790 POSTER DISCUSSION

Preoperative chemotherapy with epidoxorubicin and docetaxel in primary breast cancer

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Purpose: Preoperative chemotherapy is very effective in downstaging primary tumors, and is able to prevent the increase of metastatic growth kinetics very early in the cause of the disease. It has been shown that patients achieving a pathological complete remission (pCR) may benefit in terms of prolonged overall survival.

Methods: 50 patients entered the trial and 40 patients are now evaluable (median time of observation: 14 months range: 4–30 months). The patients suffered from biopsy-proven breast cancer (T1–T4), who would have been treated with mastectomy when conventional criteria would have been applied. They received a total of 206 cycles of chemotherapy with epidoxorubicin (75 mg/m^2) and docetaxel (75 mg/m^2) on day 1 every 21 days together with G-CSF 30 Mio.IE from days 3 to 10. Patients received at least 2 cycles (median: 5 cycles, range: 3–8) until best response was achieved judged clinically and by mammography.

Results: This neoadjuvant chemotherapy was well tolerated and all patients completed the therapy on an outpatient basis. During 206 cycles we observed only on one occasion (0.4%) leukopenia WHO-grade IV and no episodes of neutropenic fever or infection. WHO-grade III toxicity consisted of leukopenia (0.4%), diarrhea (1.9%), and stomatitis (0.4%). We observed a major response to the treatment in 34 patients (85%), with 5 patients (12.5%) experiencing a pCR of the invasive tumor (T0: n = 2, DCIS: n = 3) and 29 patients (72.5%) showing a partial pathological response. No patient showed progressive disease during therapy. In 23 patients (57.5%) a breast-conserving surgical procedure was possible.

Summary: We conclude that this preoperative treatment of primary breast cancer with epidoxorubicin and docetaxel is a safe and very effective regimen. By appliying more cycles preoperatively it might be possible to raise the rate of pCR and extend survival. A phase III-trial comparing this regime with CMF/FEC-chemotherapy is planned.

791 POSTER DISCUSSION

Phase II study of sequential docetaxel (Taxotere®, TXT) and doxorubicin (Dox) as primary chemotherapy (CT) for large operable breast cancer (BC)

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Background: Neoadjuvant chemotherapy is an adapted model for studying new therapies and allows more conservative surgery. Clinical response rates with Dox and Cyclophosphamide are in the range of 80% but pathological complete response (pCR) do not exceed 15% for large tumors (NSABP-B18). TXT and Dox are amongst the most potent cytotoxic drugs for BC. The aim of this open phase II study was to assess the efficacy of a sequential association of TXT and Dox.

Patient Eligibility: Pts < 65 years, T2–T3 (larger than 3 cm) N0–N1 M0 previously untreated BC (tru-cut biopsy).

Objectives: Primary: pCR; secondary: objective response rate (ORR), toxicity.

Treatment: TXT 100 mg/m^2 1-hour infusion 3 cycles, followed by 3 cycles of Dox 70 mg/m^2 bolus IV. Cycles were repeated every 2 weeks with G-CSF support (5 μg/kg) d5–d10. After the 6th course, surgery was performed, followed by loco-regional irradiation.

Results: Twenty-five patients had received 141 cycles. Median age was 47 years (33–63), median tumor size 57.5 mm (35–90). Pathological characteristics were: ductal invasive carcinoma 21, lobular invasive carcinoma, SBR I/II/III: 2/14/7, (not evaluable 2). Main toxicities (maximum grade/pt) were: grade 3–4 neutropenia 2, grade 3 diarrhea 1/25. Three pts presented both grade 3 neurological and ungueal toxicity. Amongst the 19 evaluable pts for efficacy, we observed 5 pCR (including persistence of DCIS) and 3 near-pCR in the breast. Axillary nodes were negative in 12/19 pts. Pathological CR in breast and axillary nodes were observed in 4/19 pts. Preliminary results showed that the toxicity profile is acceptable. Updated results of responses and tolerance will be presented.

792A POSTER

Quantitation of EGFR and c-erbB-2 expression in preinvasive compared to invasive breast cancer

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EGFR and c-erbB-2 are being explored as therapeutic targets in breast cancer. This approach will be enhanced if it is effective in pre-invasive as well as invasive disease. We have found that EGFR is downregulated and c-erbB-2 is overexpressed in 95% of invasive breast cancers, but little is known about the role of these factors in in situ disease.

In frozen sections of pure ductal carcinoma in-situ tumours (n = 24 for EGFR, n = 21 for c-erbB-2) and in invasive cancers with evidence of (DCIS), (n = 50 for EGFR, n = 47 for c-erbB-2) receptor levels were assayed quantitatively using a radiolabelled antibody method. Numbers of receptors were determined by comparison with cell lines of known receptor density and compared in each element of the tumours.

EGFR and c-erbB-2 expression each varied by a factor of several thousand. Levels of EGFR and c-erbB-2 expression in pure DCIS, in DCIS associated with invasion and in a larger group of invasive tumours (n = 193 for EGFR, n = 179 for c-erbB-2) were compared. The frequency distributions for expression of both factors were comparable in pure DCIS and in DCIS associated with invasive tumours (Mann-Whitney U test, EGFR p = 0.18, c-erbB-2 p = 0.19). Similarly, frequency distributions for expression of both factors were comparable in DCIS associated with invasive tumours and in purely invasive tumours (Mann-Whitney U test, EGFR p = 0.12, c-erbB-2 p = 0.83). Within each tumour that had both DCIS and invasion, there was no significant difference in expression of EGFR or c-erbB-2 in the DCIS and invasive components (Wilcoxon Signed Rank Test, EGFR p = 0.419, c-erbB-2 p = 0.108).

These data suggest that alterations in type I growth factor receptors occur before progression of in-situ disease to invasive cancer. High levels of c-erbB-2 overexpression in both in-situ and invasive areas suggest that the c-erbB-2 product is a potential therapeutic target for the treatment of breast cancer at an early stage.

792B POSTER

Brachial plexopathy after postoperative radiotherapy of breast cancer patients. A long term follow-up

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Purpose: To evaluate the incidence and prevalence of various signs of late morbidity, their time of appearance and pattern of progression during an observation period up to 34 years in breast cancer patients treated with post operative radiation therapy after radical mastectomy.

Methods: A group of 71 patients operated for breast cancer with total mastectomy and axillary clearance received in 1963–1965 aggressive postoperative telecobalt therapy to the parasternal, axillary and supraclavicular lymph node regions. The prescribed dose to these lymph node regions was 44 Gy in 11 fractions. Only two of the three fields were treated per day. Retrospective dose calculations showed that the total dose in the brachial plexus from the axillary and supraclavicular field was 57 Gy in 16–17 fractions over 3–4 weeks The cohort has now been followed up to 34 years.

Results: The median survival for the whole group was 12 years and there was a threefold increase in the median survival in patients who were below the median age at treatment, relative to the older group (28 years versus 9 years). 12 patients are still alive after 34 years of which four patients had positive nodes at diagnosis. There was progression of many of the late effects in the period between 5 and 34 years. The more serious morbidities of bone necrosis and of paralysis have increased progressively over the whole 34 year follow up period. 92% of the long term survivors have paralysis of their arm.

Conclusion: The neuropathy seems to be closely linked to the development of fibrosis around the nerve trunks. The use of large daily fractions, combined with hotspots from overlapping fields contributed to the severity of the complications. With the present knowledge, careful individual dose planning, and the avoidance of any field overlap in the supraclavicular region, postoperative radiotherapy has a part to play in the management of breast cancer, and the risk for BPN should be close to zero.