Thursday, 23 March 2006 08:00–08:45

EUROPA DONNA TEACHING LECTURE

Translational research – what I need to understand

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Translational research: what do I need to know?

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To date, progress in breast cancer treatment primarily occurred through large clinical trials. These represent the core of clinical research and test new treatments and therapies. While these trials provide reliable information on the "average treatment effects" for similar groups of patients, they do not provide reliable information about what is best for any *individual* patient. There is increasing awareness that this traditional clinical trial strategy is neither efficient nor cost effective: it leads to the over-treatment of many patients in order to benefit just a few, and it contributes to increases in cancer drug costs that are not always justified.

Nowadays, translational research is the most promising path towards treatment individualization, and it relies on the dialogue and close collaboration between basic scientists who make laboratory discoveries and physicians who are interested in finding the best treatments for patients. Essentially, cancer is a disease of the genes, and genetic research has opened the door to our better understanding of the way cancer works. For example, it has been found that particular gene (or molecular) and patterns (also called "gene signatures") found in tumors can predict more or less aggressive disease behavior and/or the greater or lower probability of response to treatment.

Translational research must be carried out on tumor and blood samples. For patients, this implies the generosity on their part to donate a sample of their tumor and/or blood to research; for the researchers, this implies the commitment to research that is logistically complex. Tumor materials need to be adequately collected, stored, processed and analyzed; molecular patterns identified then need to be correlated with information about individual patients.

Collaborations between laboratories with different areas of expertise are essential and often depend on the "free" circulation of tumor and/or blood samples (called "biological materials") across national borders. Existing and future legislation on biological materials is likely to either facilitate or to prevent such collaboration.

New technologies are revolutionizing our ability to analyze the thousands of genes expressed in tumors, and similar progress is beginning to occur with the study of their related proteins. Because of the complexities of such analyses and their large-scale potential, close collaboration with experts in biostatistics and bioinformatics is indispensable. In this presentation, examples of such tools and their potential for contributing to treatment tailoring will be provided, including gene signatures predicting for breast cancer recurrence in untreated women or for response to endocrine or chemotherapy.

Thursday, 23 March 2006 09:00–12:45

PLENARY KEYNOTE

Detection, prevention, screening, risk assessment

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Breast cancer prevention – history and new data

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Four trials have now reported on the use of tamoxifen for the prevention of breast cancer and one trial on the use of raloxifene. Overall over 28,000 women have participated in tamoxifen prevention trials and over 140,000 women-years of follow-up have accrued. Although early reports on the ability of tamoxifen to prevent breast cancer were apparently contradictory, with further follow-up, a consensus is now emerging indicating that 30–40% of breast cancers can be prevented by tamoxifen [1]. The benefit is restricted to oestrogen receptor positive tumours where it is about 50%, but no reduction of receptor negative tumours has been found. Thromboembolic events are emerging as the most important side effects, and endometrial cancers are increased about 2-fold, although these are almost all low/intermediate grade, stage I cancers.

Raloxifene does not have the gynecologic problems of tamoxifen, but still leads to an increase in thromboembolic events. Recent data from CORE/MORE [2] suggests that this SERM may be more effective in prevention than tamoxifen.

Seven adjuvant trials have reported on the use of aromatase inhibitors for early breast cancer. All of them show a marked reduction in contralateral tumours compared to tamoxifen [3]. The drugs are also better tolerated and have fewer side effects than tamoxifen, suggesting they are very promising agents for breast cancer prevention. Two trials are currently evaluating AIs for prevention – the IBIS-II trial is comparing anastrozole to placebo, whereas the MAP3 trial is studying exemestane vs placebo. These data will be reviewed and ongoing chemoprevention trials will be discussed.

References

[1] Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S and Boyle P (2003). Overview of the main outcomes in breast cancer prevention trials. *Lancet*, **361:** 296–300.

[2] Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, Cummings SR; CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst*. 2004, **96:** 1751–61.

[3] Cuzick J (2005). Aromatase inhibitors for breast cancer prevention. *Journal of Clinical Oncology*, **23:** 1636–1643.

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Screening with magnetic resonance

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Magnetic Resonance Imaging of the breast is evolving as the new reference standard for breast imaging, and is increasingly used in clinical patient care. Until recently, breast MRI had mainly been used as "second line" imaging modality, e.g. to clarify equivocal mammographic findings, improve local staging prior to breast conserving surgery, and to monitor response to neoadjuvant chemotherapy. Today, there is increasing evidence to suggest that MRI may also be used "first line", i.e. for screening clinically asymptomatic women without mammographic or sonographic abnormalities. So far, most experiences have been made in women who carry an increased lifetime risk for breast cancer. This may be associated with a variety of conditions, e.g. with a prior tissue diagnosis of breast cancer or of a borderline lesion (ADH, LCIS); with a history of mediastinal irradiation for e.g. Hodgkin's disease, and with a familial clustering of breast and/or ovarian cancer. Cancers arising in this latter group are usually referred to as "familial" or "hereditary" breast cancers. The vast majority of data that is available on the use of MRI for screening has been accumulated in this specific subgroup of women.

The experiences that have been reported for mammographic screening in women at increased familial risk had been discouraging. The published overall sensitivity rates for mammographic screening were low. The rate of "interval cancers" – i.e. number of cancers that become clinically apparent in between screening rounds, after a normal screening examination – has been reported to be as high as 36–56%. This rate means that mammographic screening failed in more than one-third and up to half of the women who develop breast cancer. This sobering data prompted to search for other breast imaging techniques.

The first data on multi-modality screening in women at increased genetic risk had been published by our institution in 2000. These preliminary results showed already that with MRI, the sensitivity with which familial breast cancer was identified was more than doubled compared even with the combined use of mammography and breast ultrasound. Last, the data suggested that the increased sensitivity that was afforded by MRI was not achieved at the expense of specificity or PPV. Meanwhile, a number of prospective clinical cohort studies have been published that investigated the respective "cancer yield" of MRI with that of mammographic screening alone. The results of these trials are surprisingly concordant in that breast MRI offers a substantially increased sensitivity for diagnosing familial breast cancer. The data are somewhat less consistent regarding the specificity and PPV of MRI, and the role of mammographic screening. In conclusion, the current data suggest that MRI should be considered an integral part of the surveillance protocol of women at high genetic risk. The role of mammography in this specific group of women needs to be evaluated by further clinical trials.

It is important to note that the data that are available so far do not allow an outcome analysis. This is in contrast to preventive mastectomy, for which data are available that support its use as risk-reducing strategy. However