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

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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

in a primary breast carcinoma is highly preserved in its distant metastasis. These findings suggest that metastatic capability in breast cancer is an inherent feature, and is not based on clonal selections. The results further imply that neo-adjuvant treatment given to patients based on (yet to be established) response expression profiles of their primary breast tumor might indeed prevent the outgrowth of micrometastases.

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Pharmacogenetics and genomics – prognostication and prediction: where is the future?

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Development of analytical methods as cDNA micro arrays and proteomics provides new opportunities with respect to studying cancer biology and development, early detection as well as prognostication and prediction of treatment sensitivity. Interesting findings are emerging from studies applying cDNA micro arrays to different tumour forms. Despite a substantial heterogeneity in gene expression between individual tumours [1], differences between tumours forms have been revealed [2]. Studies on breast cancer [1] and other tumours have shown that within each cancer form, individual tumours may be grouped into classes based on their gene expression profile. The identification of a subgroup of tumours expressing "basal-cell"-like characteristics, in contrast to the more common "luminal-cell" profile, has suggested a different cellular origin for tumours of the different classes [1]. Moreover, classifications based on gene expression profiles have been shown to be of prognostic value in a diversity of cancer forms [3–8]. Further, micro-array techniques have been successfully applied to in vitro experiments, exploring multiple gene activation in relation to events like restoration of p53 function [9], but also exploring mechanisms of drug resistance [10]. Contrary, only a few studies have so far evaluated use of micro arrays as tools exploring chemoresistance in vivo. These studies have involved a limited number of patients only [11,12]. While correlations between gene expression profiling and therapy response has been found, clearly the predictive value of these gene profiles need to be confirmed in larger studies. Further, these preliminary data do not suggest a predictive accurateness sufficient for therapeutic use. While the studies so far have applied different forms of global gene expression analysis, future studies may incorporate biological hypotheses, analysing expression of groups of genes known to be involved in a functional pathway.

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Combining proteomics and genomics for cancer analysis

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In the *Division of Functional Genome Analysis*, we are developing technologies for the identification, description and evaluation of cellular functions and their regulation by producing and processing biological information on a genomic scale. One emphasis in our efforts is work on DNA-, protein- and peptide-microarrays. Many chemical and biophysical issues are being addressed as part of this work in an attempt to understand the underlying procedural aspects, thereby eventually establishing superior analysis procedures. Based on the technical advances, the resulting methods are immediately put to the test in relevant, biologically driven studies on various organisms.

Concerning the analysis of human material, systems are being developed toward early diagnosis, prognosis and evaluation of the success of disease treatment with accentuation on cancer. Beside other applications, analyses are performed on the detection and use of disease-relevant polymorphisms in the area of molecular epidemiology. Also, comparative studies on epigenetic variations, transcript levels and actual protein expression by means of complex DNA- and antibody microarrays are under way. Early diagnosis from blood samples is being worked at that is based on the binding of serum components to peptide microarrays. Combining this data with clinical information permits the definition of sub-groups within an analysed cohort and eventually a means for diagnosis and prognosis as well as the identification of highly relevant targets.

(www.dkfz.de/funct_genome)

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SYMPOSIUM

Late sequelae of breast cancer treatment, are they preventable?

351 INVITED

Cognitive functions after chemotherapy

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Currently, the interest in cognitive functioning following chemotherapy is rapidly expanding, as is reflected in a growing number of published articles on this topic. Although most studies are indicative of cognitive deficits after chemotherapy in at least a subset of patients, little is known about the pattern of cognitive deficits, the course of the deficits over time and the impact of deficits on daily-life situations. Moreover, a number of important confounding factors still exists and potential mechanisms by which chemotherapy can adversely affect the brain are insufficiently understood.

In 1998, a large prospective longitudinal neuropsychological study was started in the Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital. In this study, several groups of breast cancer patients adjuvantly treated with cytotoxic agents (including high-dose CTC chemotherapy and standard dose FEC and CMF chemotherapy) were tested neuropsychologically at three points in time: at baseline (i.e. after surgery and prior to the start of chemotherapy) at 6 months and at 12 months after completion of treatment. Patients treated with chemotherapy were compared with stage I breast cancer patients not treated with chemotherapy and with healthy controls, tested at similar points in time. At each assessment point patients and controls were additionally interviewed with regard to cognitive problems experienced in daily life, psychological distress and fatigue. In co-operation with 15 hospitals in the Netherlands, approximately 400 breast cancer patients were tested.

We will present the first data of this study, and results will be related to the above-mentioned gaps in current knowledge.

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Surgery

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Since Halsted time, the surgical treatment of breast cancer has dramatically changed. The extent of demolitive operations has progressively reduced with a positive impact on the rate of complications and on the quality of patients life. Conservative surgery has allowed to achieve good cosmetic results with the same survival and without increase in local recurrence. Unfortunately a percentage of sequelae after surgery for breast cancer is still present. The most severe complication is lymphoedema of the operated arm. This is secondary to axillary dissection and normally causes functional impairment and psychological morbidity. The risk to develop lymphoedema is approximatively 25% with a great range in literature; the rate can raise if radiotherapy is associated. Once that lymphoedema is occurred, its treatment is very difficult with poor results and improvements. Manual lymphatic drainage is helpful for the initial phase and is pleasant for patients but requires specialized staff and high costs. Elastic bandage produces differentiated pressures on the arm decreasing from wrist towards shoulder. They have to be weared during activities or at rest. No importance was seen for treatment with drugs like anti-inflammatory, antihistamines and diuretics. 60–70% of patients with lymphoedema are overweight and maybe diet can play a role in the etiology of this complication. Neural "Stupor" of the brachial plexus is present in about 1% of cases and is due to an incorrect position during the operation. The patient has difficulty to move the arm in