8 mg intravenously followed by DOC 35 mg/m2 in 100 ml NS over 30 min. Pts were treated for 6 weeks followed by 2-week rest (1st cycle) and then every 3 weeks plus 1-week rest, for a maximum of seven cycles or until PD, severe side-effects or refusal. Restaging was planned after the first cycle and then every two cycles; NCI-CTC was assessed before each WEDO administration. All pts received the 1st cycle. At the first restaging we recorded 4 PR (19%), 13 SD and 4 PD without G3/4 toxicity; mild asthenia (7 pts) and tearing (3 pts) were the most common side-effects. The second revaluation showed 1 CR (lung metastases and supraclavicular nodes), 7 PR, 5 SD and 4 PD with one episode of G3

neutropenia, mild-moderate asthenia in 10 pts, excessive tearing in five, nail changes in three and severe skin toxicity in 1 pt. One PR pt went off study for toxicity. At the third check, we confirmed the CR and recorded 6 PR, 3 SD and 2 PD. Three pts suffered from DOC-related pleural effusion, 2 pts had nail loss and two severe asthenia. Five pts reported excessive tearing and one epiphora due to permanent canalicular stenosis. Five out of 12 pts refused further therapy while the remaining seven completed treatment achieving 1 CR, 4 PR and 2 PD without severe toxicity.

Conclusion: These preliminary data confirm the activity of WEDO (ORR 38%) and the low incidence of haematological side-effects, but the DOC accumulation toxicity (pleural effusion, nail loss, asthenia) needs care.

A48 REGINA ELENA NATIONAL CANCER INSTITUTE EXPERIENCE OF FIRST-LINE WEEKLY CHEMOTHERAPY FOR ADVANCED BREAST CANCER (ABC) PATIENTS (PTS): SURVIVAL OUTCOME OF 171 PATIENTS ENROLLED IN THREE PHASE II TRIALS

C. Nisticò[1], E. Bria[1], B. Vanni[1], F. Cuppone[1], C. Campanella[1], F. Calabretta[1], C. Garufi[1], D. Giannarelli[2], E. Terzoli[1]
[1]Department of Medical Oncology [2]Biostatistic Unit, Regina Elena National Cancer Institute, Rome, Italy

Weekly administration represents the clinical application of dose-density theory. In this analysis, we report the overall results of activity and efficacy of three different weekly schedules in first-line chemotherapy for advanced breast cancer patients (ABC) patients (pts).

We gathered three databases of phase II trials in ABC pts who underwent first-line weekly chemotherapy. Our major end point was to look at overall survival (OS) and time to progression (TTP).

From 1990 to 2003, 171 patients were enrolled in three phase II trials, to evaluate activity and tolerability of weekly epirubicin (25 mg/m2/week) with either lonidamine (450 mg/day) (EL, 61 pts), vinorelbine (25 mg/m2/week) (EN, 58 pts) and paclitaxel (80 mg/m2/week) (ET, 51 pts), for 24 consecutive weeks. To avoid neutropenia and to maintain dose-intensity (DI), G-CSF was part of the treatment (days 2, 4) in 93/171 pts (54.4%). Median OS was 32 months (95% CI 26–39), and median TTP 9 months (95% CI 8–10). No significant differences were found in both TTP and OS based on DI (100% versus $<100\%$) and G-CSF supply (scheduled versus as needed). Median TTP for response status was: CR: 11 months (95% CI 9–13), PR: 10 months (95% CI 8.7–11), SD: 7 months (95% CI 4–9) and P: 2 months (95% CI 1–3). Median OS for response status was: CR: 36 months (95% CI 26–64), PR: 34 months (95% CI 26–47), SD: 28 months (95% CI 21–35) and P: 7 months (95% CI 3–11). At a multivariate analysis, ORR status was significantly predictive of OS (36 versus 23 months) and TTP (10 versus 6 months) when compared to non-responders ($P<0.001$). When the 'old' (EL) regimen was compared to the 'new' (EN + ET), no significant differences were found in TTP (9 versus 9 months) and OS (32 versus 31 months). When ET was compared to EL + EN, significant differences were found in TTP (10 versus 9 months, $P=0.011$), while not significant in OS (30.5 versus 34 months, $P=0.16$). At the multivariate analysis, TTP still remains significant ($P=0.02$) together with response status ($P=0.004$) with the Cox-regression model regardless of DI and G-CSF administration.

Conclusions: In our series of pts, one of the largest sample sizes in the literature, weekly chemotherapy seems to yield a promising efficacy in survival and TTP when compared to results obtained in phase II studies with a conventional 3-weekly schedule.

A49 WEEKLY PACLITAXEL AND GEMCITABINE PLUS G-CSF IN ADVANCED BREAST CANCER (ABC): A PHASE II STUDY—PRELIMINARY RESULTS

E. Bria[1], E. Terzoli[1], B. Vanni[1], F. Cuppone[1], D. Giannarelli[2], C. Nisticò[1]
[1]Department of Medical Oncology [2]Bio-statistic Unit, Regina Elena National Cancer Institute, Rome, Italy

Background: Gemcitabine (G) has recently been demonstrated to be active and safe in advanced breast cancer (ABC). A randomized trial demonstrated that fixed-dose-rate (FDR) G infusion (10 mg/m^2/min) was superior to standard infusion from a pharmacokinetic and clinical perspective. In addition, in a phase III trial, paclitaxel (P) plus G has been shown to be more effective than P alone after anthracycline-based chemotherapy. In our previous study, we have shown that weekly P and epirubicin plus G-CSF was highly active in ABC. We designed a phase II study to evaluate the tolerability and activity of weekly P-G plus G-CSF in anthracycline-resistant ABC pts.

Patients and methods: The phase II study was designed following Simon's optimal two-stage method. With a statistical power of 80%, and an interest response rate level of 60% and rejection level of $<40\%$, 46 pts was the optimal sample size. The first step concluded after 7/16 objective responses. If less than seven, the study would be considered closed. The second step is constituted by 23 response out of the overall 46 pts. From October 2003, 12 ABC pts, anthracycline pre-treated, underwent weekly chemotherapy with P 80 mg/m^2/week i.v. 1-h infusion, immediately followed by G 800 mg/m2/week i.v., FDR of 10 mg/m^2/min, plus G-CSF support on days 2 and 4. Treatment was planned for 24 consecutive weeks in the absence of progressive disease.

Results: The following data relate to the ongoing first step study. Patient data: median age 55 years (range 41–66), positive receptor status 7/12, Performance Status 0/1: 10/2, number of metastatic sites 1/2/>2: 2/8/2; visceral metastases 50%, bone lesions 25%. Median number of delivered courses was 12 (range 4–20); median relative dose-intensity was 98.5%. All pts were evaluable for toxicity. No WHO grade 3–4 hematological toxic effects were observed; for non-hematological toxicity, moderate asthenia was seen in 8/12 pts, and grade 3 alopecia was present in 7/12 (58.3%). To date, no patient had discontinued treatment for disease progression, while in the six evaluable out of 12 pts, four partial response, one complete response and one stable disease were seen. Mature data will be displayed at the meeting.

Conclusions: Although data are very preliminary, weekly FDR G-P plus G-CSF seems to be extremely well tolerated in ABC pts. If the subsequent results will assess activity as well for this combination, weekly G-P could be considered a promising option for ABC.

A50 A PHASE 2 STUDY OF OXALIPLATIN (O)-CAPECITABINE (C) CHEMOTHERAPY IN METASTATIC BREAST CANCER (MBC) PATIENTS PRETREATED WITH ANTHRACYCLINES AND TAXANES

MariaRosaria Valerio, Gaetana Rinaldi, Giuseppe Badalamenti, Carlo Arcara, Giuseppe Cicero, Cettina Sortino, Francesca Spinnato, Oriana Maiorana, Anna Cocchiara, Antonio Russo, Gaspare Gulotta, Nicola Gebbia, Fabio Fulfaro
Department of Oncology, Università degli Studi di Palermo, Palermo, Italy

Oxaliplaten (O) and capecitabine (C) have showed interesting activity as single agents in breast cancer patients. We carried out a phase II study to evaluate the efficacy and safety of combined O and C in anthracycline and taxane pretreated MBC patients. Twenty-eight MBC patients were treated with C 1000 mg/m^2 b.i.d. per os, days 1–14 with a week of rest and O 130 mg/m^2 (2-h i.v. infusion), day 1 every 3 weeks. Inclusion criteria were: age <75, Performance Status (PS) <2, normal kidney and liver function, absence of brain symptomatic metastases, at least two prior chemotherapy lines with anthracyclines and taxanes, informed consent. Mean age was 58 years (range, 33–74 years), with a median of two involved organs. Sixteen patients had a PS = 0, eight patients had a PS = 1, four patients had a PS = 2. Sites of disease were: liver (17 pts), skin (8 pts), bone (16 pts), pleura-lung (8 pts), lymph nodes (6 pts).

Results: Twenty-two patients were assessable for response and toxicity. Six PR, 1 CR, 7 SD and 8 PD were obtained with an overall response rate of 31%. The partial responses occurred in patients with metastatic liver disease and the complete response occurred in a patient with cutaneous metastatic nodules and liver metastases. Median time to progression was 6 months (range 3–8 months) and median survival was 11.5 months (range 6–17 months). Hematotoxicity was prevalent but rarely severe, with only four patients (18%) with G3 neutropenia and two (9%) patients with G3 thrombocytopenia. G1–2 neutropenia, anemia and thrombocytopenia occurred in eight (36%), five (22%), and eight (36%) patients, respectively. One-third of patients developed grade 2–3 peripheral neuropathy, with grade 3 in only five (22%) patients. Nausea and vomiting G1–2 and diarrhea G1–2 were present in nine patients. Hand-foot syndrome G2 occurred in six (27%) patients. The O/C combination seems to be effective and well tolerated.

A51 TREATMENT OF METASTATIC BREAST CANCER (MBC) WITH VONORELBINE AND DOCETAXEL

Giuseppina Savio, Vita Leonardi, Agata Laudani, Alessio Pepe, Caterina Calabria, Caterina Scianna, Valentina Palmisano, Biagio Agostara
Division of Medical Oncology, Oncological Hospital M. Ascoli, ARNAS Civico, Palermo, Italy

Background: A phase II study was performed to evaluated the efficacy and safety of combination of vinorelbine (VNR) and docetaxel (DOC) in patients with metastatic breast cancer (MBC) who had received a previous anthracycline regimen in adjuvant or advanced disease.

Patients and methods: Forty-one advanced breast cancer patients were included in this study.

Treatment consisted of vinorelbine (VNR) 25 mg/m^2 and docetaxel (DOC) 75 mg/m^2, both 1 day every 3 weeks for a maximum of nine treatment cycles. Median age of the patients was 56 years (range 35–73) and 92% of patients were postmenopausal, P.S. 0–1.

Dominant sites of disease were viscera in 42% of patients, bone in 30%, soft tissue in 32%.

In total, 65% of enrolled patients had >2 metastatic sites of disease. Previous treatment consisted of surgery for 82%, neo-adjuvant chemotherapy in 7.3%, adjuvant in 70.7%; 20 (48.7%) patients have received a front line chemotherapy for advanced disease and two patients (4.8%) also a second chemotherapeutic treatment.

Results: A total of 273 courses were given with a mean of six cycles per patients (range 1–9). All 41 patients were assessable for toxicity; the main toxicity was alopecia in 100%. Myelosuppression was the most common adverse reaction, neutropenia G2–3 in 34%, neutropenia G4 in 9.7%. Non-hematologic side-effects were N/V G2–3 in seven patients (17%), stomatitis was noted in seven (17%), and mild to moderate diarrhea was seen in five patients. The treatment was interrupted in one patient because of severe skin toxicity; five patients had a 25% dose reduction for toxicity during treatment.

Out of 39 patients (two patients had interrupted the treatment of personal reasons), we obtained 7 (17.9%) Complete Response, 13 (33.3%) Partial Response with an overall response rate of 51.2%, 6 (15.3%) experienced Stable Disease,

13 patients (33.3%) Progressed. For four patients who obtained CR, that regimen was a second-line treatment while for three patients it was first-line. The main sites of tumor involvement in patients who experienced CR were the lung and nodes.

Mean duration of major response (CR + PR) was 15.2 months. The median time to treatment failure was 6.2 months and the median survival duration was 14 months. Thirty patients are still alive.

Conclusion: Our data seem to show an efficacy and good tolerability with low grade toxicity for the vinorelbine + docetaxel combination in patients with metastatic breast cancer previously treated with anthracyclines.

A52 CARBOPLATIN AND VP 16 IN THE TREATMENT OF ADVANCED BREAST CANCER: A PHASE II STUDY

A. Pepe, V. Palmisano, V. Leonardi, I. D'Angelo, A. Laudani, C. Porretto, G. Savio, C. Calabria, B. Agostara
Divisione di Oncologia Medica PO 'M. Ascoli' ARNAS Civico, Palermo, Italy

Refractory advanced breast cancer is one of the most controversial areas for medical oncologists. Much research is focused on the discovery of agents and schedules that produce a significant clinical response even in the face of heavy pre-treatment. For a long time, platinum analogues were considered not useful in breast cancer. Moreover, their role has been revised on the basis of results when employed in first-line treatment. VP16 is a known active drug in breast cancer, generally not included in first-line protocols, with a reported 10–20% response rates as a single agent in pretreated patients. Moreover the activity of etoposide against tumors of CNS is intriguing. With this background, we carried out a clinical study employing the carboplatin–etoposide combination in advanced pretreated breast cancer patients.

In total, 41 patients were enrolled and treated with carboplatin AUC 5 i.v. on day 1 and VP16 100 mg/m^2 i.v. on days 1, 2 and 3, every 28 days. Out of 39 assessable patients, we obtained 5 PR (12%), with a median duration of 10 months (8–26) and 10 no change (NC) (24%) with a median duration of 7 months (5–12); whereas 24 patients (58%) progressed. The median overall survival was 12 + months. In total, 11 pts (27%) had brain metastasis; out of 10 evaluable patients, we obtained 3 PR and 3 NC. Out of 41 assessable patients, the main toxicity registered was gastrointestinal with N/V G2 in eight patients; the hematological toxicity G3–G4 was recorded in 12.1% of the patients. On the basis of the low response rate, in spite of good tolerability, we do not recommend this combination as salvage treatment in metastatic breast cancer.

A53 CAPECITABINE PLUS VINORELBINE COMBINATION IN PATIENTS WITH ADVANCED BREAST CANCER

M. Giampaglia, M. Spada, A. Latorre, R. Calabrese, D. Sambiasi, A. Misino, A. Rinaldi, S. Mancarella, S. Vitale, V. Lorusso
IRCCS, Oncologico, Bari, Italy

Background: The purpose of this study was to evaluate the efficacy and toxicity of a combination of vinorelbine (VNR) and capecitabine (XEL) in patients (pts) with metastatic breast cancer who had received previous anthracyclines and/or taxanes containing regimens in advanced disease.

Patient and methods: Thirty-eight advanced breast cancer patients were included in this study. Treatment consisted of VNR 25 mg/m^2 (days 1 + 8), and XEL 2000 mg/m^2 (from 1st to 14th day) every 3 weeks. The pts characteristic were: median age 56 years (range 33–74 years); ECOG PS 0–1 in 25 pts (65.8%) and two in 13 pts (34.2%); ER+ in 21 pts (55.2%). Dominant sites of disease were viscera in 21 pts (55.2%), bone in 9 pts (23.8%), soft tissue in 8 pts (21%). Eleven pts (29%) had ≥2 metastatic sites of disease. Previous treatment: 6 pts (15.8%) had received anthracyclines; 3 pts (7.9%) had received taxanes and 29 pts (76.3%) had received both drugs, respectively. Moreover 21 pts (55.2%) had received hormonal therapy.

Results: A total of 234 courses were given with a mean of six cycles per patients (range 1–20). Thirty pts (79%) had no toxicity at all. Non-hematologic side-effects were: nausea/vomiting G2–G3 in 3 pts (7.9%), stomatitis in 1 pt (2.6%), diarrhoea G4 in 1 pt (2.6%), constipation in 1 pt (2.6%), convulsions in 1 pt (2.6%), fatigue in 2 pts (5.2%), gastric pain in 2 pts (5.2%), fever in 1 pt (2.6%), peripheral neurotoxicity in 1 pt (2.6%), muscle pain in 1 pt (2.6%). Hematologic side-effects were: neutropenia G1–2 in 2 pts (5.2%), G3 in 1 pt (2.6%), anemia G2 in 2 pts (5.6%), thrombocytopenia G2 in 1 pt (2.6%). The treatment was interrupted in 2 pts: one because of severe worsening of clinical condition after the first cycle, and one for personal reasons. According to intent to treat, these 2 pts were considered as treatment failures. Out of 38 pts, we obtained 14 (36.8%) Partial Response, 9 (23.7%) Stable Disease, and 15 (39.5%) Progressive Disease. The median time to treatment failure was 6.8 months (range 1–20.5 months) and the median survival duration was 11.3 months (range 2–34 months). Twenty-four pts are still alive.

Conclusions: Our data confirm the good efficacy and tolerability of the VNR + XEL combination in pts with metastatic breast cancer previously treated with anthracyclines and/or taxanes.

A54 THREE-WEEKLY TRASTUZUMAB PLUS VINORELBINE IN THE TREATMENT OF METASTATIC BREAST CANCER. A PHASE 2 STUDY

C. Pacilio, E. De Maio, A. Gravina, V. Labonia, G. Landi, F. Nuzzo, E. Rossi, P. Silvestro, M. Staiano, F. La Vecchia, M. Di Bonito, G. Botti, R. Thomas, G. D'Aiuto, M.R. Salzano, P. Vallone, F. Perrone, A. de Matteis
Istituto Nazionale dei Tumori di Napoli, Fondazione G. Pascale, Naples, Italy

Background and aim: Excellent activity has been reported combining vinorelbine with weekly trastuzumab in the treatment of HER2 overexpressing metastatic breast cancer (MBC). We planned a phase 2 study to describe the activity and toxicity of the same combination, with trastuzumab administered every 3 weeks, that could improve patient comfort and organization of public hospitals.

Patients and methods: Patients with MBC were eligible if they had proven HER2 positivity (3+ or FISH), a performance status not worse than 2, and had received no more than one chemotherapy regimen for metastatic disease. The treatment schedule consisted of vinorelbine 30 mg/m^2 on days 1 and 8 every 21 days plus trastuzumab every 21 days (8 mg/kg at the first time and then 6 mg/kg). Vinorelbine was planned for a maximum of nine cycles, while trastuzumab could be continued until progression or unacceptable toxicity. According to a single-stage phase 2 design, with p0 = 0.45, p1 = 0.65, type I and II error = 0.10, 39 patients eligible for response assessment are required.

Results: As of February 28, 2004, 29 patients have been enrolled, 22 eligible for response assessment (17 in first and five in second-line treatment) and a further seven patients without target lesions eligible for toxicity assessment alone. Median age is 53 (range 31–70). Out of 18 patients with sufficient follow-up to allow at least one restaging, there were 10 responses, four complete and six partial, with an overall response rate of 56. Toxicity data limited to the first six cycles are already available for 23 cases. There was one toxic death from renal failure; seven cases of grade 4 neutropenia and three cases of febrile neutropenia; one patient had a grade 2 decline in left ventricular ejection fraction (LVEF).

Conclusion: The study is still ongoing, and enrollment should be completed within a few months. Preliminary results are encouraging.

A55 MITOMYCIN-C AND CAPECITABINE IN ANTHRACYCLINE AND TAXANE-PRETREATED METASTATIC BREAST CANCER (MBC). DOSE-FINDING STUDY

Roberto Maisano, Marzia Mare, Nicola Caristi, Rita Carboni, Giuseppe Chiofalo, Carmen Priolo, Francesco La Torre
Azienda Ospedaliera Universitaria 'G. Martino' Policlinico Messina-U.O.C. Oncologia Medica

Treating patients with anthracycline- and taxane-pretreated metastatic breast cancer (MBC) represents a challenge for the oncologist. Both capecitabine and mitomycin C (MMC) possess activity as single agents in MBC. Furthermore, in a human xenograft model, capecitabine and MMC have been demonstrated to act synergically due to up-regulation of the thymidine phosphorylase activity by MMC. We sought to exploit these preclinical observed effects in a dose-finding study in pts with pretreated MBC. The dose-escalation schedule included capecitabine 1000 mg/m^2 b.i.d. days 2–15 every 3 weeks and bolus MMC on day 1 at doses of 7, 10, 12, 14 mg/m^2 (levels I, II, III, IV, respectively) every 6 weeks to cohorts of at least three pts per dose level. For the evaluation of dose-limiting toxicity (DLT), we considered a period of 42 days as the duration of each cycle. We enrolled 13 MBC pts anthracycline and taxane-pretreated (level I = 3 pts; level II = 7 pts; level III = 3 pts). Five patients had received four prior chemotherapy treatments and four had received three chemotherapy treatments for metastatic disease. No DLT and no CTC-grade 3/4 toxicity have been observed in level I and in the first 3 level II pts, whereas one level III pt suffered from anaemia G3, thrombocytopenia G3 and hyperbilirubinaemia G3. In view of the palliative only aim of treatment, we chose not to expand level III, to stop dose-escalation to level IV and to enrol pts only for the second level. To date, 7 pts received this dose level for a total of 21 cycles, with only one episode of anaemia G3, two episodes of thrombocytopenia G2, diarrhoea G2 in 1 pt and PPE G2 in 1 pt. Noteworthy 1 pt reached confirmed PR and 2 pts long-term SD (5 and 6 months). Thus, MMC 10 mg/m^2 added every 6 weeks to capecitabine (1000 mg/m^2 b.i.d. days 2–15) is the recommended dose for further studies. Accrual is ongoing in order to expand the safety data. Updates will be presented.

A56 SEQUENTIAL HIGH-DOSE CHEMOTHERAPY (HDCT) AND IMMUNOTHERAPY IN THE ADJUVANT TREATMENT OF HIGH-RISK BREAST CANCER

F. Recchia[1,2], G. Saggio[1], A. Cesta[1], S. Rea[3]
[1]Unità operativa di Oncologia, Ospedale Civile, Avezzano; [2]Fondazione Carlo Ferri, Monterotondo, Rome; [3]Chirurgia Oncologica, Università degli Studi de L'Aquila, Italy

Background: The role of (HDCT) with peripheral progenitor cell support (PBPC) in the adjuvant treatment of high-risk breast cancer patients (pts) has not been established yet. We have demonstrated, in a phase 1B study, that low-dose interleukin-2 (IL-2) and 13-cis retinoic acid (RA), could improve the immune function of chemotherapy-treated pts with advanced tumors (Recchia F Clin Cancer Res 2001; 7: 1251–1257). The aim of this study was to verify if IL-2 and RA could improve the outcome of patients, with high risk breast cancer, treated with HDCT and PBPC.

Patients and methods: From August 1994 to November 2001, 18 pts with stage IIIB breast cancer (≥10 axillary nodes), after surgery, anthracycline-based chemotherapy, paclitaxel (Taxol) (in Erb-B2+), CMF and radiotherapy, followed by HDCT and PBPC were entered into the study. Conditioning drugs included: melphalan, carboplatin, cyclophosphamide, ifosfamide and etoposide. HDCT was given day (D)1 to D3. PBPC were infused on D5. IL-2 (1.8×10^6 IU, subcutaneously) and RA (0.5 mg/kg, orally) were administered, 30 days after PBPC, 5 days/week for

two courses of 3 weeks, with 1-week rest between the two courses, for 1 year and continued according to the immune competence.

Results: Patients [median (M) age, 47 years] received a M number of 6.2×10^6 CD34+cells/kg after HDCT. No treatment related death was observed. M time to absolute neutrophil count (ANC) >500/μl and platelets $>20 \times 103/\mu l$ was 9 days. After a M follow-up of 68 months (range 27–114), disease-free survival (DFS) and overall survival (OS) at 5 and 10 years were 82% and 86%, respectively. An improvement in all evaluated immunological parameters, including CD4+/CD8+ratio, NK and a decrease in vascular endothelial growth factor (VEGF) was observed.

Conclusion: These preliminary data show that IL-2 and RA administration after HDCT and PBPC is feasible, has activity and low toxicity. A significant improvement in DFS and OS was observed, with respect to our historical controls.

A57 PRIMARY CHEMOTHERAPY FOR BREAST CANCER: 11 YEARS EXPERIENCE AT A SINGLE INSTITUTION

G. Ucci, M. Visini, L. Zavallone, D. Fumagalli, A. Recalcati, P. Tricomi
Department of Medical Oncology, Breast Surgery and Pathology, 'A. Manzoni' Hospital, Lecco, Italy

Primary chemotherapy (PC) was recently licensed as standard therapy for breast cancer (BC) by an expert panel review (Kaufmann M et al. J Clin Oncol 2003; 21: 2600); we reviewed procedures and results obtained over 11 years at the Hospital 'A. Manzoni'.

From 1992 to September 2003, 78 female pts (median age 53 years, range 22–74; 32 premenopausal) with T1–4 invasive BC were treated with PC, mostly within two prospective consecutive phase II clinical trials. All pts were judged by the surgeon as not amenable for immediate conservative surgery: preoperative tumour diameter was 1–10 (median 4) cm at imaging; 62/78 pts had clinically involved nodes. In 68 pts, diagnosis of malignancy was made by fine needle aspiration (FNAC) and in 10 by core biopsy (CB). By FNAC, pathologists were able to determine histologic type and grade in no case, receptor status in 16 pts and Ki-67% in 10; all pts who underwent CB had their tumour fully characterized.

In total, 24 patients received epirubicin (120 mg for four courses) and 52 PEV (cisplatin, epirubicin and vinorelbin for 3–4 courses); two further patients received different regimens. Following PC, 34 pts achieved clinically partial response (cPR) and 44 less than cPR or stable disease with a significant reduction in tumour diameter (median 2.2 cm at imaging, $P < 0.0001$). In total, 63 (81%) pts underwent conservative surgery, and 15 total mastectomy. At histopathology, 13 (16.7%) cases had only microscopic remnants (epirubicin 4/24 pts, 16.7% versus PEV 9/52 pts, 17.2%; P = n.s.); receptor status and biologic parameters were generally concordant with those determined by CB (but not with FNAC) with a trend to Ki-67 per cent reduction (from 38.2 to 30%; P = ns).

All patients received adjuvant therapy (CMF and/or tamoxifen or aromatase inhibitors): at a median follow-up of 85 and 35 months, respectively, 8 pts relapsed and five died in the Epi group while 11 pts relapsed and seven died in the PEV group: differences in disease free and overall survival were not significant given the different follow-up.

Preoperative chemotherapy was feasible with more than 80% of patients undergoing conservative surgery; both regimens had similar efficacy. CB allowed to fully characterize tumours preoperatively while FNAC did not; however, PC induced little changes in tumour biology and true complete remissions are rare.

A58 ADJUVANT ENDOCRINE TREATMENT OF BREAST CANCER IN POST-MENOPAUSAL PATIENTS, RANDOMIZED, MULTICENTER STUDY TO CONFRONT TAMOXIFEN (TAM) VERSUS ANASTRAZOLO (ANA)

R. Talarico[1], A. Caputo[1], R. De Simone[1], G. Dima[1], M. Arena[2], G. Cicero[3], G. Di Pinto[3], G. Condemi[4], M. Nardi[5], V. Olivito[1], A. Pomillo[6], R. Porciello[7], P. Tagliaferri[8], G. Filippelli[1]
[1]Oncologia Medica Paola (CS) [2]Oncologia Medica Vibo Valentia [3]Oncologia Medica Castrovillari (CS) [4]Oncologia Medica Siderno (RC) [5]Oncologia Medica Reggio Calabria [6]Oncologia Medica Rossano (CS) [7]Oncologia Medica Chiaravalle (CZ) [8]Oncologia Medica Università di Catanzaro, Italy

During the last few years, there have been considerable innovations in approaching the endocrine therapy of breast cancer. This is due to the availability of drugs which are more active and less toxic than their previous counterparts, to new knowledge about their mechanisms of action, and to their biological aspects. In advanced disease, Tamoxifen has indisputably represented the first line of endocrine treatment. Randomized trials demonstrated the remarkable role of new aromatase inhibitors, especially in terms of reduction in side-effects.

The outcomes from a ATAC (arimidex, tamoxifen, alone or in combination) double-blind study have demonstrated the superiority of anastrazolo compared to tamoxifen both in terms of significant statistical reduction in preventing relapses and of tolerability; the smaller number of reports of endometrial tumours, thrombotic events and cerebral-vascular strokes has been very significant.

In our centre, 150 patients should be accrued and subdivided into two arms of treatment, which include TAM and ANA reported 1:2.

Primary end point of study: To check and confirm the superiority of ANA compared to TAM both in terms of efficacy and toxicity.

Secondary end point of study: To check the superiority of ANA compared to TAM in terms of quality of life. To evaluate the mental and cognitive faculty benefit in patients treated with ANA versus patients treated with TAM.

Eligibility criteria: Women with infiltrating breast cancer, in menopausal state at least, in menopausal state at least for 2 years, operated for tumorectomy and/or quadrantectomy and/or mastectomy and lymphoadenectomy; receptor-positive status with negative gynaecological and culposcopic examination, and also women previously treated with chemo-radiotherapy.

Ineligibility criteria: Metastatic disease.

Delivery of treatment: Five-year follow-up.

Statistical considerations: A statistical analysis based on the Student t-test has been completed and the valuations on the patients has be performed every 3 months through a toxicity test and every 6 months through a mental test, providing an EORTC QLQ-C30 questionnaire and the Mini-Mental State Examination. Since July 2001 till the present, 125 patients have been accrued also by centres which depend on ours and which are executing an ad interim analysis. Only 12 patients (seven patients treated with ANA and five patients treated with TAM) are removed from the treatment because of elevated toxicity or metastatic disease. With the Student t-test, we note the following results: the t values, respectively, obtained with the toxicity test ($t1$), the Mini-Mental test ($t2$) and the EORTC questionnaire ($t3$) are $t1 = 0.631$, $t2 = -1.332$ and $t3 = 1.177$ and we can easily observe that all these values are less than the t critical value ($t > 1.972$ and $t < -1.972$) for a valuation with 125 patients; so we can affirm that the two groups are perfectly compatible. Now if we take into due consideration patient's answers in the various tests, we note a considerable reduction in side-effects and a superiority in quality of life in patients treated with ANA.

A59 MALE BREAST CANCER (MBC) IN PARMA PROVINCE: DESCRIPTIVE EPIDEMIOLOGY, MOLECULAR MARKERS AND CLINICAL VARIABLES

Maria Michiara[1], Maria Angela Bella[1], Nadia Naldi[1], Antonino Musolino[1], Paola Zanelli[2], Beatrice Bortesi[2], Marzia Capelletti[2], Tauro Maria Neri[2], Mario Savi[2], Vincenzo De Lisi[3], Paolo Sgargi[3], Vittorio Franciosi[1], Andrea Ardizzoni[1], Stefano Cascinu[4]
[1]Medical Oncology Unit [2]Medical Genetic Service, University Hospital [3]Parma Cancer Registry, Parma; [4]Medical Oncology Unit, Le Torrette Hospital, Ancona, Italy

Germ-line mutations of BRCA2 are associated with an increased risk of MBC and with a family history of female breast and/or ovarian cancer.

Through the data of Parma Cancer Registry, we collected all cases of male breast cancer (MBC) from January 1st, 1978 to December 31st, 2000. Of these, we reviewed family history, clinical and pathological records. DNA samples were obtained from 19 patients and BRCA2 mutational analysis is ongoing.

Total number of incident cases was 54. Male to female ratio for BC incidence was 1:117 during this period. Mean age of the MBC incident cases was 67 (range 32–87).

The average number of incident cases and the average crude incidence rate increased from 1.6 and 0.93, respectively (1978–82) to 3.0 and 1.57 (1998–2000), and similarly, the age standardized rate changed from 0.49 to 0.74. The relative 5-year survival rate shows an improvement from 68% (1978–81) to 93% (1990–94). Thirty-three were ductal infiltrating carcinomas, two lobular, one mucoid, two papillary, one cribriform, one tubular, eight NOS, three adenocarcinomas, two papillary adenocarcinomas and one was without microscopic confirmation. Interestingly, lobular histology was seen only in two cases of hyper-estrogenism (one case for drug exposure and the other for liver cirrhosis). No cases of Klinefelter's syndrome were observed.

The distribution by stage available for 37 patients is as follows: 9 stage I, 14 stage II, 14 stage III, 0 stage IV.

With regard to the 19 patients screened for germ line BRCA2 mutations, 6/19 (31%) and 2/19 (10%) patients had a family history of breast cancer and ovarian cancer, respectively.

Estro-Progestinic receptor status was positive in 14 (73%) cases and HER-2/neu immunostaining was positive in five out of the 12 (41%) evaluated samples.

Our results are preliminary and need to be completed with data obtained by BRCA2 direct sequencing. Our future purpose is to investigate the contribution of BRCA2 germ line mutation to the phenotype of these tumors.

A60 HER-2/NEU AMPLIFICATION IN FINE NEEDLE ASPIRATES FROM PRIMARY BREAST CANCER: IS IT A PREDICTIVE MARKER IN PATIENTS TREATED WITH NEO-ADJUVANT ANTHRACYCLINE-BASED CHEMOTHERAPY?

Cecilia Bozzetti[1], Antonino Musolino[1], Nicola Personeni[1], Rita Nizzoli[1], Maria Michiara[1], Beatrice Di Blasio[1], Guido Ceci[1], Roberta Camisa[1], Stefano Cascinu[2], Andrea Ardizzoni[1]
[1]Medical Oncology Unit, University Hospital, Parma; [2]Medical Oncology Unit, Le Torrette Hospital, Ancona, Italy

Background: The purpose of this study was to evaluate the contribution of HER-2/neu gene amplification to outcomes of breast cancer patients treated with neo-adjuvant anthracycline-based chemotherapy.

Patients and methods: The clinical and pathological records of 44 women with stage II–III, or locally advanced breast cancer who had received different regimens of neo-adjuvant, anthracycline-based therapy were reviewed. HER-2/neu status was determined by fluorescence *in situ* hybridization (FISH) on diagnostic samples obtained by fine needle aspiration biopsy.

Results: HER-2/neu amplification was observed in 13 of the 44 (29.5%) tumors. Of 13 patients with HER-2/neu amplification, one (7.6%) had a complete response (CR), seven (54%) had a partial response (PR), five (38.4%) had stable disease (SD) and none had progressive disease (PD) at the time of mastectomy. Four (13%) CR, 17 (55%) PR, 10 (32%) SD and no PD were observed in 31 patients without amplification. HER-2/neu amplification was not significantly associated with response to neo-adjuvant chemotherapy ($P = 0.198$). Although not significant, patients with HER-2/neu gene amplification appeared to obtain a lower response rate from regimens with low doses of anthracycline (cumulative dose of epirubicin and doxorubucin < 280 and $< 370\,mg/m^2$, respectively) when compared to higher doses [50% of response rate (RR) versus 71.4%; P = not significant (NS)]. This trend was not observed for patients without HER-2/neu gene amplification (65% of RR versus 70%). In the entire cohort, there was no significant difference between HER-2/neu amplified and unamplified tumors in relapse occurrences (46% versus 29%; P = NS).

Conclusion: The putative association between HER-2/neu amplification and favorable response to anthracycline-based chemotherapy in breast cancer patients remains controversial. HER-2/neu amplification may be a marker of relative resistance to lower dose of anthracycline, while no dose–response relationship was seen in patients with HER-2/neu unamplified tumors.

A61 HIGH-DOSE CHEMOTHERAPY WITH STEM CELL RESCUE IN BREAST CANCER: 5 YEARS OF CLINICAL EXPERIENCE

E. Piazza[1], A.R. Gambaro[1], S. Ferrario[1], N. Tosca[1], M.T. Cattaneo[1], L. Isabella[1], V. Filipazzi[1], E. Damiani[1], E. Sacchi[2], C. Masseroni[2]
Departments of [1]Medical Oncology and [2]Hematology, 'L. Sacco' Hospital, Milan, Italy

Between December 1997 and May 2003, 18 patients with breast cancer received high-dose chemotherapy with autologous stem cell rescue.

Patient characteristics: 12 with more than four axillary metastatic nodes, six with metastasis (three lung and three liver), mean age 43.7 years (range 30–56). We have had CD34+ mobilization with cyclophosphamide in 11 patients and with epirubicine + Taxotere in 7 pts. All the patients mobilized a good number of stem cells over the tenth day after chemotherapy. Thirty-one leucapheresis were carried out: 21 in four-node patients; 10 in the metastatic ones. Through a double access central venous catheter, we obtained an appropriate number of CD34+ for transplantation.

The least number of CD34+ for a transplantation is 2×10^6/kg. We have had an average of 9.8×10^6/kg stem cells for every patient and we have transplanted about 4.2×10^6/kg stem cells.

We have not had any important side-effects during the stem cell transplantation nor peritransplantation serious adverse events. The 12 patients with more than four axillary metastatic nodes at diagnosis are still alive; among these, 11 are illness free. One patient has bone marrow metastasis with a TTP of 24 months.

The OS is 28.9 months (range 10–54). Among the six metastatic patients, two are alive. The OS is 30 months (range 2–30) and the DFS is 17 months (range 2–36).

Conclusion: As reported in the literature, in our patients we have also observed an improvement in the DFS but not the OS.

A62 ADJUVANT THERAPY FOR MALE BREAST CANCER PATIENTS: A RETROSPECTIVE REVIEW

M. Maur, A. Frassoldati, F. Piacentini, R. Sabbatini, M. Nicolini, C. D'Ambrosio, P.F. Conte
Oncology and Haematology Department of Modena, Study University of Modena and Reggio Emilia, Modena, Italy

This study describes our experience with adjuvant chemo-hormonal therapy in male breast cancer (MBC). A retrospective review of all MBC patients referred to our institution between 1991 and 2003 was conducted.

Twenty-four men were diagnosed with a breast ductal carcinoma; 20/24 pts had invasive carcinoma; 2/24 were metastatic (lung metastasis; supraclavicular lymph node involvement). All pts underwent radical mastectomy with axillary lymph node dissection. Twelve pts (10 adjuvant, two metastatic) were treated with chemotherapy (seven with anthracycline, five with CMF) and 18 pts received adjuvant hormonal therapy (17 tamoxifen, one anastrozole). Ten pts received postoperative radiotherapy to chest wall and axilla and/or supraclavicular site according to the guidelines of our institution.

Median age was 59 years; median tumor size was 1.5 cm (0.5–3.5 cm). Tumors were ER positive in 20 pts and PgR positive in 17 samples. Pathological node involvement was seen in 10 pts and 50% of tumors were high grade. To date, 6/18 pts with early disease relapsed. Four of six pts who relapsed had received chemotherapy and radiotherapy; all tumors that recurred were >1 cm diameter at diagnosis (2/6 >2 cm). The ER and PgR were positive in 4/6 and 3/6 of pts, respectively. About 50% of cancers that recurred had a high proliferation rate. At relapse, patients received chemotherapy with anthracycline or navelbine or taxotere in addition to trastuzumab for 1 pt with erbB2 overexpression, plus hormonal therapy. One patient died from metastatic disease, 2 pts with metastatic disease are still alive.

Phenotypic characteristics of MBC are more similar to those of menopausal women. Our results demonstrated a balance in the biological characterization of relapses so we cannot draw conclusions on the benefit from different adjuvant treatments.

A63 PACLITAXEL IN COMBINATION WITH UFT + LEUCOVORIN IN THE TREATMENT OF PATIENTS WITH METASTATIC BREAST CANCER: DOSE-FINDING STUDY

Lorenzo Cecconetto[1], Roberta Maltoni[1], Patrizia Serra[2], Ilaria Massa[2], Laura Ridolfi[1], Toni Ibrahim[1], Alessandro Passardi[1], Paola Ulivi[2], Nada Riva[1], Dino Amadori[1]
[1]Department of Medical Oncology, Pierantoni Hospital, Forlì; [2]Istituto Oncologico Romagnolo, Forlì, Italy

Numerous phase II and III studies have shown that paclitaxel (Taxol) is one of the most active chemotherapeutic drugs used to treat metastatic breast cancer. UFT, a combination of uracil and tegafur, is the oral prodrug of 5-fluorouracil (5FU), which is one of the agents included in provenly effective polychemotherapeutic regimens (CMF, FAC, FEC) for the treatment of this pathology. On the basis of the confirmed clinical activity of both paclitaxel and UFT, an *in vitro* study was conducted on breast cancer cells lines (estrogen receptor-positive MCF-7 and receptor-negative BRC-230) exposed to different sequence schemes of paclitaxel and 5FU to identify the most effective sequence. A moderate synergic interaction was observed when paclitaxel was administered before 5FU. Synergy was doubled in both cell lines when there was a 48-h interval between drug administrations. The present clinical study is based on the most effective *in vitro* drug sequence and aims to determine the maximum tolerated dose (MTD) on the basis of dose-limiting toxic effects (DLT) and thus the optimal dosage of the paclitaxel + UFT–leucovorin (LV) combination to use in a subsequent phase II study. The treatment regimen is as follows: paclitaxel $150\,mg/m^2$ on day 1, UFT at the dosage level at which the patient is inserted from day 3 to 13, in association with LV (fixed dose of 90 mg/day in three administrations). Patients are recruited in cohorts of three for each of the three UFT dose levels planned ($200–250–300\,mg/m^2$). The cycle is repeated every 2 weeks. Patients will be treated for at least four cycles and the overall duration of treatment will depend on the onset of unacceptable toxicity and on the evaluation of response to therapy. Main inclusion criteria are as follows: breast cancer patients with confirmed distant metastases, with positive or negative estrogen or progesterone receptor status; patients must have undergone at least first-line chemotherapy for advanced breast cancer, performance status 0–2 (ECOG), life expectancy ≥12 weeks. Recruitment is ongoing and the definitive study objectives will be presented at the Congress.

A64 TOXICITY OF WEEKLY LIPOSOMAL DOXORUBICIN AND PACLITAXEL IN METASTATIC BREAST CANCER (MBC)

F. Longo[1], P. Pellegrini[1], F. Ceccarelli[1], A. Borgomastro[1], T. Comito[1], M.L. Basile[1], G. De Biasio[2], M. Girolami[2], B. Spalletta[1], M. Di Seri[1]
[1]Department of Experimental Medicine and Pathology, [2]IV Surgical Department, University of Rome 'La Sapienza', Rome, Italy

Object: We evaluated the toxicity of liposomal-doxorubicin (LD) and paclitaxel (P) in patients (pts) with MBC.

Patients and methods: From December 2003 to March 2004, 15 consecutive pts with MBC have received LD 25 mg/mq and P 50 mg/mq both i.v., days 1, 8, 15 every 3 weeks for six cycles. Cardiac function was assessed with ECG and FEV measurement at the beginning and after six cycles of treatment. Pts characteristics were: median age 57 years (range 30–72), PS ECOG 0/1 9/6. Dominant sites of metastasis were: liver 8/15, lung 5/15, nodes 3/15, bone 4/15, brain 1/15, skin 1/15. A single metastatic site was present 6/15 (40%), two or >2 metastatic sites in 9/15. All pts received adjuvant chemotherapy, 5/15 pts received first-line chemotherapy for advanced disease and 4/15 pts a second-line chemotherapy. In total, 9/15 pts previously received anthracycline-containing regimens.

Results: Toxicity was assessed on a total of 55 courses. The median number of cycles administered per patient was 3.6 (range 1–6). Myelosuppression and alopecia were the most common adverse events (see Table). In total, 9/15 pts were assessed for response with 6 SD, 1 PR, 2 PD. Any significant variation of ECG parameters and FEV was detected.

Conclusions: Our results show that this combination has an acceptable toxicity profile in pts with MBC.

Toxicity	G1–G2	G3–G4
Neutropenia	15/55	9/55
Anemia	16/55	
Alopecia		40/55
Astenia	20/55	
Nausea	9/55	
Stomatitis	6/55	
Neuropathy	4/55 sensitive	3/55 motory

A65 PEGYLATED LIPOSOMAL DOXORUBICIN (PLD) AND WEEKLY PACLITAXEL (T) AS FIRST-LINE TREATMENT IN METASTATIC BREAST CANCER (MBC)

Giuseppe Badalamenti, Maria Rosaria Valerio, Gaetana Rinaldi, Carlo Arcara, Giuseppe Cicero, Laura Vizzini, Maria Grazia Travagliato, Chiara Intrivici, Antonio Russo, Gaspare Gulotta, Nicola Gebbia, Fabio Fulfaro
Department of Oncology, Università degli Studi di Palermo, Palermo, Italy

Background: Doxorubicin–paclitaxel combination chemotherapy is highly active in metastatic breast cancer but in some cases may have a relevant cardiac toxicity. PLD is a new formulation of doxorubicin with significantly reduced cardiac toxicity and for this reason PLD can be given safely in elderly patients with cardiac risk factors or in younger patients with prior exposure to anthracycline-containing regimens. The main side-effect of PLD is Hand-Foot syndrome but when given in intervals not below 4 weeks and with a dose intensity not exceeding 10 mg/m^2 per week, this side-effect is clearly reduced.

Patients and methods: We carried out a phase 2 study to verify the activity of P 70 mg/m^2 weekly day 1–8–15 and PLD 30 mg/mq every 4 weeks. Inclusion criteria were: age <75, Performance Status (PS) ≤ 2, normal kidney and liver function, absence of brain symptomatic metastases, adjuvant chemotherapy with anthracyclines (relapse free survival >12 months) or patients with LVEF between 40 and 50%, informed consent.

Results: Out of the 22 patients so far included, 18 were evaluable for toxicity and response. Eleven patients (61%) showed a response including 10 PR and 1 CR, two patients (11%) obtained SD and 5 pts (27%) progressed. Median time to progression and median survival have to be reached. Haematological side-effects were: Neutropenia G1–2 in 8 pts (44%), thrombocytopenia G1–2 in 6 pts (33%). The non-haematological side-effects were mild with the total absence of grade 3–4 toxic effects. Only six patients (33%) experienced grade 2 nausea and stomatitis. G1–2 peripheral sensory neuropathy was seen in 3 pts (16%). Hand-Foot syndrome G1–2 occurred in 4 pts (22%).

Conclusion: The treatment with weekly paclitaxel and PLD with this schedule appears to be well tolerated and active in metastatic breast cancer patients.

A66 PEGYLATED LIPOSOMAL DOXORUBICIN (PLD) AND GEMCITABINE (G) COMBINATION IN METASTATIC BREAST CANCER (MBC) PATIENTS: ACTIVITY AND TOXICITY

A. Fabi[1], P. Papaldo[1], M. Ciccarese[1], N. Salesi[1], V. Lorusso[2], G. Ferretti[1], B. Di Cocco[1], P. Carlini[1], F. Cecere[1], M. Pellicciotta[1], N. Morace[1], F. Cognetti[1]
[1]Regina Elena National Cancer Institute, Rome; [2]Oncology Institute, Bari, Italy

We conducted a phase II clinical trial to determine the activity and safety of PLD and G combination either in untreated or previously treated MBC patients (pts). The pts received PLD 25 mg/m^2 i.v. on day 1 plus G 800 mg/m^2 i.v. over 30 min on day 1 and 8 of each 21-day cycle.

From January 2003 to January 2004, 41 pts were enrolled in this study. Median age was 55 years (range 33–72), median PS (WHO) was 0 (0–2), median number of previous regimens administered for metastatic disease was 1 (range 1–2). Fifteen women had previously received no treatment. Twenty-two pts (52%) were given an anthracycline-containing regimen (18 in the neo-adjuvant/adjuvant and four in the metastatic setting). A median of six cycles was administered (range 1–8).

In total, there were 29 evaluable pts (one early death, 11 not yet evaluable). Responses were observed in 13 pts (one complete response and 12 partial responses with an overall response rate of 44.8%), stable disease in eight women (27.5%) and progressive disease in 8 pts. Responses were registered in 77% of pts previously exposed to anthracyclines. Among responders, seven were chemotherapy naïve for adjuvant and metastatic setting while six had previously received first- or second-line chemotherapy. Median duration of response and time to progression were 8 months (range 7–11) and 6 months (range 1–9), respectively. Grade 3–4 neutropenia was observed in 12 pts (29%) but only one case (2.5%) of febrile neutropenia occurred. No other severe hematological and non-hematological toxic effects were registered. Seven pts (25%) complained of moderate/severe asthenia. No case of severe cardiotoxicity or LVEF reduction >10% was registered, even among pts who had previously received anthracyclines. Alopecia was never observed.

Pegylated liposomal doxorubicin in combination with gemcitabine is active and well tolerated. Clinical benefit was achieved by 73% of pts. According to these preliminary results, there is no direct evidence of cross-resistance between classic anthracycline and PLD.

A67 WEEKLY PACLITAXEL AND CARBOPLATIN AS FIRST-LINE CHEMOTHERAPY PLUS TRASTUZUMAB IN PTS WITH ADVANCED BREAST CANCER, C-ERBB2 3+

R. Lanza, M. Proietto, P. Calabrò, P. Marchei
Università degli Studi di Roma 'La Sapienza' Dip. Medicina Sperimentale e Patologia, U.O. Oncologia Clinica, Policlinico Umberto I, Rome, Italy

Patients and methods: From September 2002, 12 patients with HER-2/neu overexpressing advanced breast cancer were treated with weekly paclitaxel–carboplatin–trastuzumab. Prior adjuvant chemotherapy, included anthracycline-based therapy. Patients received weekly paclitaxel 80 mg/mq, carboplatin AUC = 2 on days 1, 8, 15 every 4 weeks. Trastuzumab was administered i.v. in a loading dose of 4 mg/kg followed by a dose of 2 mg/kg once a week until disease progression.

Patients characteristics: The mean patient age was 58.2 years (range 40–70 years), patients in premenopausal were 5/12, postmenopausal 7/12, five of these patients were ER positive, and seven ER negative; C-ERb B2 3+ in 100% of the women. The sites of metastasis were: 1 pt lung, bone; 2 pts liver; 1 pt liver, brain, lymph nodes; 6 pts liver, bone; 2 pts liver, lung, bone.

Results: After three cycles of treatment, two patients (16.7%) achieved complete and nine patients (75%) partial response; SD was present in only one patient. After six cycles, two patients (16.7%) achieved complete and 10 patients (83.3%) partial response; time to progression was 9 months. The unique collateral effect was alopecia G4 in 90% of patients, alopecia G3 in 10% of patients. At present, one patient has died, one patient presented a progression and 10 patients will perform periodical controls.

Conclusions: The results indicate that the triple-drug combination of paclitaxel–carboplatin–trastuzumab constitutes an effective and well tolerated first-line treatment of HER-2 positive metastatic breast cancer.

A68 PHASE II STUDY EVALUATING THE ACTIVITY AND TOXICITY OF A BIWEEKLY SCHEDULE OF GEMCITABINE AND PACLITAXEL IN ANTHRACYCLINE-PRETREATED BREAST CANCER

G.P. Spinelli, M. Di Seri, S. Mezi, A. Oliveti, F. Tomao, F. Petricola, S. Rosati, S. Ricciardi, D. Coletta, A. Romiti, L. Frati, S. Tomao
Department of Experimental Medicine and Pathology, University of Rome 'La Sapienza', Rome, Italy

New cytotoxic agents with activity against breast cancer have been recently introduced in clinical practice with positive impact in survival. Among these agents, paclitaxel as single agent has produced response rates of 29–62%. Many clinical trials are in progress to evaluate the most promising associations of paclitaxel with other new agents; gemcitabine has demonstrated activity in metastatic breast cancer (MBC) with response rates ranging from 12% to 29% (in pretreated pts) and from 14% to 37% (as first-line therapy) when used as a single agent. Phase II studies of gemcitabine plus paclitaxel in pretreated patients with MBC have shown impressive response rates (~50%). Recent clinical trials have demonstrated the feasibility, safety and activity of a biweekly administration of paclitaxel and gemcitabine in MBC and according to these data, a phase II study was started in order to assess this schedule in a subset of patients pretreated with anthracyclines. In a phase II study, paclitaxel (135 mg/mq) was given on day 1, followed by gemcitabine (2000 mg/mq) also on day 1, of a 14-day course. Treatments with colony-stimulating factors were allowed in order to respect the dose-density of the schedule. Twenty-two patients were recruited and their characteristics were: median age 53, PS 0–1 in 18 pts (82%) and 2 in 4 pts (18%), pre-treatment with anthracyclines in adjuvant and advanced setting. All the patients were evaluable for toxicity and activity. The treatment was feasible and well tolerated: grade 4 toxicity was very rare and occurred in only three cases (2 pts with neutropenia and one with thrombocytopenia); grade 3 toxicity was more frequent but promptly reversible (the most recurrent was anemia in 24% of cases); no febrile neutropenia was observed. We observed 13 (58%) objective responses, three complete responses (13%), 10 (45%) partial responses and five (23%) stable disease. Progression was documented in 4 pts (18%). This study confirms the evidence that the biweekly association of paclitaxel and gemcitabine is a safe and active regimen in anthracycline-pretreated patients with MBC and suggests the necessity to investigate whether the combination of gemcitabine and paclitaxel is better than paclitaxel alone in this subset of patients.

A69 TEMOZOLAMIDE AND PACLITAXEL OR CARBOPLATIN IN ADVANCED BREAST CANCER PATIENTS (PTS) WITH BRAIN METASTASES

L. Blasi, V. Leonardi, V. Palmisano, A. Pepe, G. Savio, G. Rondello, L. Pindaro, G. Amoroso, B. Agostara
Divisione di Oncologia Medica PO 'M.Ascoli' ARNAS Civico, Palermo, Italy

Brain metastases occur in up to 40% of all cancer patients with metastatic disease. The goal of this study was to evaluate the efficacy and tolerability of temozolamide (TMZ) and paclitaxel or carboplatin in patients with brain metastases from breast cancer.

All eligible pts were enrolled in this phase II study and treated with oral temozolamide (100 mg/m^2/day from 2nd to 6th day) plus paclitaxel i.v. (175 mg/m^2 on day 1) in taxane-naive pts or carboplatin i.v. (AUC 4.5 in day1) in pretreated pts. Cycles were repeated every 28 days. After two–three cycles of chemotherapy, whole brain radiation therapy (WBRT) was carried out in association with TMZ (60 mg/m^2/day during the radiation treatment) and systemic chemotherapy. After RT, responding pts were treated with a maximum of six additional cycles. To date, 10 pts were enrolled (three in the carboplatin group and seven in the paclitaxel group). The characteristics of pts were as follows: median age was 54 years, PS 0–2; previous treatments were: surgery 8 pts, neo-adjuvant and adjuvant chemotherapy 2 and 8 pts, respectively, radiotherapy 2 pts; front line and second-line chemotherapy 9 pts. All pts were previously treated with anthracycline and 6 pts also with docetaxel. All pts had more than two sites of disease.

To date, only 30 cycles were administered (range 2–8). Only 7 pts are evaluable for response: progressive disease in 5 pts, partial remission in 2 pts. The registered toxic

effects were: nausea and vomiting G1 3 pts, neutropenia G2 1 pt, asthenia G1 1 pt, hair loss G3 1 pt.
In conclusion, the preliminary data on tolerability seem to show that this combination is safe, but the study has just started.

A70 CAPECITABINE AND GEMCITABINE IN METASTATIC BREAST CANCER: A PHASE I–II STUDY

P.G. Giannessi, R. Di Marsico, F. Martella, A. Falcone
Unit of Medical Oncology, Department of Oncology, ASL 6 of Livorno, University of Pisa, Pisa, Italy

Capecitabine (C) and gemcitabine (G) are both active drugs in pretreated metastatic breast cancer patients (pts), and have synergic interactions in the preclinical model and different toxicity profiles. Therefore, we designed a phase I study in metastatic breast cancer pts to determine the maximum tolerated dose of escalating doses of G (from 750 mg/m^2 up to 1500 mg/m^2 with increments of 250 mg/m^2) at day 1 and 8 every 3 weeks in association with a fixed dose of C 2000 mg/m^2/day on days 1–14. Twelve pts were enrolled with the following characteristics: median age 59 years (35–75), median PS 1 (0–1), 5 pts (42%) with multiple metastatic sites and all pretreated with an anthracycline/taxane-based chemotherapy. Dose-escalation was stopped at G 1500 mg/m^2 in according to protocol design, because no dose-limiting toxic effects were observed; the regimen was well tolerated and only 6 pts (50%) experienced a grade 2 (WHO) toxicity (anemia in 1 pt, neutropenia in 3 pts, N/V in 2 pts, asthenia in 1 pt and mucositis in 1 pt). Eleven pts were evaluable for response: 2 pts had CR, 2 pts PR, 6 pts SD and 1 pt PD. On this basis, we began a phase II study with G at the recommended dose of 1500 mg/m^2 and C 2000 mg/m^2/day. Up to the present time, 7 pts have been enrolled in the study. All pts had multiple metastatic sites (liver 6 pts, chest 3 pts, lung 1 pt and bone 5 pts) and received the combination as second- (5 pts) or first- (2 pts) line chemotherapy, after anthracyclines and/or taxanes. A total of 35 cycles have been administered and no grade 3–4 (WHO) toxicity has been observed (mucositis G2 in 1 pt and N/V G2 in 1 pt). Four pts are evaluable for response: 1 pt with CR, 2 pts with PR and 1 pt with SD. Patient accrual is continuing in order to define the activity and toxicity of this combination.

A71 TRASTUZUMAB (T) AND VINORELBINE (V) FOR PATIENTS (PTS) WITH HER2-OVEREXPRESSING ADVANCED BREAST CANCER (ABC). A PILOT PHASE II STUDY

Francesco Ferrau'[1], Vincenzo Adamo[2], Roberto Bordonaro[3], Nicola Caristi[2], Paolo Colina[1], Alessandro D'Angelo[1], Claudia Garipoli[2], Giuseppe Lavenia[3], Domenico Priolo[1], Rosalba Rossello[2], Paolo Tralongo[4]
[1]Divisione Oncologia Medica, Taormina; [2]Cattedra Oncologia Medica, Università degli Studi di Messina, Messina; [3]Divisione Oncologia Medica, Catania; [4]Divisione Oncologia Medica, Avola, Italy

Vinorelbine (V) and trastuzumab (T) are two of the most active and well-tolerated drugs in advanced breast cancer (ABC), with an expanding role in anthracycline- and taxane-treated pts. In addition to drugs' intrinsic activity, preclinical models suggest synergy between these molecules, providing a strong rationale for testing their combination in HER2 overexpressing ABC. In this subset of pts, we conducted a pilot phase II study to determine the safety and activity of V administered concurrently with T. Eligible pts had IHC2+/3+ HER2-overexpressing ABC, measurable disease, Karnofsky Performance Status (KPS) >70, normal baseline LVEF, adequate bone marrow, renal and hepatic reserve and no prior therapy with V. Twenty-four women were treated with V (25 mg/mq, days 1 and 8, repeated every 3 weeks) and T (4 mg/kg loading dose, 2 mg/kg weekly thereafter) between September 2002 and December 2003, for a total amount of 147 cycles (mean 6/pt). Mean age was 54 years (range, 32–70), 75% (18/24) pts had visceral involvement, 87% (21/24) had received prior chemotherapy (17 adjuvant, nine advanced, seven both). The schedule was employed in 8 pts as first-line, in six as second, in five as third, in four as fourth and in one as sixth. All pts are evaluable for toxicity, 22/24 for response. The only grade III/IV toxicity recorded was neutropenia in 3 pts (12%), while G II anaemia and thrombocytopenia occurred in 4 and 2 pts, respectively. There was no >G II extrahematological (including cardiac) toxicity; notably, in 6/24 pts no >G I toxicity was recorded. Response rate was 27% (1 CR, 5 PR), median duration 7+ months, with 36% stabilization of disease, for an overall clinical benefit of 63%. The combination of V and T, in this subset of heavily treated pts, seems well tolerated and feasible and shows an appreciable response rate, suggesting further experience in earlier stages of disease.

A72 WEEKLY PACLITAXEL AND PEGYLATED LIPOSOMAL DOXORUBICIN (PEG-LD) AS FRONT LINE THERAPY IN PATIENTS WITH METASTATIC BREAST CARCINOMA

V. Palmisano, V. Leonardi, A. Pepe, L. Mesi, M. Gugliuzza, C.S Cianna, C. Calabria, R. Stefano, B. Agostara
Divisione di Oncologia Medica, P.O. 'M. Ascoli' ARNAS Civico, Palermo, Italy

Systemic chemotherapy has saved the life of many patients with cancer, but the maximum efficacy of cytotoxic agents is severely limited by their adverse effects. PEG-LD has the advantage of delivering the active anthracycline directly to the tumor site while exposing the patient to a lesser degree of doxorubicin-associated toxic effects. More recently, a regimen in which paclitaxel is infused weekly over 1 h produced little myelosuppression, but substantial antitumor activity. With this background, we designed a phase II trial to study the efficacy and toxicity of paclitaxel 70 mg/m^2 weekly and PEG-LD 10 mg/m^2 on days 1, 8, 15 q 28 administered to metastatic breast cancer patients with high cardiologic risk; all patients will be treated with steroids and pyridoxine to prevent the palmar-plantar erythrodysesthesia. To date, 10 pts have been recruited, 8 pts (80%) evaluable for efficacy (1 pt too early) and 9 pts (90%) for toxicity. Adjuvant chemotherapy had been administered in 8 pts (anthracycline-based in 4 pts); 8 pts (80%) have two or more than two sites of disease. Overall, 1 CR, 6 PR and 1 NC have been recorded with an overall response rate of 87%. No PD had been registered. Toxicity was generally manageable; the only G3–4 side-effects recorded were: PPE 22%, Mucositis 11%, WBC 11%. No cardiotoxicity, no neurotoxicity and no alopecia were seen.
The weekly paclitaxel and PEG-LD seems a well tolerated and effective approach in advanced breast cancer patients with high cardiologic risk. The study has just started and the accrual of pts in this phase II study will continue to a final sample size of 40 pts.

A73* ADJUVANT MEDICAL STRATEGIES AND PATTERNS OF RELAPSE IN BREAST CANCER (BC) PATIENTS: THE NORA PROJECT

M.E. Cazzaniga, G. Mustacchi, A. De Matteis, P. Pronzato, F. Di Costanzo, L. Porcu, I. Floriani,
On behalf of NORA Study Group.
Az. Osp. Treviglio-Caravaggio, Medical Oncology

NORA is a national observatory aimed at investigating adjuvant therapeutic modalities and relapse pattern in patients (pts) with BC, radically treated with surgery in 77 Oncological Centres (OCs). To date, 1662 eligible pts have entered the study. Median age was 58.6 years (28–92); 73.7% were menopausal. Conservative surgery was carried out in 62.3% of cases. In total, 60.1% of pts had T1 tumours, 34% T2 and 44.7% had pN+ status. 79.6% had positive hormone receptors.
In total, 97.5% of pts received adjuvant systemic therapy: chemotherapy (CHT) alone: 20.4%, hormone therapy (HT) alone: 33.3%, combination of CHT and HT: 64.6%. As regarding type of CHT, CMF and anthracycline-based regimens are the preferred therapies (46.3% and 47.8%), with a preference for three-drug combinations. Among hormone treatments, tamoxifen still remains the preferred treatment (88%), even if a small percentage of pts were treated with aromatase inhibitors (9.6%). We analysed the choice between the sole CHT or HT versus the combination of CHT and HT as regarding pathological T stage and menopausal status. T stage does not influence the choice between CHT alone or the combination; on the contrary, the latter is preferred in T2 versus T1 tumours in comparison with HT alone (54.3% versus 20.5% and 38.5% versus 41.3%, respectively). The choice between CMF or anthra-base regimens is strongly influenced by T stage (T1: 27% versus 24.2%; T2: 32% versus 39.5%). Regarding menopausal status, CHT is preferentially chosen in premenopausal women, with a prevalence of three-drug anthracycline regimens. The use of taxanes, alone or in combination with anthracycline, is confined to a small number of pts, mainly T3–4.
In conclusion, tamoxifen still remains the preferred choice in ER+ pts, alone or in combination with CHT. The choice between HT or the combination is strongly influenced by T stage and menopausal status; anthracycline-based regimens are preferred in T2 tumours in comparison with CMF; taxanes are mainly used in larger tumours.

A74* IBIS 03: ADJUVANT TREATMENT OF BIOLOGICALLY AGGRESSIVE BREAST CANCER (N−, N+ 1–3): CONTROLLED CLINICAL STUDY

Dino Amadori[1], Patrizia Serra[2], Chiara Tison[2], Donata Casadei Giunchi[1], Alberto Ravaioli[3], Piero Sismondi[4], Amelia Tienghi[5], Francesco Schittulli[6], Angelo Paradiso[6], Mario De Lena[6], Oriana Nanni[2],
[1]Department of Medical Oncology, Forlì; [2]Istituto Oncologico Romagnolo, Forlì; [3]Department of Medical Oncology, Rimini; [4]Department of Gynaecological Oncology, Mauriziano Umberto I Hospital, Turin; [5]Department of Medical Oncology, Ravenna; [6]National Oncology Institute, Bari, Italy

Retrospective and prospective studies have highlighted the role of proliferative activity, determined as [^{3}H]thymidine labelling index (TLI), as a prognostic indicator (Silvestrini et al. Int J Cancer 1997; 74: 122–127; Volpi et al. Breast Cancer Res Treat 2000; 63: 181–192) and predictor of response to systemic chemotherapy (Amadori et al. J Clin Oncol 2000; 18: 3125–3134; Paradiso et al. J Clin Oncol 2001; 19: 3929–3937) in node negative breast cancer. High proliferation is associated with a higher tumor aggressiveness but also with a higher responsiveness to cytotoxic regimens, especially those including antimetabolites (CMF) followed by anthracyclines (Silvestrini et al. Int J Cancer 2000; 87: 405–411). On the basis of this evidence, a multicentric randomized clinical protocol was activated in 1998 to verify the impact of three regimens (CMF × 4 → EPI × 4, EPI × 4 → CMF × 4 and CMF × 6) on overall survival in patients with operable, rapidly proliferating, node negative or 1–3 node positive breast cancer. Subsequently, the CMF arm was closed for ethical reasons. In view of its validated prognostic relevance and the ongoing Quality Control Program to guarantee intra- and interlaboratory reproducibility, TLI had initially been proposed to define biologically aggressive tumors.

Progressively smaller tumor size at diagnosis has led to the inclusion, for patient selection, of histopathological grade and Ki-67/MIB1 index, which can be determined on sections from paraffin-embedded blocks used for histological diagnosis. The main limitation of these markers is that quality control procedures have not yet been activated or are still ongoing. To date, out of 1000 planned patients, 978 have been enrolled by 22 participating centers and the study will be closed in the next few weeks. The variables used to define biological tumor aggressiveness are grade in 56%, TLI in 37% and Ki-67/MIB1 in 7% of cases and they were well-balanced in the two arms. Overall, treatment has been generally well tolerated and suspended in only 27 patients for reasons of toxicity. At a median follow-up of 24 months, 45 relapses, 12 deaths and seven second tumors were registered. Histological material is being retrieved for ancillary biological studies and efficacy analysis will be carried out at a median follow-up of 5 years.

Supported by CNR-MIUR grant nos. 03.00074.ST97 and 02.00449.ST97

A75* PRIMARY CHEMOTHERAPY (PC) IN OPERABLE BREAST CARCINOMA COMPARING CMF WITH AN ANTHRACYCLINE-CONTAINING REGIMEN (CMFEV): RELATIONSHIP BETWEEN THE SHORT-TERM CLINICAL COMPLETE RESPONSE AND THE LONG-TERM OUTCOME

Beatrice Di Blasio[1], Andrea Ardizzoni[1], Roberta Camisa[1], Guido Ceci[1], Giancarlo Bisagni[2], Corrado Boni[2], P. Bruzzi[3], Giorgio Cocconi[1]
[1]Medical Oncology Unit, University Hospital, Parma; [2]Medical Oncology Unit, Arcispedale 'S. Maria Nuova', Reggio Emilia; [3]Epidemiology Unit, National Cancer Institute, Genoa, Italy

Background: Randomized clinical trials comparing two chemotherapy regimens of primary chemotherapy in operable breast carcinoma are unusual. In the present study, the authors compared CMF with their regimen including, by rotation, the same agents plus epirubicin and vincristine (CMFEV).

Patients and methods: Between November 1990 and April 1995, 211 patients with stages I and II palpable breast carcinoma, with tumor diameter >2.5 cm or <2.5 cm with cytologically proven axillary lymph node involvement, were randomized to receive CMF or CMFEV regimen for four cycles before surgery. After surgery, all pts received adjuvant CMF for three cycles. The median follow-up is 116 months (range 84–146).

Results: The short-term results have already been reported and demonstrated advantages in clinically complete response (cCR) favouring the anthracycline-containing regimen which was statistically significant in premenopausal patients.

The long-term results showed that relapse-free survival (RFS) and locoregional relapse-free survival (LRRFS) favoured the CMFEV regimen. These differences reached statistical significance for LRRFS ($P = 0.002$). Considering premenopausal patients, the differences favouring the CMFEV regimen greatly increased in both parameters and showed a statistical trend for RFS ($P = 0.07$) and a greater highly statistical significance for LRRFS ($P = 0.0009$). The 10-year overall survival rates were higher in CMFEV over CMF considering all (75% versus 70%) and premenopausal patients (80% versus 72%), but these differences were not statistically significant. No meaningful differences were observed in any of the above-mentioned long-term parameters in postmenopausal patients.

Conclusions: This study demonstrated that short-term advantages in cCR, favouring one versus another regimen of primary chemotherapy, were translated, with the reproduction of the same menopausal subgroup results, in long-term adjuvant effects. In this light, cCR assessed after primary chemotherapy could be considered, in general, as a surrogate end point of the long-term outcome.

A76* IDENTIFICATION AND SURVEILLANCE OF HEREDITARY BREAST CANCER: THE EXPERIENCE OF THE 'ITALIAN NETWORK ON HEREDITARY BREAST AND OVARIAN CANCER'

Laura Cortesi[1,2], Daniela Turchetti[1,2], Emma D'Andrea[1], Generoso Bevilacqua[1], Andrea Piga[1], Alma Contegiacomo[1], Piero Sismondi[1], Alessandro Cama[1], Paolo Belli[1], Massimo Federico[1,2], Salvatore Venuta[1]
[1]Italian Network on Hereditary Breast and Ovarian Cancer ; [2]Centro per lo Studio dei Tumori Familiari della Mammella e dell'Ovaio, Dipartimento di Oncologia ed Ematologia, Università degli Studi di Modena e Reggio Emilia, Modena, Italy

In 1999, the research program 'Development of a national network for the study of hereditary breast cancer' was launched under the auspices of the Italian Ministry of University (MURST) and subsequently, the advanced research program 'Familial Breast and Ovarian Cancer. A multicentric study on biological and clinical features and on the management of at-risk individuals' was supported by MIUR for two more years. This 4-year project involved 14 centers and had two main aims: (i) homogenizing criteria for identifying familial and hereditary breast and ovarian cancer (BC and OC) in order to collect a large and homogeneous population suitable for further investigations, like BRCA analysis, (ii) homogenizing management of at-risk families.

A database comprising all families identified by participating centers was set up. In total, 1643 kindreds, including 56 221 people had been registered in this database until January 2004. Overall, 4616 BC and 733 OC cases were reported. The mean age at the diagnosis of breast cancer was 49.7 years, being 46.1 years in the hereditary group and 53.4 in the familial breast cancer group. BrCa1 mutations had been identified in 130 out of 1003 families analysed (13%), BrCa2 in 70 out of 732 (9.6%). Two BrCa1 founder mutations were identified: 5083del19 and 1499insA. The evaluation of related cancers in hereditary breast ovarian cancer families has shown a prevalence of gastric tumours followed by colo-rectal cancer. Medullary carcinoma or ductal infiltrating carcinoma with aggressive phenotype (GIII, hormonal receptor negative, high proliferative rate) were most likely associated with BrCa1 mutations.

Among 1108 women in follow-up with mammography, ultrasound and, in specific cases, magnetic resonance, 37 breast cancers were identified with a detection rate of 9.7/1000 persons/year. The standardized incidence ratio was 3.3 ($P < 0.001$).

In conclusion, the operational criteria adopted by the Italian Network on Hereditary Breast and Ovarian Cancer seem useful in identifying family group at high risk of developing BC to offer adequate surveillance strategies.

A77* TOPOISOMERASE II-ALFA PROTEIN EXPRESSION CORRELATES WITH PATHOLOGIC RESPONSE AFTER ANTHRACYCLINE-BASED PREOPERATIVE CHEMOTHERAPY FOR BREAST CANCER

Alessandro Minisini, Mauro Mansutti, Carla Di Loreto, Stefano Pizzolitto, Giovanni Cardellino, Stefania Russo, Andrea Piga, Fabio Puglisi
Breast Unit, Clinical Oncology, University of Udine, Udine, Italy

Background: Preoperative chemotherapy for breast cancer (BC) is an interesting clinical model to study the factors that could predict response to anticancer drugs. In addition, pathologic response after preoperative chemotherapy has been shown to be associated with long-term outcome. The purpose of this study was to evaluate the role of several biological markers, such as proliferation (topoisomerase IIa, MIB-1, E2F) and apoptotic (AI) indices, DNA-repair proteins (Ape/Ref-1, p53), and other biological features (c-ErbB-2, estrogen receptors, progesterone receptors, histological grading) as predictors of pathologic response after anthracycline-based preoperative chemotherapy for BC, and to study their modification after antiblastic treatment.

Patients and methods: The biological markers were investigated by immunohistochemistry (and by TUNEL assay for AI) in a consecutive series of 50 pre-treatment core biopsy and their corresponding post-treatment surgical samples from patients receiving preoperative anthracycline-based chemotherapy for BC. Pathologic response was evaluated according to macroscopic and microscopic changes in tumour tissue.

For each marker, differences between pre- and post-treatment expression were evaluated by paired Student's t-test; logistic regression was performed to assess the relationship between biological findings and pathological response.

Results: Significantly lower expression of topoisomerase IIa ($P = 0.005$), E2F ($P < 0.0001$), estrogen ($P = 0.007$) and progesterone ($P = 0.01$) receptors was found in the post-treatment samples compared with the pre-treatment core biopsies. Conversely, Ape/Ref-1 expression showed a statistically significant increase in the post-chemotherapy samples ($P = 0.005$).

Higher levels of topoisomerase IIa in the pre-treatment samples predicted pathological response ($P = 0.01$). Grade 3 tumours were marginally associated with better pathological response ($P = 0.06$).

Conclusions: Immunohistochemical evaluation of topoisomerase IIa may be useful in predicting response to anthracycline-based preoperative chemotherapy for BC.

A78* EVALUATION OF THE PREDICTIVE SIGNIFICANCE OF SERUM HER-2/NEU, CA15-3 AND EGFR IN HER-2/NEU POSITIVE METASTATIC BREAST CANCER IN A PHASE IIB STUDY: PACLITAXEL (PCT) VERSUS PCT + TRASTUZUMAB (T)

Matelda Zancan[1], Stefano Rocco[1], Alessandro Morabito[2], Sabrina Meo[1], Diana Crivellari[3], Gianfranco Filippelli[4], Vittorio Silingardi[5], Livia De Sio[2], Paola Papaldo[6], Guido Carillio[2], Roberta Sarmiento[2], Antonella Spada[3], A. Veronesi, Antonio Caputo[4], Dino Amadori[7], Francesco Cognetti[6], Massimo Gion[1], Giampietro Gasparini[2]
[1]ABO Association, c/o the Center for the Study of Biological Markers of Malignancy, General Regional Hospital, ULSS 12, Venice; [2]San Filippo Neri Hospital, Division of Medical Oncology, Rome; [3]CRO, Aviano; [4]Presidio Ospedaliero, Paola; [5]Università di Modena, Modena; [6]Istituto Regina Elena, Rome; [7]Ospedale Morgagni-Pierantoni, Forlì, Italy

The aim of this study was to investigate whether therapy with PCT + T or PCT alone was associated with a significant variation of serum HER-2/neu (sNeu) and EGFr levels in HER-2/neu positive metastatic breast cancer (MBC) patients (pts) enrolled in a prospective randomized study. Serum levels of CA15-3, a tumor burden indicator, were also assayed. Overall, 83 pts were enrolled in the study; inclusion criteria were: untreated MBC with HER-2/neu overexpression (2+/3+ by Hercep test), age ≥ 18 and ≤ 70 years, ECOG PS scale ≤ 2. The schedules of treatment were: weekly PCT 80 mg/m^2 (arm A) and PCT + T (loading dose of 4 mg/kg, followed by weekly doses of 2 mg/kg) (arm B). CA15-3 and sNeu concentrations have been evaluated employing a new automated assay (Bayer Immuno 1TM). EGFr levels were measured using a manual kit (EGFr Microtiter ELISA OncogeneScience) Abnormal sNeu levels were found in 48.9% (cut-off 20 ng/ml) and high CA15-3 levels in 58.3% of the patients (cut-off 31 U/ml). Arm B pts showed a significant decrease in sNeu levels, from 124 + 39 ng/ml to 13 + 5 ($P < 0.05$), compared with those of arm

A. The levels of CA15-3 did not showed significant variations in relation to both the treatments. All the patients (n = 5) with high basal sNeu levels (>50 ng/ml) treated with PCT + T had a favourable clinical outcome in terms of disease-free survival, 275 + 53 versus 112 + 62 days observed in PCT arm (n = 4) ($P < 0.05$). In both the arms, when high sNeu levels were not decreased below 20 ng/ml after therapy, prognosis was poor (124 + 35 days). Decreased CA15-3 was significantly associated with objective response. The normalization of sNeu levels was more frequently observed during PCT + T therapy (7/8 cases). EGFr levels were not significantly correlated with HER-2/neu values (Spearman correlation $P = 0.389$) nor with response to therapy. In conclusion, sNeu is predictive of efficacy of therapy with T, in particular the pts with very high basal sNeu levels (>50 ng/ml) were significantly more responsive to PCT + T treatment. On the contrary, EGFr levels did not show predictive value.

A79* PRIMARY CHEMOTHERAPY FOLLOWED BY SURGERY OF RESIDUAL DISEASE IN METASTATIC BREAST CANCER: A SINGLE INSTITUTION PROSPECTIVE STUDY

Paola Sperone, Simone Bonardi, Maria Pia Brizzi, Alberto Bottini, Giovanni Allevi, Alfredo Berruti, Daniele Generali, Sergio Aguggini, Manuela Milani, Luigi Dogliotti
Department of Oncology, University of Torino at San Luigi Hospital, Orbassano, Italy; Breast Unit, Istituti Ospitalieri, Cremona, Italy

From 1990 to 2001, 328 consecutive patients with metastatic breast cancer were submitted to systemic therapy with anthracycline-containing regimens. One hundred fifty-seven patients (48.3%) had bone metastases, 130 (40.0%) lung, 93 (28.0%) liver, 123 (37.7%) skin/lymph nodes, three (12.5%) brain and 16 (4.9%) other sites. One hundred ninety-two (58.5%) patients had one site of disease, and 136 (41.5%) two or more. Fifty-six patients (17.4%) attained a complete response, 141 (43.9%) a partial response, 72 (22.4%) a stable disease, while 31 (9.7%) progressed. After systemic treatment, all patients were evaluated for surgery of residual disease and 19 (5.8%) were radically resected (one showing a complete response, 15 a partial response, two a stable disease and one progression). Nine (47.4%) of them had liver metastases, six (31.6%) lung, three (15.8%) bone, and one (5.3%) spleen metastases. At the last follow-up in December 2003, 14 (73.7%) radically operated patients progressed and 11 (57.9%) died. Median time to progression in radically resected patients was higher (91.4 months) compared to the overall population (10.9 months) and to the subset attaining a disease response (13.6 months). All patients with radically resected metastatic bone disease showed disease progression in bone, whereas the patient with spleen metastasis had liver progression. Among the nine patients with liver metastases radically operated, three did not progress, four progressed in liver, two in bone, and one in lung. In patients with radically resected lung metastases, three did not progress, one progressed in bone, one in lung and one in liver. Median overall survival was 30.6 months in overall cases and 95.4 in those radically resected. Radical surgery of metastatic breast cancer could lead to an extremely long time to progression and overall survival but is feasible in a very small proportion of patients. This treatment modality is not curative but sometimes it may change the natural history of the disease, as suggested by the recurrence in bone after removal of visceral metastases.

Supported in part by a grant from Consiglio Nazionale delle Ricerche (CNR), Rome

A80* WEEKLY PACLITAXEL (PCT) + TRASTUZUMAB (T) AS FIRST-LINE THERAPY OF PATIENTS (PTS) WITH HER-2/NEU POSITIVE METASTATIC BREAST CANCER (MBC): A MULTICENTER RANDOMIZED PHASE II TRIAL

Giampietro Gasparini[1], Diana Crivellari[2], Gianfranco Filippelli[3], Alessandro Morabito[1], Vittorio Silingardi[4], Livia De Sio[1], Antonella Spada[2], Paola Papaldo[5], Guido Carillio[1], A. Veronesi[2], Matelda Zancan[6], Massimo Gion[6], Antonio Caputo[3], Francesco Cognetti[5], Dino Amadori[7]
[1]San Filippo Neri Hospital, Division of Medical Oncology, Rome; [2]CRO, Aviano, Italy; [3]Presidio Ospedaliero, Paola; [4]Università di Modena, Modena; [5]Istituto Regina Elena, Rome; [6]ABO Association, c/o the Center for the Study of Biological Markers of Malignancy, General Regional Hospital, ULSS 12, Venice; [7]Ospedale Morgagni-Pierantoni, Forlì, Italy

The aim of the study was to demonstrate whether weekly PCT-T is superior to PCT alone in patients with HER-2/neu positive MBC. Inclusion criteria were: untreated MBC with HER-2/neu overexpression (2+ or 3+ by IHC HercepTest), age >18 and < 70 years, adequate organ functions, ECOG PS scale < 2.

The schedules of treatment were: weekly PCT 80 mg/m^2 (arm A) and weekly PCT + T (loading dose of 4 mg/kg, followed by weekly doses of 2 mg/kg) (arm B). In total, 109 pts have been enrolled up to January 2004; 85 are evaluable (A = 40; B = 45).

Pts distribution was well balanced: median age 53 years (A) and 55 years (B), tumor involvement in >2 sites in 66% (A) and 49% (B), respectively. Median number of cycles was 20.

Both the treatments were well tolerated with no therapy-related deaths. Grade 3 neutropenia was observed in 12% (A) and 13% (B) of pts; grade 3 neuropathy was observed in 4% (A) and 6% (B) of pts, respectively. Left ventricular ejection fraction (LVEF) did not decrease during the treatment in both the arms. The intent-to-treat overall response rate in evaluable pts (n = 85) was 60% for PCT and 78% for PCT + T. PCT + T induced a better overall response than PCT alone also in pts with HER-2 3+ (86% versus 52%), with visceral disease (73% versus 55%) and in those pretreated with adjuvant anthracyclines (77% versus 52%).

Median TTP was 28+ weeks in the PCT arm versus 52+ weeks in PCT + T. The 1-year progression-free survival was 21% (A) versus 48% (B), respectively.

In conclusion, both the treatment arms were feasible and active in MBC pts with HER-2 overexpression. T improved response rate, TTP and OS in particular in those pts with HercepTest 3 plus, visceral disease or pretreated with adjuvant anthracyclines.

A81* SURVIVAL OF PATIENTS WITH HER2-POSITIVE ADVANCED BREAST CANCER (ABC) NOT CONTINUING TRASTUZUMAB (T) BEYOND DISEASE PROGRESSION AFTER DOCETAXEL (D) AND TRASTUZUMAB

Filippo Montemurro, Roberto Faggiuolo, Michela Donadio, Stefania Redana, Monica Minischetti, Antonio Durando, Roberta Buosi, Guido Vietti-Ramus, Massimo Aglietta
Institute for Cancer Research and Treatment, IRCC, Candiolo, Italy

Background: Continuing T beyond disease progression in patients with HER2-positive ABC is a widespread policy supported only by retrospective studies, which are subject to a severe selection bias. For example, patients with rapidly progressing disease after an initial T-based treatment are not likely to have been included in these analyses. Thus the overall survival data may appear encouraging in favor of continuing trastuzumab beyond disease progression. However, patients whose disease progresses at a rate that additional treatment is possible may fare equally well with chemotherapy or endocrine therapy without T. For this reason, we studied the overall (OS) and post-progression survival (PP-OS) of patients who, upon progression during a T-based multi-institutional protocol, received different forms of therapy without T.

Patients and methods: In total, 53 consecutive pts received D (75 mg/m^2 q3w for six cycles) and T (4 mg/kg, followed by 2 mg/kg/week until disease progression) as initial T-based treatment of HER2-positive (immunohistochemistry 2/3+ or FISH+) ABC. Post-progression treatment was not protocol-specified.

Results: At a median follow-up of 22 months (range 4–53), 39 pts progressed, three stopped treatment because of toxicity, and 31 died. After progression, 8 pts continued T+/− chemotherapy, seven received supportive care+/− palliative RT, and 24 received chemotherapy without trastuzumab and/or endocrine therapy. The median OS and PP-OS for patients not continuing on trastuzumab were 24.4 (3.5–53.3+) and 15.1 months (0.9–32+), respectively. However, considering only those 24 pts who could receive at least one dose of post-progression therapy, the median OS and PP-OS were 29 (11–53+) and 19 (3–32+) months, respectively.

Conclusions: Survival of pts with HER2-positive ABC not receiving T beyond disease progression was in the range of that reported in retrospective analyses of patients continuing T beyond disease progression. While additional research is warranted to clarify mechanisms of resistance to T '*in vivo*', the worth of continuing T beyond disease progression needs to be studied in randomized trials.

A82* EXPANDED EXPERIENCE WITH INTRAVENOUS OR ORAL VINORELBINE (VNR) PLUS TRASTUZUMAB (T) IN CHEMONAIVE PATIENTS WITH HER-2 OVEREXPRESSING METASTATIC BREAST CANCER (MBC)

A. Bernardo[1], R. Palumbo[1], G. Villani[1], M. R. Strada[2], G. Bernardo[1]
[1]Oncologia Medica II; [2]Oncologia Riabilitativa; Fondazione Maugeri-IRCCS, Pavia, Italy

We report the updated results of our previous experience with VNR/T combination as first-line treatment in HER2+ MBC. A total of 58 consecutive pts with histologically confirmed, measurable MBC, tumors scored as +3 positive for HER2 by immunohistochemistry or FISH+, no prior chemotherapy for metastatic disease have been treated. Median age was 53 years (range 32–70); prior adjuvant chemotherapy in 63%; prior hormonal in 45%; visceral metastases in most pts (liver 56%, lung 34%). Treatment consisted of i.v. T (4 mg/kg loading dose as a 90 min infusion, then 2 mg/kg weekly in 60 min) followed by i.v. VNR (25 mg/m^2 weekly as 10 min infusion) without a break, with one cycle consisting of four consecutive weeks.

A total of 286 cycles were given (median 5 per patient, range 3–12). VNR dose was reduced by 25% in 18% of weekly administrations because of WHO grade 3 neutropenia (no G-CSF support was used); there were no dose adjustments for T. The worst toxicity was hematological (grade 4 leukopenia in 11% of pts, 17% of cycles); no significant cardiac or neurological side-effects occurred. An overall objective response rate (RR) of 86% was observed (95%CI 58–82%), with five complete (three in the lung, two in the liver) and 36 partial remissions (17 in the liver, 15 in the lung and four in the bone), 15 stabilizations and two progressions. The median time to response was 12 weeks, median response duration was 9 months (range 6–19).

Based on these findings, a following phase II trial is ongoing to test the same regimen with VNR given orally at the dose of 60 mg/m^2. Preliminary results are encouraging, confirming a high antitumoral activity (2 CR and 7 PR after the third cycle on the first evaluable 12 pts, RR 83%), favorable toxicity profile and good patient compliance. The accrual is ongoing to better define the optimal timing and duration of such a schedule.