References

1. Lipton A, Coleman RE, Diel IJ, Mundy G. Update on the role of bisphosphonates in metastatic breast cancer. Semin Oncol 2001; 28 (Suppl 11): 2–91.
2. Marx RE. Pamidronate (Aredia) and Zolendronate (Zometa) induced avascular bone necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003; 61: 1115–1118.
3. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 2003; 21: 4253–4254.
4. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: review of 63 cases. J Oral Maxillofac Surg 2004; 62, 527–534.
5. Green JR, Bisphosphonates: preclinical review. The Oncologist 2004; 204, 9 (Suppl 4): 3–13.

doi:10.1093/annonc/mdi206
Published online 22 April 2005

Comment on 'Cancer genetic counselling' by P. Mandich et al. (Ann Oncol 2005; 16: 171)

With the advent of genetic tests, genetic counselling is attracting increasing attention, as also shown by the recent letter by Mandich et al. [1], which addressed some aspects of our oncologist-based multistep model of cancer genetic counselling [2]. Perhaps the features of our model can be appreciated if we explain the rationale that prompted it. The philosophy and practice of the model emerged from a clinical oncological setting [2]. It was specifically designed to meet the user's needs of physical, mental and social well-being as recommended by the WHO [3], and is in keeping with the Italian National Health Plan in force when the model was designed, in that it empowers users to make an informed, fully aware choice among the various preventive, diagnostic and therapeutic options available [4]. The model, which employs an interdisciplinary team, identifies and manages at-risk subjects, and promotes the early diagnosis of invasive and preinvasive hereditary and familial tumours.

Pedigree construction and genetic testing (T1) occur only when the user is fully empowered to decide whether he/she wishes to know their cancer risk. Decisional empowerment derives from extensive information-giving about all aspects of familial or hereditary cancer (T0). At this step, the counsellor also obtains all the information necessary, including clinical-pathological files, to construct the pedigree and to estimate risk, thereby avoiding piecemeal data collection that would delay risk estimation. Communication modalities are geared to the user's educational/cultural level and their motivations and expectations in requesting counselling. The oncologist defines the user's risk profile (hereditary, familial or personal) and informs them of the possibility, limits and implications, also for their family, of risk estimation, and of prevention options so that the user can decide whether to proceed or not with counselling. At crucial steps of counselling, the psycho-oncologist evaluates also the user's coping style, which is an indicator of psychological well being [5]. A grave cognitive deficit and a severe psychopathologic condition preclude continuation of counselling because fully aware consent (i.e. 'empowerment') and not just informed consent is required to proceed from step to step of the model. The counsellor verifies acquisition of information by questioning the user. The counsellor–user relationship is considered a partnership in which a dynamic feedback of information from and to the user is established. Gene testing is not appropriate for everyone [6]. Not all users have a genetic risk.

Given the high psychological impact of cancer, global counselling is particularly important and requires the specific professional figures in the field of hereditary and familial cancer. It is conceivable that, given their training and daily exposure to patients, oncologists are able to estimate personal risk, to propose diagnostic/therapeutic strategies and to explain these to the user considering their healthy or disease status.

The multistep counselling model, endorsed by the Italian National Health Service for application in patient care, is being used in some centers of the Network for Hereditary Breast and Ovarian Cancer. Information provided by the media or on educational websites, even when 'officially' sanctioned, needs to be 'interpreted' by the health professional according to each user's needs.

In conclusion, our multistep model is not intended to replace classical genetic counselling, but rather to provide an alternative that fosters the oncologist–user partnership in order to promote early diagnosis and prevention.

A. Contegiacomo[1]*, M. Pensabene[1], I. Capuano[1], L. Tauchmanova[1], M. Federico[2], D. Turchetti[2], L. Cortesi[2], P. Marchetti[4], E. Ricevuto[4], G. Cianci[4], V. Barbieri[3], S. Venuta[3] & V. Silingardi[2]

[1]Department of Molecular and Clinical Endocrinology and Oncology, University of Naples 'Federico II', Naples; [2]Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena; [3]Department of Clinical and Experimental Medicine 'G. Salvatore', University of Catanzaro 'Magna Graecia', Catanzaro; [4]Department of Experimental Medicine, University of L'Aquila, L'Aquila, Italy
(*E-mail: impact.jgilder@tin.it, contalma@unina.it)

References

1. Mandich P, Cavalli P, Pasini B. Cancer genetic counselling. Ann Oncol 16; 1: 171
2. Contegiacomo A, Pensabene M, Capuano L et al. An oncologist-based model of cancer genetic counselling for hereditary breast and ovarian cancer. Ann Oncol 2004; 15: 726–732.
3. WHOQOL Group. The development of life assessment instrument (the WHOQOL). In Orley J, Kuyken W (eds): Quality of Life Assessment: International Perspective. Heidelberg: Springer Verlag 1994; 41–57.

4. National Health Plan (NHP) 1998–2000. Available online at http://www.fdgdiabete.it/psn2000/psnindex.htm (24 January 2005, date last accessed).
5. Nordin K, Lidén A, Hansson M et al. Coping style, psychological distress, risk perception, and satisfaction in subjects attending genetic counselling for hereditary cancer. J Med Genet 2002; 39: 689–694.
6. Euhus DM, Smith KC, Robinson L et al. Pretest prediction of BRCA1 or BRCA2 mutation by risk counselors and the computer model BRCAPRO. J Natl Cancer Inst 2002; 94: 844–851.

doi:10.1093/annonc/mdi219

Does the concurrent use of anthracycline and granulocyte colony-stimulating factor influence the risk of secondary leukaemia in breast cancer women?

Topoisomerase II inhibitors and alkylating agents induce secondary acute leukaemia (sAL) differently. The risk of this complication peaks 5–10 years after the start of chemotherapy in patients receiving alkylating agents. These patients frequently present with myelodysplasia (MDS), which may then progress to overt acute myeloid leukaemia (AML). Unlike the sAL associated with alkylating agents, that induced by anthracylines is monocytic, involves a specific cytogenetic abnormality (11q23) and develops within a few years (generally 2–3 years) after treatment, without prior MDS in some cases [1].

Although granulocyte colony-stimulating factor (G-CSF) induced the growth of primary acute myeloid leukaemic blasts *in vitro* in about 50% of cases, it was not leukaemogenic and even had an antileukaemic effect in some preclinical models [2]. In early breast cancer, Crump *et al.* [3] found no cases of sAL among patients given epirubicin-based adjuvant chemotherapy plus G-CSF, and Citron *et al.* [4] reported no correlation between the use of G-CSF and the incidence of sAL among 2005 patients randomized to standard or dose-dense chemotherapy. Conversely, in the cross-protocol analysis on six complete NSABP trials with different regimens of anthracycline and cyclophosphamide, Smith *et al.* found a positive association between the use and the dose of G-CSF and the risk of sAL in patients receiving standard anthracycline and dose-intensified cyclophosphamide [5]; the estimated risk of AML/MDS was 3.58 for patients given more than the median dose of G-CSF (242 μg/kg).

A total of 497 evaluable stage I–II breast cancer patients were randomly assigned to receive epirubicin 120 mg/m^2 and cyclophosphamide 600 mg/m^2 i.v. (hEC) on day 1 every 21 days for four cycles with or without lonidamine and with or without prophylactic G-CSF according to a factorial 2×2 design [6]. Among these patients we encountered, at median follow-up of 55 months, a 58-year-old woman who developed AML (monocytic, M5) 19 months after completion of chemotherapy. She had received filgrastim (480 μg/day s.c) every other day on days 8, 10, 12 and 14 of each hEC course and chest-wall irradiation (50 Gy plus a boost of 10 Gy) after completion of chemotherapy. She died 10 days after diagnosis of sAL. Although the cumulative epirubicin dose (480 mg/m^2) was less than that reported by Crump et al. [3], we found no other cases of sAL among the 243 evaluable patients in our series receiving hEC without G-CSF. Thus the crude incidence of sAL after adjuvant hEC with G-CSF support was 0.41%.

The case presented here and the recent update on the incidence of sAL after adjuvant chemotherapy for early breast cancer deserve some consideration. Several studies have demonstrated the possibility of achieving a modest to moderate increase in dose intensity using growth factors as an adjunct to higher-dose or dose-dense chemotherapy regimens, which were able to improve the clinical outcome. However, since the dose intensity of anticancer therapy has increased in parallel with the introduction of G-CSF in current clinical practice, distinguishing the contribution of intensified therapy versus G-CSF is often difficult. Above all, the leukaemogenic hazards of cancer treatment should always be weighed against its therapeutic benefits. Considering the recent development of indications even for subgroups of patients at moderate risk of relapse, it is crucial to balance the absolute survival benefit against the risk of severe complications caused by chemotherapy itself, particularly secondary acute leukaemia. In conclusion, this single case cannot prove the role of G-CSF in the development of sAL, but does point out the importance of being prudent when prescribing high-dose chemotherapy with growth factor support.

S. Di Cosimo*, G. Ferretti, P. Papaldo, P. Carlini, A. Fabi, E. M. Ruggeri, A. Alimonti, C. Nardoni & F. Cognetti

Division of Medical Oncology A, Regina Elena Cancer Institute, Rome, Italy (*sdicosimo@hotmail.com)

References

1. Shapiro CL, Rech A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001; 344: 1997–2008.
2. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. N Engl J Med 1992; 327: 99–106.
3. Crump M, Tu D, Shepherd L et al. Risk of acute leukemia following epirubicin-based adjuvant chemotherapy: a report from the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003; 21: 3066–3071.
4. Citron ML, Berry DA, Cirrincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21: 1431–1439.
5. Smith RE, Bryant J, DeCillis A, Anderson S. National Surgical Adjuvant Breast and Bowel Project Experience. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National