Beside explaining the occurrence of unexpected breast cancer among very young patients, one would have thought genetics may highlight certain specific phenotypic, biologic and behavioural characteristics of breast cancer among the youngest. Indeed, BRCA1-linked breast cancer shares certain specific characteristics with that of young women, such as a high grade, high proliferation rates and the frequent absence of hormone receptors. As well, recent descriptions of gene expression profiles appear similar and might plead for a common stem cell progenitor. However, although this remains controversial, genetics do not appear to account for the high prevalence of local recurrence of breast cancer in the populations of young women. We showed that among breast cancer patients with a strong family history and treated with conservative surgery, young age remained the only risk factor of local relapse, whereas the presence of a BRCA1/2 mutation was not.

We will discuss on the bases of recently acquired knowledge, the specific care of young carriers of BRCA1 or BRCA2 mutations, as well as the care of very young women affected with breast cancer, whether genetically-determined or not.

35 INVITED

Early breast cancer in very young women: the interphase between endocrine and chemotherapy treatment

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One in forty women with breast cancer is very young (<35 yrs). Outcomes in this age group have unique aspects. St Gallen Guidelines on Early Breast Cancer exclude women <35 from minimal risk category because of higher relapse risk.

IBCSG found women <35 yrs had higher risk of relapse after adjuvant CMF with 10 yr DFS of 35% which was significantly worse than 47% in older premenopausal women [1]. The relapse rate in women <35 yrs was particularly high in ER+ve group, who had a worse outcome than women <35 yrs with ER−ve tumors (10 yr DFS in <35 yrs: ER+ve = 25%, ER−ve = 47%). When US groups studied trial outcomes, a similar pattern was seen [2]. For ER−ve tumors, the outcome in women <35 yrs was similar to the older premenopausal women.

In premenopausal women with ER+ve cancer who receive chemotherapy, the outcome is better if amenorrhea occurs. The poor outcome for very young with ER+ve tumors treated with chemotherapy alone, maybe due to failure to achieve endocrine benefit of amenorrhea in this age group.

Adjuvant ovarian ablation is effective in women <50, but if chemotherapy is also given, ovarian ablation is of uncertain benefit [3]. The data are mainly from women aged 40–50 yrs who become menopausal from chemotherapy. This may underestimate benefit for very young.

US Intergroup randomized premenopausal receptor positive women to CAF, CAF + goserelin, or CAF + goserelin + tamoxifen. There was no significant benefit overall with addition of goserelin [4]. Retrospectively the subgroup <40 yrs appeared to benefit from goserelin. IBCSG randomized premenopausal women to CMF, or goserelin, or CMF then goserelin [5]. Goserelin after CMF resulted in a non-significant benefit. In an unplanned analysis, it appeared the ER+ve subgroup <40 yrs derived benefit from goserelin after CMF.

US groups assessed outcomes of very young ER+ve women compared with their older premenopausal counterparts, from trials with chemotherapy followed by tamoxifen. The results suggest an increased relative risk for those <35 yrs [2].

Very young women with receptor positive cancer deserve attention because of their poor outcome. Optimal chemo-endocrine strategies will be tested in a suite of 3 trials (**SOFT**, **TEXT** and **PERCHE**) led by IBCSG and joined by Breast International Group (BIG) and North American Breast Intergroup.

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36 INVITED

Mastectomy: the preferred treatment in young women?

C.J.H. van de Velde[1], T.C. van Sprundel[1,2], J. van der Hage[1,3], M.J. van de Vijver[4]. [1]*Leiden University Medical Center, Department of Surgery, Leiden, The Netherlands;* [2]*M, .Medical Research Fellow to the EORTC Task Force for Hereditary Breast Cancer;* [3]*M, .Medical Research Fellow to the EORTC Breast Group;* [4]*Netherlands Cancer Institute, Department of Pathology, Amsterdam, The Netherlands*

Nowadays, breast-conserving therapy is a generally accepted and widely embraced treatment modality for the majority of patients with early-stage breast cancer. Trials comparing breast-conserving therapy versus mastectomy revealed comparable results with respect to overall survival. However, several studies demonstrated the influence of young age as an independent risk factor of poor disease outcome. Patients with breast cancer diagnosed at younger age present more frequently with factors associated with a poor prognosis, such as larger tumours, vascular invasion, high-grade tumours, lymph node involvement, negative hormone receptors, and tumours with high S-phase fractions and overexpression of p53. In addition, young age has also been shown to be an independent risk factor. So the question arises whether breast-conserving surgery is justified as a treatment option in the management of early-staged, young breast cancer patients.

Randomised-controlled trials that studied mastectomy versus breast-conserving surgery without radiotherapy indeed showed a difference in overall survival in favour of more aggressive surgery. It is assumed that local recurrence after breast-conserving therapy arises from tumour cells that are left in the breast after local excision. Apart from the emotionally devastating events of any recurrence for the patient, distant metastasis may develop as a result of local recurrence. Furthermore, tumour bed re-excisions are performed more frequently in the younger age group, although no differences are observed in the final negative margin status among the other age groups. This might indicate the difficulties encountered when trying to achieve negative resection margins in younger patients and suggesting the presence of an extensive intraductal component or multifocal disease in younger women. Remarkably, no trials exist whom specifically compare breast conservative surgery versus mastectomy in women diagnosed at young age. A meta-analysis of three randomised EORTC-trials 10801, 10854, and 10902 revealed that patients of 35 years and younger diagnosed with breast cancer not only have almost three times higher local recurrence rates, but also a lower survival rate. However, adjuvant radiotherapy demonstrated very similar survival patterns when compared to mastectomy alone and seems to reduce the risk of local recurrence. Especially in women with early-onset breast cancer, perioperative chemotherapy demonstrated also a reduction of local recurrence rate. To date, no clinically useful risk factors for local recurrence have been identified within the population of young breast cancer patients. This is an important area of breast cancer research; especially gene expression profiling using microarray analysis is a promising method tho investigate this problem.

But should adjuvant treatment compensate for possibly inadequate surgery? After all, adjuvant radiotherapy trials have also demonstrated a beneficial effect for radiotherapy on overall survival after mastectomy in early breast cancer patients. Patients with limited nodal involvement benefited more from adjuvant radiotherapy than patients with extensive nodal disease. Although excessive radiation and chemotherapeutic regimes are obsolete, the long-term effects on in particular cardiovascular disease have to be taken into account when planning an optimal strategy in young breast cancer patients.

Finally, women with early-onset breast cancer are more likely to harbour one of the breast-cancer susceptibility genes, BRCA1 or BRCA2, or to have another genetic predisposition. Overall, the prognosis of breast cancer in carriers of a BRCA1- or BRCA2-mutation seems to be similar to that in age-matched patients with so-called sporadic breast cancer. In addition, since normal BRCA1/2 function may be associated with DNA repair, the possibility of an increased rate of radiation-induced malignant disease in carriers of BRCA1/2 mutations has been raised. An international collaboration study found no significantly increased rates in local recurrence after 10 years when comparing breast-conserving therapy in women with germline BRCA1/2 mutations to matched sporadic controls. However, it is noteworthy that significantly higher rates of contralateral events are observed in the genetic predisposed group. Bilateral mastectomy has demonstrated a substantially reduction of subsequent breast cancers in this group of patients. Although no evidence exists that overall or disease-specific survival is impaired by opting for conservative treatment, careful monitoring will be necessary for early detection.

The management of young women with newly diagnosed breast cancer still remains a challenging problem with complicated medical, psychological, and social implications. Although eventually breast-conserving therapy is regarded as the prime option, mastectomy and subsequent

reconstruction should always be discussed as a treatment alternative. It should be emphasized that quality of life after 5 years is generally better after amputation as opposed to breast conservative therapy. If the risk of local recurrence exceeds 1% per year, which is the case in the very young, then mastectomy with reconstruction should be seriously considered as the method of choice. In particular in young breast cancer patients, unnecessary locoregional recurrence should be avoided and therefore optimal local therapy should be achieved.

37 INVITED

Having breast cancer at 29!

T. Chomiak-Salvi. *EUROPA DONNA European Breast Cancer Coalition, Milan, Italy*

I will take a personal approach to this presentation, describing the circumstances of my diagnosis and subsequent treatment. My story will introduce a few issues of concern to young women who are dealing with breast cancer: our relationships with our doctors and our expectations of them; our medical issues; the type of support we need during and following treatment. I was 29 years old in 1996 when I was diagnosed with breast cancer. I was at the beginning of a demanding career in the U.S. foreign service. I had been very healthy until my diagnosis, with no significant family history of cancer. Needless to say, I knew nobody who had been diagnosed with breast cancer at that age, nor did any of the doctors I saw at the time. Seven years later, I have not had any recurrences and I am once again very healthy. I have continued in my foreign service career, and I have begun a family. In the intervening years, I have made the disease my hobby, focusing especially on the ways it affects young women. I have observed what are young women's needs in dealing with breast cancer, and I have witnessed significant progress toward providing for those needs. My presentation is intended to open a discussion of those needs. My observations come from my experience in the U.S.A. However, I have lived and worked in Europe for a few years, including working on breast cancer issues, so I will make comments in a Transatlantic context.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Micrometastatic disease – what have we learnt?

38 INVITED

The nature of hypothetical micrometastases

M. Baum. *The Portland Hospital, Department of Oncology, London, UK*

Since the revolution in our thinking about the nature of breast cancer in the early 1970s we have inherited and codified a new set of dogma. These presume that the outcome of treatment is predetermined by the extent and growth characteristics of micrometastases present at the time of diagnosis.

To a significant degree these beliefs have been vindicated by the successes of conservative local therapy and adjuvant systemic regimens. However the time has arrived to challenge the new dogma, which fail to explain many clinical observations and the failure of screening and systemic cytotoxic treatment to fulfill their promise. The following observations have to be explained with a unifying hypothesis that can both incorporate the successes of the past and accommodate the failures:

- Anecdotal evidence of trauma provoking the outgrowth of distant metastases.
- Failure of local control has a significant impact on survival after all.
- Distant metastases are rare at the time of presentation yet within three years their rate of appearance is proportionate to the size of the tumour at diagnosis.
- There is not a constant hazard rate for recurrence over time but a steep peak at three years.
- The results of adjuvant chemotherapy and high dose chemotherapy in particular are very disappointing.
- There is an ***increase*** in breast cancer mortality in the early years of screening for the premenopausal women.
- The point in the menstrual cycle at which a young woman is treated may have an influence on outcome.

I propose that screen detected DCIS or the micrometastases in the established disease are ***not*** in an active state of proliferation but in a state of dynamic equilibrium that can be perturbed by the very act of diagnosis of latent pathology or the surgery for the established disease [1]. To explain these phenomena one has to invoke the mathematics of complex systems (chaos theory) and reject simplistic notions of logarithmic or Gompertzian growth.

The accumulated evidence to support this contention was recently reviewed in *Lancet Oncology* [2].

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39 INVITED

Micrometastases in bone marrow

M. Osborne. *The Strang Cancer Prevention Clinic, New York, USA*

The majority of patients with breast cancer present with Stage I or II disease; approximately one third relapse at distant sites and subsequently die of the disease. Distant metastases occur because local-regional disease sheds tumor cells into the blood circulation. Some of these tumor cells are capable of the multistep process of establishing micrometastatic, and subsequent clinically apparent, disease. Currently the key prognostic factors predicting distant metastatic disease and survival are the maximum tumor diameter, the presence of lymph node metastases and, in lymph node negative patients, tumor histologic or nuclear grade and/or the presence of peritumoral lymphovascular invasion.

Studies carried out since the late 1970's have consistently shown bone marrow micrometastases (BMM) to be present in 25–35% of patients at the time of initial surgery [1–5]. These studies have also shown that the presence of BMM correlates with short term increased distant relapse rates and reduced survival [2–7]. The presence of BMM has, in some studies, been shown to be an independent prognostic factor [8] and, in one study, the strongest single predictor of prognosis [5]. BMM do not predict for site of relapse but appear to be a biological marker for relapse at any site.

One long-term study showed that BMM did not independently predict relapse or survival [1]. We used a different statistical model for non-proportional data and with 15 years of follow up showed that BMM was an independent prognostic factor [9]. Further long-term confirmatory studies are required to determine the value of BMM as a long-term prognostic factor. The ACOSOG Z-10 trial is currently evaluating the prognostic value of bone marrow aspiration carried out at the time of initial surgery.

Cytokeratin positive cells in the bone marrow have been shown to be rarely proliferating, based on studies using Ki-67, and there was no reduction in BMM after adjuvant chemotherapy suggesting that non-proliferating, dormant cells may not be susceptible to chemotherapy [10]. Persistence of BMM after adjuvant chemotherapy indicates a poor prognosis [11].

Bone marrow micrometastases can be detected by immunofluorescence [2], immunocytochemistry [12] and polymerase chain reaction (PCR) [13]. Sensitivity studies in a model system using immunocytochemistry have shown that one cancer cell can be detected in one million normal bone marrow cells [12]. The molecular detection of cancer cells in bone marrow can be accomplished by amplifying DNA or mRNA of malignant cells using rtPCR, which may detect one tumor cell in up to 10 million normal cells [13]. However, this technique may be overly sensitive and difficult to quantify.

In conclusion, the presence of bone marrow micrometastases is an independent prognostic indicator of early relapse and survival and may also indicate long-term prognosis. The role of sequential detection of BMM to monitor adjuvant chemotherapy needs further study. Long-term studies are required to evaluate the utility of BMM detection and the molecular features of the primary tumor associated with BMM [14].

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