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The contribution of radiotherapy to breast conservation

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Breast-conserving therapy has clearly become the preferred loco-regional approach for the majority of breast cancer patients in West European countries, where early-stage presentation is the rule and access to radiotherapy is relatively easy. This privileged position is undoubtedly the consequence of unequivocal findings from certain key randomised clinical trials, all of which are well known. However, it is also quite clear (and sometimes forgotten) that breast conservation was not *invented* by clinical trialists. Breast-conserving techniques had been practiced with some success on a limited scale since the 1930s, based upon the known effectiveness of radiotherapy (RT) in the treatment of breast cancer. With the introduction of cobalt machines treatment of operable breast cancer by radical RT doses became technically feasible, often associated with "excisional biopsy" for debulking of macroscopic disease ("primary RT"). Local control and survival associated with these techniques seemed satisfactory, but widespread acceptance of breast conservation awaited publication of the NSABP Trial B-06 in 1985. The trials not only proved the equivalence of breast-conserving and ablative approaches, but they introduced new rigor into the practice of conservation surgery. As a consequence surgery came to be considered the primary treatment, with RT relegated to an adjuvant role. However, even with optimal surgical quality local recurrence rates in unselected patients remain unacceptable in the absence of breast irradiation. Fractionated whole-breast RT (50 Gy/25 fractions) remains the standard, resulting in a reduction of local failure by a factor of about 3–4. A localised boost has been demonstrated to further improve local control in the reference quadrant, where most local failures occur. Analysis of clinical trial data suggests that breast RT not only increases local control, but also improves long-term breast preservation rates and reduces the risk of uncontrolled local disease, metastasis, and breast cancer mortality. This lecture will discuss three key research questions: Can more convenient dose-fractionation schedules be advocated? What are the respective roles of RT limited to the tumour-bearing area compared with whole-breast RT? For which patients might conservative surgery without RT be safely proposed?

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Breast conserving surgery: the contribution of neoadjuvant treatment

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Neoadjuvant treatment was successfully applied in the 70, mainly with chemotherapy for advanced and inflammatory breast cancers. Without any randomised trial, it became obvious that primary chemotherapy allowed for local treatment in good carcinologic conditions and was able to improve outcome of such poor prognostic tumors. In the 80, the concept of neo-adjuvant chemotherapy was applied to operable tumors whose size was too big to be treated with initial conserving surgery. Several phase II studies were conducted before phases III trials were able to respond the questions raised:

- survival is neither improved nor worsened by neoadjuvant chemotherapy in comparison with adjuvant chemotherapy;
- breast conserving surgery can be obtained more than one out of two whereas mastectomy would have been the optimal classical treatment;
- the third initial objective to test chemosensitivity is still in the research fields.

The present/future of neoadjuvant treatment has to go to several ways:

- to improve the means to increase breast conservation by use of non cross resistant chemotherapeutic regimens (anthracycline-taxanes) or of new compounds directed against specific molecular markers;
- to test predictive factors of response to neoadjuvant chemo- or endocrine therapy;
- to use surrogate markers, such as obtention of pathological tumor response, to assess efficiency of treatment regimens and to evaluate accuracy of disease response monitoring (MRI, pet-scan);
- to use imaging of expression of particular gene products to direct biologically targeted therapy.

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Saving the breast: an important motivation for women in favour of early detection

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Since the dawn of civilisation, women have believed that breast cancer is synonymous with disfigurement, disability and death. Right up to the mid-1970s, having breast cancer was incomparably more traumatic and devastating an experience than it is today. Faced with the threat to her survival, the standard treatment required the removal of a woman's breast, usually to the extent of a Halstead radical mastectomy. Adjuvant therapies were crude and damaging. The patient suffered the mutilation of her body and bore the stigma of having the disease; she feared rejection by her partner, friends and even her family. She saw herself as deformed, stripped of her femininity and therefore sexually unattractive and an individual of less worth.

Into that society, where few people even mentioned the word 'cancer' and not too many felt comfortable about uttering the word 'breast', prominent American women such as Betty Ford and Happy Rockefeller revealed their diagnoses and extent of their surgery to the world. The effect of such disclosures was revolutionary. Regardless of social status, women everywhere realised their vulnerability to a disease that was normally mentioned only in whispers. On the other hand, they saw for the first time the positive role model of women with breast cancer – women who were alive, looked well and functioned normally in society.

Ford, Rockefeller and one or two other contemporaries had sown the seeds of breast cancer awareness; their personal courage opened the way towards public understanding of the scale of the disease and its impact.

Coincidentally, those historical disclosures occurred during a period of great social, technological and scientific progress. Of specific importance was a) the development of mammography, b) the ground-breaking technique of breast conserving surgery and c) the introduction of Tamoxifen. These advances formed three cornerstones of modern breast cancer management. They also provided the necessary stimulus for powerful public education campaigns to be developed with the aim of dispelling the myths and misconceptions and of promoting the importance of early detection and diagnosis.

This presentation will discuss the contribution made by advances in breast surgery towards motivating early detection, influencing survival and enhancing quality of life.

Friday, 19 March 2004 14:15–15:45

SYMPOSIUM

Optimal management of the patient with an HER2 overexpressing tumour

345 INVITED

Challenges in assessing overexpression

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Targeted biologic therapies offer new treatment options for patients with breast cancer but also present therapeutic challenges: patient selection and screening strategies, appropriate use and duration of treatment, and integration with other therapeutic agents. These issues will be examined as they pertain to treatment of metastatic breast cancer (MBC) with HER2-targeted monoclonal antibodies (trastuzumab and rhuMAB2C4), and with small molecule inhibitors targeting epidermal growth factor receptor (HER1/EGFR; erlotinib and gefitinib, or anti-HER1/EGFR antibodies (cetuximab and ABX-EGF).

Trastuzumab has shown the greatest clinical efficacy, including survival benefit, in MBC patients that have the highest HER2 levels, defined by a immunohistochemistry [IHC] score of 3+, or HER2 gene amplification as determined by fluorescence in situ hybridization [FISH]. Recent data from two large adjuvant trials demonstrate a poor correlation between IHC analysis performed within clinics compared to IHC or FISH done in central laboratories. In the adjuvant NSABP-B31 study, an 18% of the community-based assays, could not be confirmed by HercepTest IHC or FISH by a central testing facility. Likewise, a poor concordance (74%) between local and central testing for HER2 status was observed in the N9831 study. This two report provides a snapshot of the quality of HER2 assays performed in laboratories nationwide. Positive FISH status correlates with improved survival of MBC patients receiving trastuzumab. Additionally, FISH is generally more reproducible than IHC in assessing HER2 status. For biologics directed at HER1/EGFR, including gefitinib, erlonitib and cetuximab there does not appear to be a direct relationship between expression levels and efficacy, although HER1/EGFR levels have been reported to have prognostic value. Other aspects of HER1/EGFR -related proliferative activity may provide more direct correlation with clinical efficacy, such as levels of ligand involved in autocrine-loop stimulation, or levels of phosphorylation of HER1/EGFR or downstream molecules. The activity of rhuMAB2C4, which prevents dimerization of HER2 with HER1/EGFR and other HER family molecules and the resulting proliferation signaling,

is not dependent on HER2 overexpression. rhuMAB2C4 may therefore be effective in patients with intermediate or low levels of HER2 expression.

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Optimal primary treatment of patients with an HER2 overexpressing tumour

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HER2 overexpressing breast cancer (BC) is an aggressive disease that can be differentiated from other breast tumours (BT) by a distinct pattern of gene expression: it requires proper identification in the clinic (currently through HER2 immunohistochemistry ± FISH), and new thinking in terms of 'optimal' management.

Trastuzumab (Herceptin™) has already made a dramatic impact on the outcome of women who relapse with this disease, and ongoing trials are refining its use in advanced BC. However, the greatest therapeutic advances are expected to come from the appropriate use of trastuzumab in the adjuvant setting.

Currently, five trials are investigating adjuvant trastuzumab treatment, with a total foreseen accrual of 13.000 patients. Their status is summarized in Table 1. The questions to be answered are whether the addition of trastuzumab to chemotherapy or their sequential use provides an additional benefit for early BC patients with tumours overexpressing HER2. In all the trials, patients with endocrine responsive tumours receive 5 years of adjuvant hormonal treatment, and radiotherapy is administered according to institutional policy. Overall survival, disease free survival and cardiac toxicity are their main end points. As the risk of cardiac failure with this therapy is a source of major concern, all the studies have well defined cardiac endpoints, with interim safety analyses planned to ensure that the rate of cardiac failure does not reach an unacceptable threshold, defined as an absolute 4% excess in comparison to the control arm.

Conclusions: The large and comprehensive adjuvant program of trastuzumab should provide important information about the benefits/risks associated with the use of this agent in HER2 overexpressing BC in 2006–2007.

Table 1

Trial (expected accrual)	Nodal status	Arm 1	Arm 2	Arm 3	TRA sched.	Duration of therapy	TRA and RT
NSABP B-31 (2700)	+ve	AC×4 → P×4	AC×4 → P×4 + TRA	N/A	Weekly	1 year	Concurrent
NCCTG N9831 (3000)	+ve	AC×4 → P×4	AC×4 → P×4 + TRA starting concurrently with P	AC×4 → P×4+ TRA starting after P	Weekly	1 year	Concurrent or sequential
BCIRG 006 (3150)	+ve or high-risk −ve	AC×4 → D×4	AC×4 → D×4 + TRA starting concurrently with P	D + CDDP or CBDP×4 + TRA	Weekly with chemo, then every 3 wks	1 year	Concurrent
BIG 01–01 (4400)	Any[a]	CT alone	TRA 1 yr after CT	TRA 2 yrs after CT	Every 3 wks	1 or 2 years	Sequential
FNCLCC 04/0005 (400, 2nd rd)	+ve	CT alone FEC vs. DE	TRA after CT	N/A	Every 3 wks	1 year	Sequential

[a]Small (<1cm) node negative tumours not eligible.

Abbreviations: TRA, Trastuzumab; CT, chemotherapy; AC, Doxorubicin + Cyclophosphamide; FEC, 5 Fluorouracil, Epirubicin and Cyclophosphamide; P, Paclitaxel; D, Docetaxel; CDDP, Cisplatin; CBDP, Carboplatin; rd, randomization; N/A, not applicable.

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Advanced disease setting

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Women with HER2-overexpressing breast cancer are patients with distinct prognosis, distinct patterns of sensitivity and resistance to conventional drugs, and specific indication for therapy with trastuzumab. The observation that a survival advantage persists for women who received trastuzumab with chemotherapy in the pivotal randomized study even though 75% of women in the control arm received the antibody at progression suggests that trastuzumab should be applied as early as possible. As for optimal application of trastuzumab, monotherapy is endowed of favorable therapeutic effects. However, it was never tested in a randomized study against combinations with chemotherapy, so that its adoption is left to considerations of clinical opportunity, patient's decision and doctor's opinion. Several cytotoxic drugs have been tested with trastuzumab in Phase II trials, and in few randomized studies showing superiority of including trastuzumab with anthracyclines and taxanes. More recently, trastuzumab with carboplatin and paclitaxel proved better than with paclitaxel alone, and initial findings suggest that weekly-scheduling of carboplatin and paclitaxel with trastuzumab are better tolerated and possibly more efficacious than three-weekly. In summary, availability of trastuzumab has changed the approach to patients with HER2-overexpressing advanced disease. Optimal management of these patients should strongly consider using trastuzumab with chemotherapy, a field in which non-anthracycline containing regimens, such as with carboplatin and paclitaxel, are a very promising therapeutic option. Monotherapy is an alternative lacking the support of randomized trials to rule out that its application is sub-optimal. In women receiving monotherapy and progressing, the addition of chemotherapy to trastuzumab should be considered to exploit possible synergisms. Finally, patients with HER2-overexpressing tumors and positive estrogen receptor status represent a special case. Resistance to and less than optimal benefit from tamoxifen can be expected in these women, while aromatase inhibitors may be less affected. Preclinical evidence suggests that a HER2-targeting can positively modulate the effects of hormonal treatment. Although trials of trastuzumab and endocrine therapy are still ongoing, such combinations deserve special attention for their possible long-term applicability at cost of expected good tolerability. The results of such trials, together with an improved ability of predicting sensitivity to trastuzumab, and the characterization of newer HER2-targeting drugs will contribute to further refining the optimal approach to therapy of women with advanced breast cancer overexpressing HER2.

Friday, 19 March 2004 14:15–15:45

SYMPOSIUM

Clinical pharmacogenomics in breast cancer

348 INVITED

Micro arrays and the need for chemotherapy

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Microarray gene expression profiling combined with advanced bioinformatics is beginning to show its power in delineating disease entities that are otherwise indistinguishable. This refinement in tumor classification allows a more accurate prediction of outcome of disease for patients that present with the same stage of disease based on conventional clinical and histopathological criteria. Gene activities determining the biological behaviour of the tumor may indeed be more likely to reflect the aggressiveness of the tumor than general parameters like tumor size, age of the patient, or even tumor grade. Therefore, the immediate clinical consequences are that treatment schemes can be tailored based on the gene activity patterns of the primary tumor.

Using gene expression profiling with cDNA microarrays, Perou et al. showed that there are several subgroups of breast cancer patients based on unsupervised cluster analysis: those of "basal type" and those of "luminal type". These subgroups differ with respect to outcome of disease in patients with locally advanced breast cancer. In addition, microarray analysis has been used to identify diagnostic categories, e.g., BRCA1 and 2; estrogen receptor status.

We used gene expression profiling with DNA microarrays harboring 25,000 genes on 78 primary breast cancers of young lymph node negative patients to establish a signature, predictive for a short interval to distant metastases. This 'poor prognosis' signature consists of genes involved in cell cycle, invasion and angiogenesis. The prognosis signature is superior to currently available clinical and histo-pathological prognostic factors in predicting a short interval to distant metastases (OR=18 (95% CI 3.3–94), p<0.001, multivariate analysis). We have validated our findings of this poor prognosis profile on a large unselected consecutive series of LN0 as well as LN+ (lymph node positive) young breast cancer patients (n=295). The analyses confirm that the profile is a strong independent factor in predicting outcome of disease for LN0 patients in general. Furthermore, the profile is also powerful for LN+ patients. At present, the prognostic significance of the 70 genes is tested in older age breast cancer patients.

Nowadays, consensus guidelines in the management of breast cancer select up to 95% of lymph node negative young breast cancer patients for adjuvant systemic therapy (e.g., NIH and St Gallen consensus criteria). As 70–80% of these patients would have remained disease-free without this adjuvant treatment, these patients are 'overtreated'. The 'poor prognosis' signature provides a novel strategy to accurately select patients who would benefit from adjuvant systemic therapy and can greatly reduce the number of patients that receive unnecessary treatment.

Our data revealed that already small tumors display the metastatic signature and recent results show that the molecular program established