Thursday, 18 March 2004 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Management of breast cancer in the elderly

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Management of breast cancer in the elderly

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Providing a good management of breast cancer for the elderly poses from many aspects important and difficult challenges. It is in many European countries already today a large quantitative problem with about 25% of all breast cancer patients being 75 years of age or older. Due to mainly demographic changes – and to a minor extent to an increase in risk – the problem will become larger in the near future with a rapidly increasing number of elderly with breast cancer up to 2020. Few national health plans have developed strategies to meet this challenge.

Despite common belief, breast cancer specific survival is not better in the elderly. On the contrary, several studies point towards a worse prognosis. The reasons for a worse breast cancer prognosis with increasing age are not clear. A more aggressive tumour biology, a less good host-defence towards malignant tumours, and diminished tolerance to treatments have been suggested as explanations. However, a low diagnostic and therapeutic activity have also been discussed as reasons; e.g. few women over 70 are offered screening. A debate is rising whether there are inappropriate selection mechanisms – such as low therapeutic activity based on age only rather than sound biological or clinical considerations – in play. One empirical underpinning to such a debate is that prognosis in breast cancer among elderly is different in different regions, even in regions geographically close to each other.

A clinical dilemma is that few trials have included women over 70. Very few have been specifically designed for elderly women. This is true for trials in primary treatment, adjuvant treatment and for treatment of recurrence – the latter being especially problematic given the worse prognosis discussed above. Thus, there is little empirical data to support rational clinical guidelines, leading to uncertainty about management of elderly and in the worst case contributing to age-biased treatment decisions. An important issue for clinical breast cancer doctors in Europe is to rapidly decide how we are going to meet these challenges.

Thursday, 18 March 2004 10:30–12:30

KEYNOTE SYMPOSIUM

The management of elderly women with breast cancer

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The local treatment of elderly women with breast cancer

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Local treatment of breast carcinoma in elderly women is becoming an important issue. The expansion of life-span, especially in women, is at the root of the increasing number of women over 70 that need a treatment of their breast carcinoma, a disease which is very common in old ages.

The main problem is that, for this group of patients, widely accepted guidelines are difficult to be formalized because the large number of variables make each case different from the others.

The main advantages of the management of breast cancer in old ages are: first that mammography regularly performed is very effective and may detect very small lesions, and secondly that the cancer cells are endocrine-dependent in a very high percentage of cases.

The main disadvantages are psychological in nature. In fact, very often the disease in old ages is accepted with fatalism and resignation. The motivations to resist and to fight the cancer are much weaker than in earlier ages. Also mutilations are badly accepted. Mastectomy is surprisingly difficult because an old woman sees this mutilation as "the beginning of the end" and as a first step to the final physical disintegration.

215 INVITED

The adjuvant treatment of elderly women with breast cancer

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Breast cancer is the most frequently diagnosed cancer in women living in industrial countries. Almost 50% of women who are diagnosed with breast cancer are >65 years old. Despite that, very few older patients have been included in clinical trials of adjuvant therapies, and few trials have been designed specifically to answer questions related to therapies for older women. One of two such trials designed and conducted during the late seventies was the IBCSG (formerly Ludwig Breast Cancer Group) Trial IV. Patients aged 66 to 80 were randomized to a tamoxifen-based endocrine therapy for one year or no further therapy after surgery for node-positive breast cancer. After 21 years median follow-up, patients who received the adjuvant treatment program had an approximately 30% reduction of chance of relapse. Disease-free and overall survival were both significantly in favor of the treatment group (p=0.003 and 0.05, respectively) despite the large proportion of patients who died without relapse (due to competing causes of mortality in old age).

Once diagnosis, surgical treatment and pathological characterization of the disease are concluded, adjuvant decision-making algorithms include:

- Estimation of risk of relapse;
- Estimation of potential endocrine responsiveness;
- Extrapolation from results of previous clinical trials conducted in populations similar to that of the individual patient and her disease characteristics (usually in younger postmenopausal women)
- Evaluation of co-morbid conditions on life;
- Assessment of patient preferences and age-related concerns, of the patient, family and care-providing team.

Progress may be made through clinical trials which answer the following questions:

- Are there easily-manageable but effective chemotherapy regimens to offer to elderly patients with endocrine non-responsive disease?
- Should chemotherapy be prescribed to women with endocrine responsive disease and at high risk of relapse?
- Are there endocrine therapies which are more suitable for elderly women than tamoxifen given for 5 years?

The tendency to extrapolate information from experience in younger patients on one hand, and to neglect offering adjuvant therapies due to older age on the other, could be avoided if specific information is obtained for elderly women with breast cancer through clinical trials.

216 INVITED

Systemic treatments for metastatic disease in elderly women: cost–benefit considerations

L. Balducci. *H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL, USA*

The systemic management of breast cancer in older women involves four setting: chemoprevention, neo-adjuvant and adjuvant treatment, and management of metastatic disease. A number of clinical trials have demonstrated that systemic treatment with tamoxifen "in lieu" of local treatment resulted in shorter freedom from progression and reduced overall survival in women aged 70 and older, and this practice has been all but abandoned. As chemoprevention has not produced yet a reduction in breast cancer-related mortality, this strategy should be considered experimental in older women. In the following discussion we will collapse together neo-adjuvant and adjuvant treatment that have similar implications in terms of cost benefits.

Adjuvant hormonal treatment of breast cancer has reduced recurrence rate and mortality to comparable rates in women under 60 and over 70, while the benefits of adjuvant chemotherapy seem to fade with age. At least two explanations, inability to administer full dose of chemotherapy and more indolent tumors, may account for the declining benefit of adjuvant chemotherapy with the patient age. Adjuvant chemotherapy appears a reasonable option for women with hormone-receptor poor tumors, and for those with lymph node involvement, especially in the presence of HER2/neu rich tumors. Patient selection should involve estimate of life-expectancy and of tolerance of treatment, while hemopoietic support with filgrastim or pegfilgrastim may allow the administration of full doses of drugs.

Management of metastatic disease involves hormonal treatment with aromatase inhibitors, Selective Estrogen Receptor Modulators (SERMs) and progestins in patients with hormone-receptor rich tumors, while the use of high dose estrogens and of androgens has been abandoned in the majority of cases. Aromatase inhibitors and the pure estrogen antagonist faslodex appear active even in HER2/neu rich tumors. Chemotherapy

may be indicated for life-prolonging treatment and symptom management in hormone-receptor poor tumors, in hormone-receptor rich tumors progressing during endocrine treatment and in the presence of life-threatening metastases, such as lymphangitic lung lesions. With the exception of life-threatening disease, single agent sequential treatment is preferable to combination chemotherapy due to lower risk of complications. Of special interest to elderly individuals are capecitabine, gemcitabine, vinorelbine, liposomal doxorubicin, weekly taxanes.

217 INVITED

Favoring empirical extrapolation from trials in younger postmenopausal women with breast cancer

Abstract not received.

218 INVITED

Favoring specific clinical research for elderly women

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Multidimensional geriatric assessment has been shown to significantly add information on elderly cancer patients to be entered in clinical trials, allowing their division into three gross categories:

1. fit patients, who may be treated as adult patients,
2. vulnerable patients, who should receive treatments adapted to their limited organ reserve and partially compromised functional status, and
3. frail patients, who are candidates to palliative cares only.

The high response rate with combination chemotherapy in advanced breast cancer is probably not worth the added toxicity in elderly vulnerable patients. No results from the usual combination chemotherapy regimens have been so far published in women older than 70 years. The preferred first step should be then that of conducting single agent phase II–III studies with the potential advantage of avoiding excessive toxicity. At progression the choice could be again that of testing a new non-crossresistant drug. The results with weekly docetaxel, weekly paclitaxel, gemcitabine and capecitabine need to be confirmed on a larger number of vulnerable patients, while vinorelbine has been already proven as an active and well tolerated drug. Another interesting anthracycline with reduced cardiotoxicity is liposomal doxorubicin, which has a good activity without excessive toxicity in adult patients with breast cancer, therefore specific studies addressed to older patients are warranted. The new monoclonal antibody trastuzumab should also be tested in old patients due to its mild toxicity, with the possible exception of cardiac effects if used with anthracyclines. No adjuvant chemotherapy regimen can be considered as standard in women older than 70 years, since the classical, but also the i.v. CMF every 3 weeks, can be administered in general only at a reduced dosage and have not been tested in the frame of controlled clinical trials specifically designed for unselected elderly patients. Retrospective studies on adjuvant chemotherapy have been showing that only a part of patients at risk are treated and in some of them adjuvant therapy has to be prematurely interrupted. The best design of clinical trials of adjuvant chemotherapy for elderly vulnerable patients could possibly compare single agents (liposomal doxorubicin, vinorelbine, capecitabine) versus no therapy.

Thursday, 18 March 2004 14:15–15:45

ROUND TABLE

Challenges for translational research

219 INVITED

Translational research – key to the understanding of clinical trials

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The landscape for cancer research is profoundly different today from that only one decade ago. Basic science is moving rapidly and biotechnological revolutions in molecular targeting, profiling and immunology have completely modified the opportunities and concepts for cancer treatment. Following this rapid evolution the concept of translational research has been developed to characterize the process linking clinical research and sound laboratory experiments which are needed to validate the hypotheses emerging from basic and pre-clinical research. Translational research in early clinical trials (Phase I and II) is an integral aspect of the development of the new generation of cancer drugs as it is necessary to implement radically different clinical trial design and to validate new biological endpoints if the full potential of these new agents is to be realized. The "proof of principle with mechanistic analysis" strategy will allow optimisation of therapy from the beginning, and provide important feedback to pre-clinical drug developers. Translational research is also essential in late (phase III) clinical trials to identify prognostic and/or predictive factors that will help defining different patient populations that may benefit to differing degrees from new treatments, and thus provide further insight and refine clinical practice in a more and more patient-tailored approach.

However, the implementation of translational research as a key component of drug development and clinical research is complex and involves patients in various ways. Thereby it imposes some new ethical, legal, logistical and management constrains. Moreover translational research may require highly sophisticated machines, specific imaging techniques, biochemistry laboratories and imposes other infrastructural prerequisites, some of which should be in the direct vicinity of the clinical trial site. The usefulness of data generated along translational research projects is highly dependent on the quality of the assays and the availability of sufficient numbers of samples to conduct valid analyses. The most common sources of tissues for research are residual surgical material and blood removed in the course of diagnosis and treatment of disease. These have the greatest potential as research tools but the real integration of translational research into a routine research agenda still face a number of challenges which relate to ethics (commercial or non commercial research, how should a patient consent, confidentiality), regulations (responsibilities, transfer of material across countries, property of material and research findings, confidentiality), logistics (collection of tissue, storage of tissue, tumor banking), scientific (defining the priorities to use the tissue) and costs (who will pay and what are the implications).

220 INVITED

Women's involvement

D. O'Connell. *Europa Donna Ireland, Dublin 6, Ireland*

At its most basic women's involvement in translational research in breast cancer comes about because of each woman's cancer and because of the scientific need for research material. The involvement presents challenges on all sides. The woman is challenged by the cancer diagnosis itself and by decisions about treatment. The request to sign a consent form, perhaps asking for consent to unspecified future research, is a further challenge. The medical team also faces a number of challenges in this process, including the obligation to ensure that the woman is making a truly informed choice (rather than consent).

Challenges for scientists and health professionals include the areas of collaboration with women in the administration and conduct of translational research, effective communication, gaining trust, working with laws and guidelines, information giving, allowing time for real decision making.

Challenges for women are to inform themselves, to value research, to communicate their views, to participate in decision making, to be prepared to active participants in the translational research process.

There are also challenges for society – to support translational research, to support clinical trials and those who take part in them, to ensure that the dignity and rights of trial participants are maintained, to legislate for the proper conduct of trials, to ensure that people (and their families) are not discriminated against on genetic grounds.

221 INVITED

Challenges of translational research: legal aspects

C. Trouet. *Pharma.be, Brussels, Belgium*

Translational research may impose the collection of tumor tissue during the investigational treatment. The increasing possibilities for using tissues for research and the developments in genetics have made stored human biological materials as well very important. We will focus on the legal and ethical problems raised by tissue banking for translational research.

Using human biological materials raises a lot of legal and ethical questions (commercialization, protection of privacy of the source, implementation of informed consent, new findings, role of research ethics committees etc.). Research with human subjects and research with personal data is covered by detailed European regulation. The research use of human biological materials however has not been regulated in a detailed manner so far. On the EU level, there is the draft European Directive on human cells and tissues, but this text covers only the therapeutic use of cells and tissues, not research use. The EU directive on the legal protection of biotechnological inventions deals with the question of informed consent for tissue retrieval in an indirect manner. On the level of the Council of Europe, the European Convention on Human Rights and Biomedicine provides for two general articles, one covering the principle of non-commerciality, the other covering the informed consent principle. A draft instrument on the research use of stored tissue is on the agenda of a specific working group of the Council of Europe.