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EPIDOXORUBICIN VS IDARUBICIN CONTAINING REGIMENS IN INTERMEDIATE AND HIGH GRADE NON-HODGKIN'S LYMPHOMA: PRELIMINARY RESULTS OF A MULTICENTRIC RANDOMIZED TRIAL

MAURA BRUGIATELLI [1], MASSIMO FEDERICO [2], PAOLO G. GOBBI [3], PAOLO AVANZINI [4], VINCENZO CALLEA [1] LUIGI CAVANNA [5], ANDREA DE PASQUALE [6], ALFREDO U. DI PRISCO [7], NICOLA DI RIENZO [8], VITTORIO SILINGARDI [2] CARLO MAURI [9], on behalf of the ITALIAN LYMPHOMA STUDY GROUP (GISL)

Background. **In recent years many therapeutic regimens have been designed in order to improve response rate and response duration in non-Hodgkin's lymphoma (NHL). In 1991 the Italian Lymphoma Study Group (GISL) started a prospective randomized trial on treatment of aggressive and advanced NHL, focused on the efficacy of two Pro-MACE-CytaBom (P-C) derived protocols.**

Methods. **From April 1991 to March 1993, 243 cases of intermediate and high grade NHL (Groups D-H according to the Working Formulation) in stage I bulky, II-IV have been registered from 19 institutions and randomized to receive 6 courses of either epidoxorubicin, 30 mg/m^2 (P-E) or idarubicin, 6 mg/m^2 (P-I) containing P-C. The present study deals with the results of an interim analysis of the first 96 cases enrolled up to December 1991 (median follow up of surviving cases 19 months, range 15-23), in terms of overall response rate, toxicity and dose intensity of the two schedules, and overall survival.**

Results. **The overall response rate was: 55 CR (64.0%), 15 PR (17.4%), 5 NR (5.8%) and 11 PG (12.8%). The actuarial survival rate was 61% at 24 months. Hematological and non-hematological toxicity was comparable in the two arms. Dose intensity was high and similar for the two schedules (90% vs 89%).**

Conclusion. **This interim analysis demonstrates that in aggressive NHL both P-C derived schedules with epidoxorubicin or idarubicin are effective, safe and well tolerated, also when used in a large multicentric setting.**

KEY WORDS: Non Hodgkin's lymphoma, chemotherapy, epidoxorubicin, idarubicin, randomized trial, toxicity, dose intensy.

The main purpose of first-line treatment of aggressive non Hodgkin's lymphoma (NHL) is to achieve a durable complete remission, regardless of the different prognostic factors [1]. The very poor outcome of patients obtaining partial or no response after the initial therapy justifies an aggressive first-line treatment for the largest possible number of cases and suggests the advisability of an early monitoring of the response. The introduction of doxorubicin in combination chemotherapy of NHL has substantially improved the response rate and the survival [2,3]. In recent years several doxorubicin-containing regimens have been developed, including CHOP [4], CHOP-Bleo [5], m-BACOD [6], MACOP-B [7,8], F-MACHOP [9], and Pro-MACE-CytaBOM [10]. These regimens determined complete remission rates ranging between 50% and 80%, even though the results obtained in multicentric trials indicate lower complete remission rates than those in the original reports [11]. More recently, new anthracyclines and anthracycline-like compounds have been used with comparable or even higher activity and reduced toxicity [12-14].

In view of these findings, the Italian Lymphoma Study Group (Gruppo Italiano per lo Studio dei Linfomi, GISL) has designed a randomized multicentric trial for advanced intermediate and high grade NHL. Gastro-intestinal lymphoma has been included in this study, before or after surgery, since it is well demonstrated that chemotherapy is highly beneficial in these cases [15]. ProMACE-CytaBOM (P-C) schedule has been chosen as induction therapy. P-C is a third-generation regimen developed at NCI [10], already em-

From the [1] Dipartimento di Ematologia, Ospedali Riuniti, Reggio Calabria; the [2] Cattedra di Oncologia, Università di Modena; the [3] Istituto di Clinica Medica II, Università di Pavia; the [4] Divisione di Medicina I, Ospedale Santa Maria Nuova, Reggio Emilia; the [5] Divisione di Medicina I, Ospedale Civile, Piacenza; the [6] Istituto di Clinica Medica, Università di L'Aquila, Teramo; the [7] Cattedra di Ematologia, Università di Modena; [8] Divisione di Ematologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo; the [9] Professore Emerito di Clinica Medica, Università di Pavia.

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Correspondence: Dr. Maura Brugiatelli, Dipartimento di Ematologia, Ospedali Riuniti, 89100 Reggio Calabria.

ployed by the GISL with satisfactory results and acceptable toxicity [11].

The aims of the study are: 1) the comparison of two anthracyclines, namely epirubicin (EPI) (Epidoxorubicin, Farmitalia) and idarubicin (IDA) (4-demethoxydaunomycin, Erbamont Inc.), included in a P-C schedule as induction therapy; 2) the evaluation of a post-induction short maintenance treatment for patients achieving complete remission; 3) the comparison of two conventional salvage regimens for resistant and relapsing cases.

The present report, based on an interim analysis while the trial is still open, deals only with the comparison between EPI versus IDA containing P-C in terms of toxicity and dose intensity (DI) and with the very preliminary results in terms of response rate and overall survival to both induction treatments.

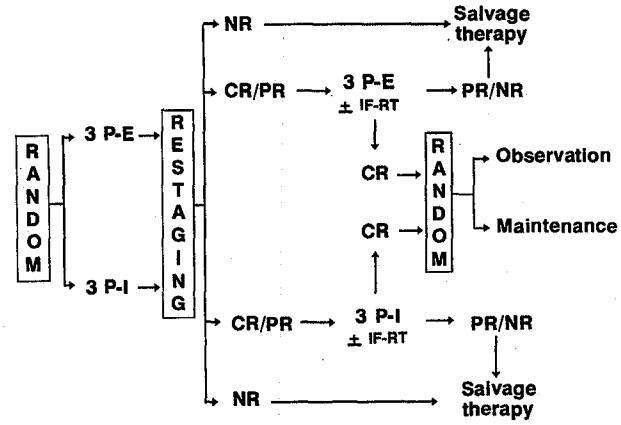

Fig. 1. - Design of the study. CR = Complete remission. PR = Partial remission. NR = No response. P-E = ProMECE-CytaBOM. P-I = ProMICE-CytaBOM. IF-RT = Radiotherapy on bulky lesion.

Patients and methods

Patients

The study enrolls patients affected with advanced intermediate and high grade NHL, according to the Working Formulation. It is to be note that the histologic diagnosis, although not centralized, is performed by two pathologists for the vast majority of cases.

Out of 243 patients who entered the study from April 1991 to March 1993 from 19 cooperative institutions, 96 cases had been admitted up to December 1991 and have been considered for this interim analysis. Inclusion criteria are: histologically documented NHL classified according to the Working Formulation, stage II, III, IV and stage I with bulky disease according to the Ann Arbor system, no previous treatment and negative HIV serology.

The mean age of patients was 55 yrs (range 18-76 yrs) with 10 cases older than 70 yrs, because, although the suggested upper age limit is 70, older patients can be included provided that they present a very good performance status in the absence of underlying coronary artery and pulmonary disease.

Staging procedures include full history, physical examination, blood cell count and differential, liver and renal function tests, ESR, serum LDH and B_2 microglobulin, bone marrow biopsy, chest X ray and computed tomography (CT) of chest, abdomen and pelvis.

Design of the study

As shown in Fig. 1, all cases are initially randomized either for EPI (P-E) or for IDA (P-I) containing P-C. After three cycles, a formal restaging has to be performed. Non-responding patients (NR) are randomized for one of two salvage regimens, while patients in complete (CR) or partial (PR) remission receive three additional P-C courses, followed, when indicated, by the irradiation of the original bulky lesion. Then, cases in CR are again randomized either for a post-induction maintenance therapy lasting 4 months or for observation only.

Regimens

The regimens employed in this study are listed in Table 1.

The P-C schedule is used according to the original scheme [10] with the replacement of doxorubicin by EPI, 30 mg/m² (P-E) or IDA 6 mg/m² (P-I). Cycles are repeated every three weeks.

Maintenance consists of four blocks of two drugs, according to the following schedule: thioguanine 300 mg/m² on days 1-4 and cyclopshosphamide 600 mg/m² on day 5; hydroxyurea 2400 mg/m² on days 1-4 and epidoxorubicin 50 mg/m² on day 5; methotrexate 10 mg/m² on days 1-4 and carmustine 60 mg/m² on day 5; cytarabine 150 mg/m² on days 1-4 and vincristine 1.5 mg/m² on day 5. Each block is administered every two weeks; after the fourth block the sequence is repeated once, starting from block 1.

MJMA consists of mitoxantrone, 10 mg/m², on day 1, carboplatinum 100 mg/m² and methylprednisolone 500 mg/m² both on days 1-4, and cytarabine 2000 mg/m² on day 5.

MIPE consists of mitoxantrone 12 mg/m², on day 1, etoposide 120 mg/m² on days 1-3, ifosfamide 1200 mg/m², prednisone 60 mg/m² and mesna 600 mg/m² x 2 on days 1-5.

Both MJMA and MIPE are repeated every 4 weeks for a total of 6 courses.

Some cases received prophylactic G-CSF; the remaining cases have been treated with cotrimoxazole and ketoconazole or fluconazole. Anti-emetic prophylaxis with ondansetron has been currently used.

Definition of responses

Response is defined as CR when all signs and symptoms of the disease disappear at the physical, laboratory, radiographic and CT scan examination for at least one month after the end of therapy. Moreover, the response is defined as CR also in the presence of a small residual lesion demonstrable at CT scan and unmodified after 6 months of ob-

Table 1. - *Chemotherapy schedules used in the present study.*

Schedule	Dose		Route	Day
ProMECE-CytaBOM				
Cyclophosphamide	650 mg/m^2		i.v.	1
Epidoxorubicin	30 mg/m^2		i.v.	1
Etoposide	120 mg/m^2		i.v.	1
Prednisone	60 mg/m^2		orally	1-14
Cytarabine	300 mg/m^2		i.v.	8
Bleomycin	5 mg/m^2		i.v.	8
Vincristine	1.4 mg/m^2		i.v.	8
Methotrexate	120 mg/m^2		i.v.	8
Leucovorin	10 mg/m^2	×5	orally	9,10
Cycles are repeated every 21 days				
ProMICE-CytaBOM				
As ProMECE-CytaBOM replacing epidoxorubicin by:				
idarubicin	6 mg/m^2		i.v.	1
Cycles are repeated every 21 days				
MAINTENANCE				
1st Block:				
Thioguanine	300 mg/m^2		orally	1-4
Cyclophosphamide	600 mg/m^2		i.v.	5
2nd Block:				
Hydroxyurea	2400 mg/m^2		orally	1-4
Epidoxorubicin	50 mg/m^2		i.v.	5
3rd Block:				
Methotrexate	10 mg/m^2		i.m.	1-4
Carmustine	60 mg/m^2		i.v.	5
4th Block:				
Cytarabine	150 mg/m^2		i.v.	1-4
Vincristine	1.5 mg/m^2		i.v.	5
Blocks are administered every 2 weeks. The sequence is repeated twice.				
MJMA				
Mitoxantrone	10 mg/m^2		i.v.	1
Carboplatinum	100 mg/m^2		i.v.	1-4
Methilprednisolone	500 mg/m^2		i.v.	1-4
Cytarabine	2000 mg/m^2		i.v.	5
Cycles are repeated every 28 days.				
MIPE				
Mitoxantrone	12 mg/m^2		i.v.	1
Ifosfamide	1200 mg/m^2		i.v.	1-5
Prednisone	60 mg/m^2		orally	1-5
Etoposide	120 mg/m^2		i.v.	1-3
Mesna	600 mg/m^2	×2	i.v.	1-5
Cycles are repeated every 28 days.				

servation (CRU). PR is defined by a greater than 50% reduction of each measurable lesion, lasting for at least one month. No response is defined by less than 50% regression or by stable disease. Progression (PG) is defined by the enlargement of the original lesion or by the appearance of a new lesion.

Toxicity has been classified according to WHO criteria.

Dose Intensity

DI analysis was calculated according to the method of Hryniuk as the amount of each drug administered over the length of the protocol divided by the amount of each drug scheduled in the protocol [16]. For DI analysis we considered the amount of each drug, normalized to the body surface area, administered during the first 122 days (122 days are required to deliver the total amount of drugs, with cycles every 21 days according to the schedule).

Statistical Methods

All data were collected in a data-base and analysed with the Statistical Package for the Social Sciences (SPSS) [17]. Survival was calculated from the beginning of treatment until death for all causes and was estimated by the life-table method [18]. Pearson test was used to analyse contingency tables of response rates, clinical characteristics and toxicity for each investigated parameter.

Results

As reported in Table 2, the two groups of patients, randomized for P-E vs P-I, are fully comparable in their main clinical features, without any statistically significant difference.

Since the trial is still open, it would not be appropriate to report the results differentiating the response rate according to the two induction regimens. The data monitoring committee has observed no differences between the two arms such as to suggest interrupting the trial for ethical reasons.

Table 2. - *Main clinical characteristics of patients.*

	P-E Arm	P-I Arm
Enrolled Pts.	126	117
Evaluable Pts.	58	38
Sex M/F	34/24	22/16
Mean Age	56	52
Over 60 yrs	49%	37%
Histology:		
Intermediate No. (%)	47 (81)	29 (76)
High No. (%)	11 (19)	9 (24)
Stage:		
I-II No. (%)	17 (29)	13 (34)
III No. (%)	11 (19)	6 (16)
IV No. (%)	30 (52)	19 (50)
B Symptoms No. (%)	23 (40)	13 (34)
Bulky Disease No. (%)	20 (34)	13 (34)
Mean Karnofsky Value	81%	77%
Mean LDH level	431 UI/L	617 UI/L
Mean β2-microglobulin	3.0 μ/ml	2.7 μ/mL
Mean Hb level	12.2 g/dl	12.2 g/dl

Response

After the 3rd couse, the overall response rate to P-E and P-I, evaluable on 86/96 patients at March 1993 is as follows: 27 CR (31.4%), 49 PR (57.0%), 3 NR (3.5%) and 7 PG (8.1%) (Table 3).

Table 3. - *Overall response rate.*

	After 3rd course	After 6th course
Evaluable Pts No.	86/96	86/96
CR No. (%)	27 (31.4)	55 (64.0)
PR No. (%)	49 (57.0)	15 (17.4)
NR No. (%)	3 (3.5)	5 (5.8)
PG No. (%)	7 (8.1)	11 (12.8)

Ten cases who received less than 3 courses were not evaluated for response but only for survival. After the 6th course, the response was evaluable on 86 cases showing 55 CR (64.0%), 15 PR (17.4%), 5 NR (5.8%), and 11 PG (12.8%) (Table 3). It is noteworthy that 13 cases, initially considered in partial remission, could be defined as being in CR after consolidation radiotherapy because the residual small mass was unchanged 6 months after the end of induction therapy (CRU). At the time of this analysis 12 out of 55 CR cases have relapsed. The comparison between the results obtained after the 3rd and the 6th cycle indicates that about half CRs are achieved after the initial courses.

The actuarial survival rate of 96 evaluable patients is 77% at 12 months and 61% at 24 months. Thirtytwo patients died after the enrollment; the death causes were 23 disease progressions, 2 treatment-related infections, 1 B-hepatitis, 2 sudden deaths, 3 strokes; 2 patients died for unknown reasons. The distribution by arm of the death causes is reported in Table 4.

Table 4. - *Causes of death.*

Cause	P-E Arm	P-I Arm
Disease Progression	14	9
Infection	1	1
B Hepatitis	0	1
Sudden Death	1	1
Stroke	1	2
Unknown	2	0
Total	18/58	14/38

Dose Intensity

A satisfactory DI was achieved in both regimens with no difference between the two arms (average relative DI 90% vs 89% for P-E and P-I, respectively). Most of the patients received more than 85% of the planned dose.

Toxicity

The evaluation of toxicity could be performed on a total of 129 cycles of P-E and 101 cycles of P-I, for a total of 460 chemotherapy administrations.

The hematological toxicity was negligible in both arms (Fig. 2). In detail, the mean hemoglobin level decreased no more than 10% of the initial value. The lowest level of leukocytes and neutrophils (80% and 74% of the initial values, respectively) was detected at the beginning of the 6th cycle. Platelet count remained substantially unchanged during the treatment.

The difference between the two regimens is, so far, not significant for incidence and grade of infections, mucositis, pulmonary and cardiac toxicity (Table 5). For the latter toxicity it should be noted that the observation period is still too short for a correct evaluation.

Table 5. - *Main toxicity of P-C modified schedules.*

	P-E Arm	P-I Arm
No. of patients	58	38
No. of CHT Administrations	258	202
VOMITING		
Grade 1	12.0	19.0
Grade 2	9.0	6.9
Grade 3	1.5	0.0
MUCOSITIS		
Grade 1	17.0	19.0
Grade 2	6.0	0.0
Grade 3	0.7	0.0
INFECTIONS		
Grade 1	6.9	0.9
Grade 2	1.5	4.9
Grade 3	0.7	2.9
Grade 4	1.5	0.9
PULMONARY		
Grade 1	1.7	1.6
Grade 2	3.4	2.6
Grade 3	1.7	0.0
CARDIOTOXICITY		
Grade 1	0.0	2.6
Grade 2	0.0	0.0
Grade 3	1.7	2.6
TOXIC DEATHS No.	1	2

Grade is defined according to WHO criteria. Toxicity is expressed as follows: vomiting as % of chemotherapy administrations, mucositis and infections as % of cycles, pulmonary and cardiac toxicity as % of patients.

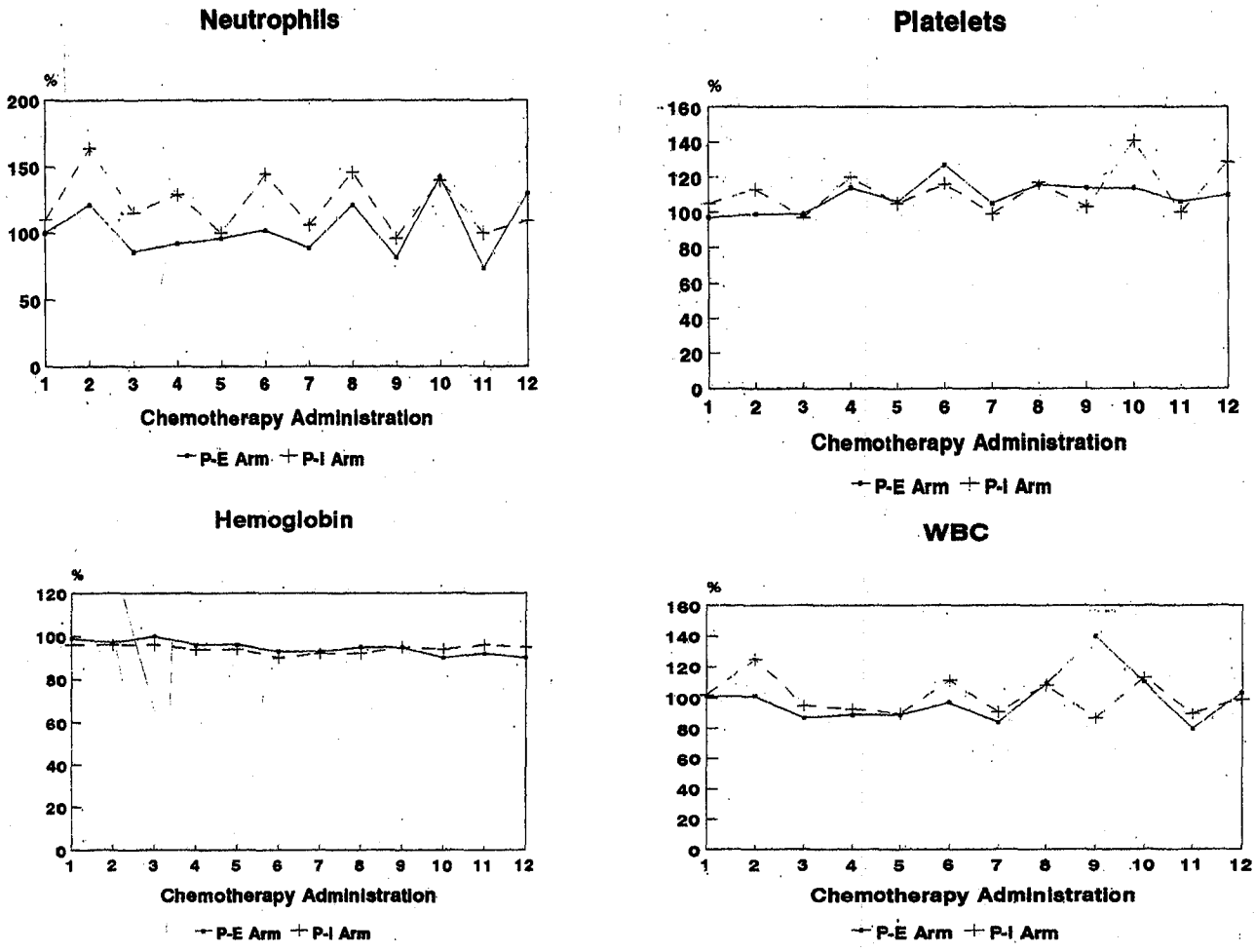

Fig. 2. - Myelotoxicity of P-C modified schedules. Peripheral count variations are expressed as percentage of the mean initial values.

Treatment-related deaths were due to infection in two cases.

Two patients suffered sudden death, apparently but not certainly unrelated to the treatment.

Cycles have been delivered on time in the majority of cases with the mean length of each cycle ranging between 22 and 27 days (Table 6). The longest delay observed before the 4th course may be due to the restaging procedures prescribed by the protocol after the 3rd cycle.

Table 6. - *Mean length of P-C cycles.*

	P-E Arm	P-I Arm
Cycle 1 (Days)	24	23
Cycle 2 (Days)	24	24
Cycle 3 (Days)	27	27
Cycle 4 (Days)	25	25
Cycle 5 (Days)	23	23
Cycle 6 (Days)	23	22

Discussion

The real advantage of third-generation regimens over conventional doxorubicin-containing treatments is, at the moment, under debate [2 19 20] and very recently, a large clinical randomized trial demonstrated a comparable efficacy of CHOP, mBACOD, MACOP-B and P-C [21]. It has, however, been suggested that when chemotherapy related toxicity is acceptable, the treatment of choice for advanced and aggressive NHL should be adequately intensive but familiar to the physicians in charge of the patient [2]. P-C regimen has been already used by the cooperating GISL institutions with effectiveness and low toxicity [11]. The present report confirms that both the modified EPI and IDA containing P-C are well tolerated. Excluding two cases of sudden death, the two treatment-related deaths (2.1%) represent a similar rate to those of other experiences with third-generation regimens where a fatal toxicity of 3-13% has been reported [2 21]. These results could be related

to an effective anti-infectious prophylaxis and to the use of G-CSF in some patients.

The tolerability of the P-C schedules is paralleled by an elevated DI, which is reported to be an important parameter for the final outcome [16]. The design of the schedule, in fact, allowed many drugs to be administered at intermediate dosages without significant delays. In particular, the use of IDA at the dose of 6 mg/m^2 in one of the regimens did not prolong the cytopenic period after therapy, as expected.

The CR rate of 64.0%, including those late CRs obtained with consolidation radiotherapy, observed in this preliminary analysis, is comparable with the 58% CR obtained by our groups in a previous study using the P-E protocol [11] and with the 65% reported by Miller et al. [22]. Longo and coworkers reported 86% CR in patients treated at NCI with the original P-C schedule [23]. The CR rate of the present report could have been influenced by many factors such as the large inclusion criteria and the multicentric character of the trial. In particular, more than 40% of our patients were over 60 yrs of age and selected cases aged over 70 in very good general condition have been enrolled, since conservative treatment does not appear satisfactory in aggressive lymphoma in the elderly [24].

In conclusion, the preliminary analysis of this study demonstrates that both regimens are well tolerated and effective in aggressive NHL, especially in the absence of bulky disease.

Besides, the future evaluation of the results of the complete design of the study should be able to add important information on the advantage of an early change of therapy in resistant cases, on the advisability of post-induction therapy in CR patients and, finally, on the best salvage schedule for cases ineligible for high-dose chemotherapy with autologous bone marrow transplantation.

Appendix

GISL Cooperative Institutions

Cattedra e Divisione di Oncologia Medica, Università di Modena (Prof. V. Silingardi, Dr. M. Federico). Clinica Medica II, Università di Modena (Prof. U. Torelli, Prof. G. Curci). Cattedra e Divisione di Ematologia, Università di Modena (Prof. A.U. Di Prisco, Prof. F. Narni). Clinica Medica II, Università di Pavia (Prof. E. Ascari, Dr. P.G. Gobbi). Servizio Autonomo di Ematologia, Centro Malattie del Sangue «G. Marcora», Istituto di Scienze Mediche dell'Università di Milano (Prof. A.T. Maiolo, Dr. L. Baldini). Divisione di Medicina I. Ospedale Civile, Piacenza (Prof. L. Buscarini, Dr. L. Cavanna). Divisione di Medicina I., Ospedale S. Maria Nuova, Reggio Emilia (Prof. F. Gobbi, Dr. P. Avanzini). Divisione di Ematologia, Università di Chieti-Pescara (Prof. G. Torlontano, Dr. M. Lombardo). Clinica Medica, Università di L'Aquila-Teramo (Prof. D. Quaglino, Dr. A. De Pasquale). Divisione di Ematologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (Dr. M. Carotenuto, Dr. N. Di Rienzo). Dipartimento di Ematologia, Ospedali Riuniti, Reggio Calabria (Dr. F. Nobile, Dr.ssa M. Brugiatelli). Divisione di Ematologia, Ospedale «A. Pugliese», Catanzaro (Dr. A. Alberti, Dr. S. Molica). Istituto di Oncologia, Università di Messina (Prof. S. D'Aquino, Dr. V. Pitini). Cattedra di Ematologia, Università di Palermo (Prof. A. Cajozzo, Prof. V. Abbadessa). Servizio di Oncologia Medica, Università di Palermo (Prof. A. Rausa). Cattedra di Oncologia Medica, Università di Palermo (Prof. S. Palmeri). Unità Operativa di Medicina, Istituto Oncologico, Bari (Dr. G. Colucci, Dr. E. Naglieri). Divisione di Medicina II, Ospedale Predabissi, Melegnano (Milano) (Prof. G. Santagati, Dr.ssa L. Dezza). Divisione di Medicina, Ospedale Civile, Sassuolo (Modena) (Prof. G. Fontana, Dr. G. Partesotti). Unità Operativa di Oncologia Medica, Ospedale S. Maria, Terni (Dr. F. Di Costanzo). Divisione di Medicina, Ospedale del Ponte, Varese (Prof. O. Piccinelli, Dr. R. Bettini).

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