622 POSTER

Induction chemotherapy with weekly docetaxel (Taxotere) in unfavorable locally advanced breast cancer (LABC)

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Introduction: Taxotere showed a high response rate (45% to 60%) in metastatic breast cancer. Phase II studies of Taxotere on a weekly schedule showed similar results with marked marrow-sparing effects. We report such a regimen in the neoadjuvant setting.

Patients and Methods: Stage IIIA(T3) or IIIB breast cancer. Treatment: 2 cycles as follows: Taxotere 36mg/m2 weekly x 6 followed by a 2-week break. Objectives: (1) Objective clinical response rate(ORR); (2) Pathologic response; and (3) Biological correlates (hormone receptor and HER-2).

Results: Between March and September 2000, 37 patients were included in this multicentric phase II trial. Median age: 50 years (34 - 67); clinical TNM: 35% IIIA, 65% IIIB; median of major diameter: 67mm (30-150mm), 54% ER+ and 42% PgR+, 17% HER-2++ and 21% HER-2+++ (DAKO). All patients were evaluable for safety. Of a total of 398 infusions, no grade III/IV hematologic toxicity was observed. Alopecia grade II-occurred 31% of patients, and sensory neuropathy grade II in only one patient (3%). Other non-hematologic grade III toxicity: diarrhea: 11%, nausea and vomiting: 3%, and local skin reaction: 1 patient (3%). Injection site reaction: 1 case (3%). Grade IV toxicity: elevation of SGOT and SGPT in 1 patient (3%), sensory neuropathy in 1 patient (3%).Of 37 patients included, two were excluded from analysis of efficacy (1: protocol deviation, 1: hepatic toxicity before 3rd infusion). At the time of this analysis, 32 patients were evaluable for clinical response. After 2 cycles the ORR was of 69% (22/32) with PR of 47% and CR of 22%.

Conclusion: Weekly Taxotere is extremely well tolerated with minimal side effects. This regimen resulted in a clinical response of 69%. Our study shows encouraging results in a group of patients with unfavorable prognosis. Data will be updated at the time of the meeting including pathologic response. Supported by Aventis Pharma Brazil.

623 POSTER

A randomized study of ibandronate and pamidronate in hypercalcemia of malignancy (HCM). Ibandronate is more effective in the subset of patients with severe HCM and has at least equal efficacy to pamidronate in HCM patients with less elevated baseline calcium levels

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Background: Ibandronate is a third-generation aminobisphosphonate around 50 times more potent than pamidronate in vitro and in vivo. Both bisphosphonates are used in treatment of hypercalcemia of malignancy (HCM) and can correct hypercalcemia when given as a single infusion. The recommended dose of either bisphosphonate varies according to the severity of hypercalcemia. The purpose of this study was to compare the safety and efficacy of ibandronate and pamidronate.

Patients and Methods: A total of 72 patients with HCM (corrected serum calcium (CSC) >2.7 mmol/L) in 19 centers were stratified according to baseline CSC and randomized to treatment with ibandronate (n=37) or pamidronate (n=35). Within each treatment group, the dose of bisphosphonate administered was determined by baseline CSC, according to the package insert for each drug. Ibandronate (2 mg or 4 mg) was infused over 1 h and pamidronate (15 mg, 30 mg, 60 mg or 90 mg) over 1-1.5 h, and CSC monitored daily.

Results: The mean reduction from baseline CSC after 4 days (primary efficacy variable) was -0.73 mmol/L for ibandronate and-0.57 mmol/L for pamidronate (intent-to-treat population). Rates of response, time to response and time to onset of calcium lowering were also similar. However, in the two strata of patients with higher baseline CSC (3.5-<4.0 mmol/L and ≥4.0 mmol/L), mean reduction from baseline CSC was significantly greater in the ibandronate group (-1.31 and -1.56) than in the pamidronate group (-0.46 and -0.77) (p=0.046, per-protocol analysis). The number of adverse events and their profile did not differ between the ibandronate and the pamidronate group.

Conclusion: Ibandronate is at least as effective as pamidronate in treatment of HCM. In a subset of patients with severe HCM (initial serum calcium ≥3.5 mmol/L), ibandronate therapy appears to be superior to pamidronate treatment in restoring normocalcemia.

Adjuvant therapy

624 POSTER

The ATAC (Arimidex, Tamoxifen, alone or in combination) trial in post-menopausal patients with operable breast cancer

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Arimidex (anastrozole) is a potent, highly selective, non-steroidal aromatase inhibitor, suitable for post-menopausal patients (pts) with hormone receptor positive disease. Its tolerability profile makes it an ideal candidate for adjuvant therapy. The ATAC trial evaluates Arimidex in a three-way randomised double-blind design, either alone or in combination with tamoxifen, compared with tamoxifen alone. Endpoints include recurrence-free survival, tolerability, time to distant metastasis, overall survival and incidence of new breast primaries. We recruited over 9300 pts (median age 63 yrs) from 380 centres (21 countries, 30 mths). 21% of pts had received chemotherapy prior to randomisation. 61% were N-ve and 64% had tumours 2 cm or less. 73% of pts were receptor positive. Mastectomy was performed in 48% and 95% had axillary surgery: 63% clearance and 32% sampling. Large variations between countries were observed in choice of primary surgery.

Biological issues and quality of life have also been addressed - pharmacokinetics (357 pts), bone mineral density (307 pts), endometrial status (285 pts), and quality of life (1105 pts).

The ATAC trial is the largest adjuvant trial ever conducted in post-menopausal patients with early breast cancer. The size and the global nature of the trial will allow international variations in data to be compared, in addition to answering the main objectives of the trial. Preliminary analysis of the data is expected in 2001.

625 POSTER

Supportive therapy with epoetin-alpha in breast cancer patients (pts) receiving dose-dense sequential chemotherapy with epirubicin, paclitaxel and cyclophosphamide (ETC)

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Purpose: Dose-dense sequential chemotherapy with ETC is feasible in high-risk breast cancer pts. Results of a phase I/II study have shown that transfusions of packed RBCs are required in about 20% of pts. receiving ETC. The prevention of anemia and reduction of transfusions may optimize the therapeutic results and improve the pts quality of life.

Methods: Breast cancer pts with 4 and more positive lymph nodes are randomized between ETC or a standard regimen (4xEC followed by 4xT). The ETC regimen consists of three cycles each of Epirubicin (150 mg/m2), Paclitaxel (225 mg/m2)and Cyclophosphamide (2500 mg/m2). The standard regimen consists of 4 cycles of EC (90/600 mg/m2) and 4 cycles of paclitaxel (175 mg/m2). The ETC regimen is given at 2-week intervals and supported by G-CSF day 3-10. Until now 684 pts have been recruited in this trial. The prevention of anemia and reduction of transfusions by epoetin-alpha is tested by a second randomization in the ETC-arm. Epoetin-alpha is given in a dose of 150 IU/kg three times weekly.

Results: 343 pts have been enrolled in the ETC arm, 341 in the standard arm. Median age is 51 years, 7 positive lymph nodes are found in the median. 244 pts are evaluable for hematotoxicity. Hematotoxicity was greatest during cyclophosphamide treatment. The median Hb-value in the standard arm remained above 11,5g%. In the ETC arm without epoetin-alpha it dropped from 12,9 g% (cycle 1) to 10,4 g% (cycle 9). In contrast, the median Hb-value remained stable in the ETC-arm with epoetin-alpha (12,6 g% in cycle 1 and 12,2 g% in cycle 9). There was a highly significant difference (p<0.0001) in anemia grade 3/4 between the two arms (9% vs. 1%).The difference in the number of transfusions per cycle (5% of cycles vs. 2% of cycles) was also significant (p=0,015). 27% vs. 4,1% of pts required transfusions of packed RBCs.

Conclusion: The first interim analysis of this randomized trial suggests that epoetin-alpha is highly sufficient in preventing anemia and RBCs transfusions in pts receiving dose-dense sequential chemotherapy with ETC.