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

M.J. Piccart, G. Demonty, L. Dal Lago, S. Dolci, C. Straehle. *Institute Jules Bordet, Brussels, Belgium*

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

L. Gianni. *Instituto Nazionale Tumori, Division of Medical Oncology A, Milan, Italy*

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

L.J. van 't Veer. *The Netherlands Cancer Institute, Department of Pathology, Amsterdam, The Netherlands*

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