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.

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PLENARY KEYNOTE

Detection, prevention, screening, risk assessment

199 Invited

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

whether or not intensified surveillance will be effective in terms of reducing morbidity and mortality remains to be seen. This lack of evidence must be communicated to individuals at increased genetic risk, and this lack of proven outcome needs to be considered in the decision making process for appropriate management strategies in each individual case.

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Prophylactic surgery and oophorectomy in the management of high risk individuals

Abstract not received.

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Optimal genetic testing in 2006

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Genetic testing for breast cancer predisposition was greatly improved during these ten past years thanks to the identification of breast cancer predisposing genes. At the present time, 4 genes may be tested in the setting of a cancer genetic clinic: *BRCA1*, *BRCA2*, *TP53*, and *PTEN*; 3 genes may be tested, but still in a research setting: *ATM*, *CHK2*, and *STK11*. All these genes are associated with an increased risk of breast cancer through a germ-line mutation transmitted according to a dominant mode and leading to a biological inactivated protein. At the tumour level, a second mutation event has, in most cases, inactivated the second allele, leading some people to call these genes "tumour suppressor genes" (TSG). However, the *BRCA1, BRCA, and ATM* genes must be regarded as caretaker genes as there are involved in the maintenance of the genome stability rather than in the negative control of cell cycle.

Due to the high number of different mutations scattered in the coding sequence of each gene and due to the lack of information brought by a negative result at the end of a complete gene screening, two types of tests have to be considered: index case test which aim is to understand the family history by the identification of a causal mutation and thus to allow a genetic test in the relatives. The index case test needs the complete screening of the chosen genes; the test in relatives is tagged on the mutation identified in the index case. In order to be in the best situation to understand the origin of the family history and thus to identify a mutation, the index case is in general a women previously affected with breast or ovarian cancer. The indication of genetic testing and the choice of the gene to be tested rely on the personal and family history of breast cancer patients. In front of a family history of breast and/or epithelial ovarian cancer without any other phenotypic features, the *BRCA1* and *BRCA2* genes are screened.

The strategy chosen for the identification of mutations in index cases must be able to identify both point and small size mutations located in the coding sequence of the gene or at the exon-intron junctions and large gene rearrangements (partial or complete gene deletion or duplication). Indeed, at the present time, it is estimated that 10 to 20% and 5 to 10% of mutations are large rearrangements of the respectively *BRCA1* or *BRCA2* genes. We will review the different techniques that may be used for the detection of point mutations and large gene rearrangements.

One of the greatest difficulties in breast cancer genetic testing is that the number of expected mutations is unknown. At the present time, about 80% of women affected with breast cancer and tested for *BRCA1/2* gene mutation are not found to be mutation carrier. Many reasons may explain these results: lack of sensitivity of mutation detection methods, detection of gene variants of unknown significance (unknown variant, UV), test of a sporadic case in a family where a *BRCA1/2* mutation is running, test of familial aggregation occurring by chance. Conversely, women whose personal and family history does not meet genetic testing criteria may be carrier of *BRCA1/2* mutation.

Altogether, the improvement of genetic testing and the identification of a tumour signature indicating the involvement of a specific predisposing gene are urgently needed to optimise breast cancer risk estimation and thus the management of women at risk of breast cancer.

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PLENARY KEYNOTE

Local and regional treatment

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Molecular prediction of local behaviour

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In this abstract, the clinical and pathological aspects of locoregional recurrence are discussed separately for chestwall recurrence after mastectomy and for local recurrence after breast conserving treatment; followed by a discussion of genetic techniques that can be used to find additional risk factors for local recurrence.

1. Local recurrence after mastectomy.

It has been shown that risk factors for local recurrence after mastectomy include young age, the presence of lymph node metastases and large tumor size. At present, there is still heated debate on which patient subgroups should receive postoperative radiotherapy to the chestwall.

It has been shown in a number of studies that radiotherapy to the chestwall decreases the percentage of chestwall recurrences. It depends on the population of breast cancer patients what the magnitude of the benefit from radiotherapy is. For example, for some populations of breast cancer patients the chestwall recurrence rate may decrease from 10% to 5% by giving radiotherapy. This is an important improvement of local control, but goes at the cost of treating 90% of the patients with radiotherapy without providing benefit. At present, there are no molecular markers of local recurrence after mastectomy. At present, a prospective clinical trial (termed the SUPREMO trial) is being started, in which patients after mastectomy will be randomised between radiotherapy and no radiotherapy to the chestwall. The collection of tumor tissue for genetic testing will be part of the trial; this will provide the possibility to identify risk factors for local recurrence after mastectomy; and identify subgroups of patients that will benefit from radiotherapy after mastectomy.

2. Local recurrence after breast conserving therapy.

Nowadays, 60–70% of patients undergo breast-conserving therapy. As the status of the resection margins is a very important factor determining risk of local recurrence, optimal work up of surgical specimens is extremely important.

It has also been shown that an extensive component of intraductal carcinoma (EIC) which has been incompletely excised, is an important risk factor for local recurrence after breast conserving therapy. For this reason the ductal carcinoma in situ (DCIS) component in and around the tumour should be assessed.

The reason that EIC is a risk factor for local recurrence is that a large amount of DCIS may be left behind in the breast after excision in some patients. For this reason, the most important task for the pathologist in this respect is to estimate the likelihood that a large amount of DCIS is left behind in the breast.

In most published series, only poorly differentiated DCIS has been evaluated as a risk factor for local recurrence. Much less is known about residual well differentiated DCIS left behind in the breast; it is likely that also an extensive component of well differentiated DCIS is a risk factor for local recurrence, but after a much longer interval.

Lobular carcinoma in situ (LCIS) adjacent to invasive disease has not been associated with an increased risk of local recurrence.

When the margins are free or only focally involved, young age is the most important risk factor for local recurrence. We have previously found that patients younger than 40 years of age have a 6-fold increased risk of local recurrence compared to patients older than 60 years. For this reason, our research to identify risk factors for local recurrence is mostly aimed at patients younger than 50 years.

3. Genetic techniques to predict local recurrence.

For the treatment of breast cancer, especially the choice of adjuvant systemic treatment, determining oestrogen receptor status, progesterone receptor status and HER2 status is extremely important.

In the past 20 years, much research has been devoted to identity prognostic and predictive factors, especially to guide adjuvant systemic therapy.

All this research has resulted in thousands of scientific papers, but only recently, some of these assays are starting to be used in day-to-day clinical decision-making, mainly in the form of incorporation of these assays into clinical trails. It is to be expected that in the coming years the process of bringing this knowledge from scientific research into the clinic will be proceeding at a higher speed than we have seen in the past 20 years.