1303 PUBLICATION

Continuous infusion (CI) of 5-fluorouracil (5-FU) and oral leucovorin (LCV) in the treatment of metastatic breast cancer (MBC)

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Purpose: To evaluate the efficacy and toxicity of CI of 5-FU and oral LCV in patients (pt) who had failed to prior bolus 5-FU containing regimens.

Methods: Between 07/95 and 10/98, 52 pt were treated with CI of 5-FU 200 mg/m^2 on d1–10 and oral LCV 45 mg/d on d1–10, repeated q3w. Therapy was administered on outpatient basis through a permanent central venous device (CVD) and a disposable Multiday Infusor. All but one pt had received prior chemotherapy (CT), with bolus 5-FU containing regimens. Prior anthracycline therapy was given to 88%. Median number of prior CT lines for MBC was 1 (0–4), with 78% of pt receiving CI-5-FU + LCV as 2nd–5th line. Median age 50 y (33–80). Multiple metastatic disease sites were found in 56% of pt. Visceral organs were dominant sites of disease in 69%. Pt received a median of 6 cycles (1–23) of CI-5-FU + LCV.

Results: Overall response rate was 17%: CR 2 (4%), PR 7 (13%), S 30 (58%), PD 13 (25%). Median duration of response was 6 mth (2–14). Median time to progression was 18 weeks (3–69). Estimated median survival of all pt from the start of therapy was 18 mth (1–34). The most frequent side effect was stomatitis, grade (g) 3 in 16%, and g 2 in 10%. Diarrhea g 2 was seen in 6% of pt, and g 3 in 2%. Hand-Foot syndrome g 3 in 2%, and g 2 in 2%. CVD-related complications: subclavian vein thrombosis in 2 pt and bacteremia in 1 pt.

Conclusions: Combination of CI of 5-FU and oral LCV provided useful disease stabilization for some pt with MBC who failed to previous regimens containing bolus injections of 5-FU. This therapy yielded only a low rate of g 3 toxicity, with no g 4 toxicity observed, and could be given for prolonged periods.

1304 PUBLICATION

Five year results of neoadjuvant chemotherapy with cyclophosphamide, doxorubicin and 5-FU (CAF) for locally advanced breast cancer

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Purpose: Evaluation of the role of neoadjuvant chemotherapy CAF in achieving the goal of breast conserving surgery and its impact to survival.

Methods: 59 pts with stage III breast cancer received 3–6 cycles of neoadjuvant chemotherapy CAF. The chemotherapy regime was: 5-FU 500 mg/m^2, cyclophosphamide 500 mg/m^2, and doxorubicin 50 mg/m^2 once every 3 weeks. Forty one pts were treated postsurgically with 2–5 more cycles of CAF. Radiotherapy was given to 50 pts, 43 pts received tamoxifen.

Results: Overall 42 pts (71.2%) responded to CAF, 6 pts (10.2%) achieved complete response (CR) and in 3 pts (5.1%) CR was confirmed by postsurgery pathological examination. Fifty one pts underwent modified radical mastectomy (86.4%) and 8 (13.6%) underwent lumpectomy and axillary lymph node dissection. Forty three pts (72.8%) had positive lymph nodes. Twenty four pts (40.7%) recurred at the mean time of 18 months from surgery. The 5-year relapse free survival (RFS) for responders to CAF vs non responders was 54.2% and 29.5% respectively. The 5 year RES was 92.3% for node negative pts, 41.7% for 1–3 nodes positive pts and 13.6% for 4 or more node positive pts.

Conclusion: The proportion of lumpectomies was small in our study. The drugs other, than doxorubicin must be used in adjuvant settings for non responders to neoadjuvant CAF. New active agents must be introduced for the neoadjuvant treatment of locoregional advanced breast cancer in order to improve the results of node positive pts.

1305 PUBLICATION

Weekly docetaxel (D) plus gemcitabine (G) or vinorelbine (V) in refractory advanced breast cancer (ABC) patients. A parallel dose-finding study

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Purpose: The present study aimed at determining the MTD of T when combined with G or V in ABC pts who had received at least one previous chemotherapy regimen for the advanced disease.

Patients and Methods: ABC pts aged between 18 and 70, with ECOG PS 0–2 who had not responded to or had relapsed after first-line anthracycline-based chemotherapy were randomized to receive G 1,000 mg/m^2 or V 25 mg/m^2 in combination with escalating doses of D (starting from 30 mg/m^2), all on d 1 & 8 every 3 wks. Escalation was stopped if >33% of pts treated at a given dose level showed DLT at 1st cycle.

Results: To date 22 pts with locally advanced (4) or metastatic disease (17) have been treated, for a total of 48 cycles delivered. 11 pts have received D in combination with G and the remaining 11 with V. All pts have been pretreated with anthracyclines, and 21/22 have also received weekly dose-dense Taxol. D doses of 30 and 35 mg/m^2 proved to be safe when combined on d 1 & 8 with esther G 1,000 mg/m^2 or V 25 mg/m^2. No episode of DLT occurred at 1st cycle, and grade 3–4 neutropenia and thrombocytopenia occurred in only 5 and 2 pts. Nonhematologic toxicity was mild, except for one case of grade 2 peripheral neuropathy. We are now testing a D dose of 40 mg/m^2 in both groups (5 pts have been entered in each group).

Conclusion: The weekly D administration in combination with either G or V represents a well tolerated treatment for heavy pretreated ABC pts The study still continues until the definition of D MTD.

1306 PUBLICATION

Lack of cardiotoxicity in metastatic breast cancer (MBC) patients (pts) receiving doxorubicin/Paclitaxel (DOX/PAC) combination

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Purpose: to evaluate the cardiotoxicity of Dox/Pac combination in MBC pts.

Methods: Since Nov. 1994, 56 MBC pts received Dox 50 mg/m^2 i.v. bolus followed by Pac 175 mg/m^2 3 hour infusion every 3 weeks 6 cycles. Pt characteristics: median age – 50 (32–68), premenopausal – 20 pts, visceral metastasis – 24 pts, previously adjuvant CMF – 8 pts. All pts had normal renal, liver, cardiac (left ventricular ejection fraction (LVEF) > 50%) and hematological functions and ECOG status 0–2 before treatment. Cardiac function was evaluated by clinical examination, ECG and bidimensional echocardiography before treatment, every 2 courses, after treatment and every 3 months during follow up.

Results: 56 pts received 307 cycles of treatment (median 6, range 2–6). The overall response was 60% (5 CR and 28 PR) with median time to progression of 12 months and median overall survival of 19 months. Median cumulative dose of Dox was 300 (100–300) mg/m^2. Median LVEF before and after treatment consisted 66% and 64% respectively, no congestive heart failure was registered on treatment and during follow up.

Conlusion: Dox/Pac combination, highly active and tolerable regimen in metastatic breast cancer, does not damage the cardiac function seriously if the doxorubicin dose consists no more than 300 mg/m^2.

1307 PUBLICATION

First line chemotherapy with paclitaxel (P) and mitoxantrone (M) metastatic breast cancer (MBC). A phase II study

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Objectives: The aim of this study was to evaluate the feasibility, efficacy and toxicity of Paclitaxel (P) and Mitoxantrone (M) combination as first line chemotherapy in patients with Metastatic Breast Cancer.

Patients and Treatment: Between April 1997 and October 1998 fifty (50) patients (mean age 63 yrs, range 31–76 yrs) with Metastatic Breast Cancer were enrolled in this study. Twenty three (23) patients had received adjuvant combination chemotherapy, fourteen (14) CMF and nine (9) FEC, sixteen (16) patients had received adjuvant radiotherapy and twenty nine (29) hormonal therapy. All patients were treated on an outpatient basis with Paclitaxel (P) 175 mg/m^2 in 3 hours infusion and Mitoxantrone (M) 12 mg/m^2 in 30 minutes infusion i.v every 3 weeks for 6 courses. Patients were premedicated with standard antiemetic and antiallergig regimens. All patients received GCSF for 5 days.

Results: All patients were evaluable for toxicity and response. Grade 3–4 toxicity included neutropenia (12 pts), thromboytopenia (1 pt), peripheral neuropathy (7 pts) and cardiac toxicity (5 pts). Febrile neutropenia occurred in 2 pts. Grade 3 alopecia was observed in all patients. The ojective response rate was 44% (16% Complete response and 28% Partial response). The mean survival was 18, 36 ± 1.06 months (C.I. 16, 29–20, 43).

Conclusions: Combination chemotherapy with Paclitaxel and Mitoxantrone is feasible, well tolerated and higly effective as first line treatment in patients with Metastatic Breast cancer.

1308 PUBLICATION

A phase II trial of gemcitabine as prolonged infusion in metastatic breast cancer

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Gemcitabine is all active agent in the treatment of metastatic breast cancer. The objective of this phase II trial was to determine the efficacy and safety of gemcitabine as prolonged infusion in patients with metastatic breast cancer.

20 Patients [median age 50.4 yrs, range 35–63 yrs; performance status EORTC 0 (17 pts), 1 (2 pts), 2 (1 pt)] with metastatic breast cancer were treated with 250 mg/m^2 gemcitabine as infusion over 6-hours on days 1, 8 and 15 q3 weeks for up to 6 courses (median 3.9 courses). Treatment was 1st line for 4 pts, 2nd line for 5 pts and ≥3rd line for 11 pts. Metastatic sites were liver in 14 pts, bone in 12 pts, pleuropulmonar in 8 pts and lymph nodes in 9 pts. 9 patients presented 2 metastatic sites, 3 pts 3 and 5 pts 4. All patients were evaluable for response and toxicity. One patient (5%) achieved a CR and 4 patients (20%) a PR (1 pt with CR of visceral metastases but stable bone metastases), for an overall response rate of 25% (5/20). In addition, 6 patients (30%) had stable disease and 9 (45%) failed to response to the treatment. Time to progression ranged from 2–23 months with a median of 6.3 months. Hematologic toxicity was mild with leukopenia grade 3 in only 3 pts (15%) and no grade 3 thrombocytopenia. Moderate elevations of liver enzymes (3 pts grade 3), nausea and vomiting (2 pts grade 2) and mild alopecia were observed, but only 1 patient had to be withdrawn due to toxicity.

In conclusion gemcitabine as prolonged infusion is an effective treatment in metastatic breast cancer. Toxicity especially myelosuppression is surprisingly mild Therefore, gemcitabine seems to be ideal for combination therapies.

1309 PUBLICATION

Sequential therapy of taxol followed by vinorelbine and cisplatin as second line in advanced breast cancer

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Introduction: This study was based in results obtained in several secuential treatments, recent clinicals evidences in schedules of dose dense and introduction of new active drugs in the treatment of breast cancer. Patients with advanced breast cancer and previously treated, received a secuential therapy with shortening the intertreatment interval with Taxol followed by combination Vinorelbine plus Cisplatin.

Materials and Methods: Up to date, 20 patients were enrolled with diagnostic histology of breast cancer with metastatic disease and normal hematologic, renal and hepatic functions, who had previously received any chemotherapy. Treatment was Taxol 175 mg/m^2 given as a 3 hours infusion repeated every two weeks for four courses followed by combination of Vinorelbine: 20 mg/m^2 day 1 and Cisplatin: 75 mg/m^2 day 1 repeated every two weeks for three courses. The combination was administered 14 days after Taxol. Granulocite colony stimulating factor was used in this trial at 5 mcg/kg days 3–10 when hematologic toxicity was observed.

Results: Median age was 48.5 years, ranging from 41 to 65 years. 139 courses of Taxol and Vinorelbine plus Cisplatin were administered. The toxicity per cycle observed was: 1 anemia grade III–IV (0.71%); 8 neutropenia grade III–IV (5.7%) and 31 nausea/vomiting (22.3%). Of 17 patients evaluables for response, the responses obtained have been: five complete responses (29.4%), ten partial responses (58.8%), one stable disease and one progression. Response rate obtained was 88.2%. At a median follow-up of 8 months (ranging from 3 to 13+ months), 14 are alive, 2 of them without disease. Three patients died of progression disease, one during time of treatment and two during foloow-up.

Conclusion: Up to date, results obtained show hematologic and non-hematologic toxicity acceptable and high objective response in patients treated with Taxol followed by Vinorelbine and Cisplatin.

1310 PUBLICATION

Long-term weekly paclitaxel over 1 hour infusion with limited premedication. A phase II trial report

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Preclinical data have shown that Paclitaxel (P) is a schedule dependent drug, however the optimal schedule of administration remains undefined. In addition, preclinical reports have documented that paclitaxel has apoptotic and antiangiogenic properties.

The feasibility, activity and toxicity of protracted weekly 1-hour infusions of Paclitaxel were evaluated in 34 patients (pts) with metastatic breast cancer previously treated (adjuvant only: 26%, metastatic: 74%).

Paclitaxel 80 mg/m^2 weekly was administered over 1 hour on an outpatient basis until disease progression or limiting toxicity. Dexamethasone 8 mg, diphenhydramine 30 mg, and ranitidine 50 mg were given i.v. immediately prior to each dose of P. All pts gave written informed consent. Pts characteristics were: median age: 60 (35–80), PS: 0–2, pre/postmenopausal: 11/23 pts. Dominant metastatic site included were: lung (38%), liver (18%), bone (41%) and soft tissue (50%). Ninety-one percent of the patients received prior anthracycline treatment.

Having administered 951 weekly infusions (median 27 doses per patient, range: 4–78) no serious hypersensitivity reactions were noted. Median cumulative dose was 2160 mg/m^2 (320–6240). The overall response rate was 18/34 (53%, 95% CI: 36–69), CR: 3/34 (9%), PR: 15/34 (44%), SD: 9/34 (26%) and PD: 7/34 (21%). Median time to progression: 9 months, median survival: 14 months (2–35). Toxicity (NCI criteria): No Grade 4 toxicity was observed. No febrile neutropenia. The worst neuropathy was grade 3 (1 pts) Onycholysis/onychomycosis was noted in 10 pts (30%).

Conclusions: Long-term weekly administration of Paclitaxel is an active regimen with manageable toxicity. This schedule allows a high cumulative dose of P without cumulative myelotoxicity or prohibitive neurotoxicity. This weekly regimen deserves further exploration.

1311 PUBLICATION

Docetaxel in paclitaxel-pretreated advanced breast cancer patients

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Purpose: Preliminary data obtained both in vitro and in vivo suggest that paclitaxel and docetaxel may not be fully cross-resistant drugs in breast cancer. A recent series reported by Valero (JCO '98) showed a response rate of 18% in 46 paclitaxel-refractory breast cancer patients after docetaxel treatment.

Methods: From January '97 to September '98 14 patients with metastatic breast cancer, previously exposed both to epirubicin and paclitaxel-containing regimens, were treated with Docetaxel 100 mg/sqm every 3 weeks plus G-CSF (lenograstim 150 mcg/sqm every other day for 4 doses starting on day 4). Premedication with dexamethasone 8 mg i.m. on days – 1, 0, 1, 2 was applied to all pts.

Results: Patient data: median age 56 yrs (range 37–63); all patients were postmenopausal; PS 0–1/2–3: 9/5 pts; dominant metastatic sites: viscera 10 pts, bone 2, soft tissue 2; >2 metastatic sites: 8 pts; docetaxel was a IInd line therapy in one pt, IIIrd line in 7 and IVth line in 6 respectively. Previous median cumulative dose was 1050 mg/sqm for paclitaxel and 600 mg/sqm for epirubicin; previous response to paclitaxel-based regimen: partial response in 3 pts, stable disease in 9 and progression in 2. Median number of docetaxel courses was 6 (2–6) and median cumulative dose was 600 mg/sqm (200–600). All pts were evaluated for toxicity and response. G2 anemia was observed in one pt, with no G3–4 neutropenia or throm-