improvement and strategies are being implemented to change this picture. A large national breast cancer project is being planned and soon will incorporate screening mammography after the age of 50.

The increasing costs associated with treatment add to the burden of dealing with breast cancer in Brazil. Currently, breast cancer represents approximately 1/4 of the Government costs with systemic treatment (chemotherapy and hormonal therapy) in cancer.

In summary, breast cancer incidence and mortality are increasing in Brazil. During the next decade, the main challenge will be the development of a coherent strategy for its management based on detection at an earlier stage.

Thursday, 18 March 2004 16:00–17:15

PROFFERED PAPERS

Advanced disease

237 ORAL

Gene expression profiles of primary breast tumors maintained in lymph node- and distant metastases

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Background: Metastases at distant sites are the main cause of death in breast cancer. It is largely unknown whether the characteristics of breast cancer that define the growth rate and therapy response of the primary tumor are alike in the metastases. Furthermore, it is still unclear whether metastases derive from highly metastatic subpopulations of tumor cells within the primary site, or whether they originate from a random fraction of tumor cells. To test this, we compared pairs of human primary breast carcinomas and their lymph node metastases as well as primary breast tumors and their metastases developed years later at distant sites, both by gene-expression profiling.

Patients and methods: Surgical specimens of primary breast tumors and their matching lymph node metastasis of 15 patients, and specimens of primary breast carcinomas and their matching distant metastasis from different localizations of eight patients were collected from the frozen tissue bank of our hospital. RNA from these tissues was isolated, DNase treated and cRNA was generated using T7 RNA polymerase. Fluorescently labeled cDNAs were hybridized to an 18k human microarray (Central Microarray Facility, Netherlands Cancer Institute). Intensities of scanned images were quantified, normalized and ratios were calculated and compared to the intensities of a reference pool. Gene clustering and tumor clustering were performed using an unsupervised hierarchical clustering algorithm (Pearson correlation coefficient).

Results: We show, by gene-expression profiling, that human primary breast tumors are strikingly similar to their regional lymph node metastases as well as to their distant metastases of the same patient. Unsupervised hierarchical clustering, multidimensional scaling, permutation testing, as well as the comparison of significantly expressed genes within a pair, reveals their genetic similarity.

Conclusions: Our results show that the molecular program established in a primary breast carcinoma is not only highly preserved in its regional lymph node metastasis but also 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 the response expression profiles of their primary breast tumor might also prevent the outgrowth of micrometastases.

238 ORAL

The clinical and prognostic implications of isolated supraclavicular fossa recurrence

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Introduction: In 2003, AJCC changed the classification of breast supraclavicular fossa (SCF) node metastasis. This is now classified as stage 3C. We have reviewed our experience in the light of these changes.

Methods: Review of case notes and database of 8691 patients with a diagnosis of breast cancer and either isolated ipsilateral or contralateral SCF metastasis. All patients had completed treatment for primary breast cancer and had no previous evidence of metastatic disease. Patients diagnosed with metastatic disease at other sites either at the time of SCF recurrence or within the next three months were excluded.

Results: There were 125 cases of ipsilateral (I-L) SCF recurrence (SCFR) and 22 separate cases of contra-lateral (C-L) disease. The median time from primary diagnosis to SCFR was 1.92 yrs for I-L disease and 3.32 years for C-L (p=0.0229). Patients had originally presented with node positive cancer in 79% of cases (I-L 80%, C-L 73%, p=0.58) and locally advanced disease in 9.5% (I-L 8.8%, C-L 13.6%, p=0.75). 57% were primary invasive ductal carcinomas, 3% infiltrating lobular carcinomas and 40% other types. At diagnosis 2.5% were grade 1, 46% grade II and 52% grade III. There was no significant difference in tumour type or grade between I-L and C-L. Treatment for SCF recurrence comprised combinations of chemo and hormonal and radiotherapy. Median time to first relapse after SCF recurrence was 11 months. Sites of first relapse were lung in 16%, pleura 9%, bone 8%, liver 10%, skin 7%, brain 3%, mediastinum in 3%, ascites in 2%, local breast recurrence in 31%, and other mets in 18%. The median time from SCF recurrence to death not significantly different between C-L (1.89 yrs) and I-L (2.63 yrs, p=0.184) recurrence. There were no patients who did not eventually die from their disease (survival = 0%), but 15% were still alive at 5 yrs (3/22 C-L and 19/125 I-L), and 3.4% at 10 years (0/22 C-L and 5/125 I-L). Median survival was 25 months for chemotherapy alone (12.2%), 28.3 months for those treated with combined RT and systemic (hormonal and/or chemotherapy) and 40.6 months for hormonal therapy (21.1%).

Conclusion: This is the largest published series of SCF recurrence. It demonstrates that SCF recurrence is associated with subsequent systemic metastases and eventual death in 100% of cases. I-L disease is diagnosed at an earlier stage than C-L, but both have a similarly poor prognosis. SCF recurrence might be better regarded as stage IV disease.

239 ORAL

Trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone as first-line treatment of HER2-positive metastatic breast cancer (MBC): results of a randomised multicentre trial

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Background: The H0648g trial showed a significant survival benefit for Herceptin (H) plus paclitaxel compared with paclitaxel alone, and as a result the combination is licensed for the treatment of HER2-positive MBC as first-line therapy. Phase II studies have shown that the combination of Herceptin plus docetaxel (HD) is also active in patients with HER2-positive MBC. A large, multicentre randomised trial (M77001) was conducted to compare HD versus docetaxel alone (D) as first-line therapy in HER2-positive MBC.

Patients and methods: 188 patients (pts) with HER2-positive MBC and at least one measurable lesion were randomised to either HD or D given as first-line treatment. Two pts in the HD arm received no study treatment and were excluded from analysis. Ninety-five percent of pts had IHC 3+ and/or FISH-positive disease. Herceptin dosing was 4 mg/kg iv (loading) followed by 2 mg/kg weekly until disease progression, and docetaxel 100 mg/m^2 iv q3w $\times$ 6 cycles. Patients progressing on D alone were allowed to cross over to receive H. Response was assessed according to WHO criteria and radiologically confirmed by an independent review board. Patient demographics were generally balanced between the arms, although more D than HD pts were hormone-receptor positive (56% v 41%), and more HD than D patients had received adjuvant anthracyclines (64% v 55%).

Results: At 12 months after last pt enrolment, efficacy in the HD arm was significantly better than in the D arm: overall response rate 61% v 34% (p=0.0002); median time to progression 10.6 v 5.7 months (mo) (p=0.0001); median duration of response 11.4 v 5.1 mo (p=0.0011). Survival was significantly superior for HD (p=0.0062) (median overall survival 30.5 mo in the HD arm v 22.1 mo in the D arm), despite at least 48% of pts in the D arm crossing over to receive H. Pts who crossed over from D to receive H had a longer estimated median survival (24.5 mo) than those who did not cross over (19.1 mo). Grade 3/4 non-haematological toxicity was similar in the two arms. The incidence of febrile neutropenia was slightly higher in the HD arm (23%) than the D arm (17%) but was generally manageable; two septic deaths occurred in the D arm. Symptomatic heart failure occurred in 2 pts in the HD arm (2%), but both cases were in the

context of progressive disease and, in one case, the pt had subsequently received an investigational anthracycline.

Conclusion: The addition of Herceptin to docetaxel significantly improved response rate, duration of response, time to progression and overall survival, with little exacerbation of toxicity.

240 ORAL

Intermittent/alternated therapy with tamoxifen and medroxyprogesterone acetate prolongs time to resistance to tamoxifen without benefit for (progression free) survival in patients with advanced breast cancer. Results of an EORTC phase III study (trial 10863)

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Introduction: Patients with advanced breast- or prostate cancer, who relapse after stopping endocrine treatment during response may have repeated remissions when the same treatment is given again. In this study results of intermittent tamoxifen (T) or intermittent T alternated with medroxyprogesterone acetate (MPA) during response were evaluated.

Patients and methods: Postmenopausal patients with possible hormone responsive advanced breast cancer who had an objective remission or stable disease after 4 months of first line T therapy were randomised to continue T (40 mg daily) or to intermittent T (2 months break, two months treatment etc.) or intermittent/alternated T and MPA (300 mg daily). If progression occurred during break or during MPA, patients received T continuously. Endpoints of the study were proven resistance to T and (progression free) survival.

Results: As reported earlier [1], and after a median follow-up time of 8 years the median time to resistance to tamoxifen in 276 randomised patients were 12.2, 12.4 and 23.3 months for T, intermittent T and T/MPA respectively. The difference between T and T/MPA was statistically significant ($p<0.001$). After reinstitution of T in patients who relapsed during break or MPA, only 30% achieved stable disease. The median survival times did not differ significantly (36.1, 36.1 and 32.1 months respectively). Although data about subsequent therapy after resistance to tamoxifen are missing, it is plausible that a considerable number of patients from the T and intermittent T arms received MPA or another endocrine modality explaining that survival times in the tree arms were about equal.

Conclusion: It appears that the longer time to resistance to tamoxifen (or endocrine treatment in general?) in the T/MPA group but not in the intermittent T group is predominantly a consequence of the non cross resistant character of this modality and not of the intermittent administration of the therapy.

References

[1] L. Beex et al. Continuous vs. intermittent tamoxifen versus intermittent/alternated T and medroxyprogesterone acetate in advanced breast cancer. An EORTC phase III study. Breast Cancer Res Treat 2002; 76: S72. Abstr. 252.

241 ORAL

First results of a randomized phase III trial comparing exemestane versus tamoxifen as first-line hormone therapy (HT) for postmenopausal women with metastatic breast cancer (MBC) – EORTC 10951 in collaboration with the exemestane working group and NCIC Clinical Trials Group

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Introduction: Over the last three decades, the antiestrogen Tamoxifen (T) remained the standard first-line HT in postmenopausal women with hormone-responsive MBC. Recent data from randomized phase III trials indicated however that third generation non steroidal aromatase inhibitors (AI) like Anastrazole and Letrozole may be as efficient, or even more active, with a different toxicity profile, than Tamoxifen. Exemestane (E) is another third generation AI, which is in fact the sole displaying a steroidal structure. Interestingly, it permanently inactivates the aromatase and is devoid of total cross-resistance with NSAI. Because of this, and in view of its demonstrated activity against MBC progressing after 1st- or 2nd-line HT, the EORTC Breast Group initiated in 1996 a randomized phase II–III clinical trial aiming at comparing the efficacy and safety of E versus T.

Methods: Patients with measurable disease were eligible if they had received no prior hormone therapy for MBC and had either an hormone receptor positive status, or an unknown status with a long disease-free interval. They were randomized to T 20 mg/day or E 25 mg/day in this open-label study. The primary endpoints of the phase II and III were respectively activity (Response Rate – RR) and efficacy (Progression Free Survival – PFS). The phase III trial aimed at identifying a median PFS increase of 3 months (i.e. from 7 to 10 month) in favor of E. Safety was a secondary endpoint for each step.

Results: Between 10/1996 and 07/2002, 382 patients were randomized by 81 institutions from 25 different countries. The results of the initial phase II part of the study, which accrued 122 patients, showed a promising overall RR, clinical benefit rate and response duration in favor of E. The incidence of serious toxicity was low and E was well tolerated; moreover, no adverse effects on the lipid profile were observed, at variance with observations made on NSAI. All conditions were fulfilled to continue with a randomized phase III trial (Paridaens et al., Ann. Oncol, 14, 1391–8, 2003). Presently, 284 (74%) patients have either progressed or died.

Conclusions: The number of events needed to perform the primary efficacy analysis has recently been reached and the data base is in its final stage of cleaning. A full (efficacy and safety) report of the results of this trial will be presented at the meeting.

242 POSTER HIGHLIGHT

Staging in patients with locoregionally recurrent breast cancer: current practice and perspectives for PET

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Background: At least 20% of patients with locoregionally recurrent (LRR) breast cancer develop distant metastases within 18 months after diagnosis and salvage treatment of the recurrence. The yield of the current staging procedures among asymptomatic patients with an early stage of primary breast cancer is low. Since 1997 new diagnostic modalities such as 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) have emerged with promising results as a highly sensitive and accurate method for restaging patients with suspected breast cancer recurrence. However, one of the first steps in the assessment of new and expensive technology is to obtain adequate knowledge of the efficiency of current clinical practice without the new test.

Objective: The aim was to obtain representative data on the extent and yield of daily clinical practice when staging patients with a LRR of breast carcinoma and to discuss the perspectives for PET.

Methods: We used the population-based Eindhoven Cancer Registry to select all breast cancer patients in the southeast of the Netherlands with a first episode of LRR between January 1, 1994 and June 30, 2000. Additional data were collected from medical records at the departments of surgery and internal medicine. Furthermore, we asked all physicians responsible for treatment of LRR about their opinions on staging procedures and actual treatment policy.

Results: Medical records showed that clinicians used a relatively homogeneous set of routinely applied screening tests, which was confirmed by the outcome of the questionnaire. At LRR presentation, 16% of patients were found to have distant metastases. Patients with diagnosed distant metastases were less likely to undergo locoregional surgery and more often received systemic treatment than patients without distant metastases after staging. Within 18 months, an additional 24% of the patients proved to have clinically overt distant metastases. The questionnaire revealed that 44% of clinicians were not satisfied with the yield of the conventional imaging techniques; 33% indicated that the sensitivity was too low.

Conclusion: Current staging procedures detected only 40% of distant metastases in patients with LRR breast cancer (based on 18 months of follow-up). This result is in accordance with the opinion of many clinicians who were not satisfied with the yield of conventional imaging techniques and warrants a study of more sensitive imaging techniques such as PET.