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-

bocytopenia; non-hematological toxicity consisted of mild fluid retention in one patient and a G3 skin reaction in another one. Partial responses were found in 7 pts, stable disease in 3 and progressions in 4.

Conclusion: our experience confirms that docetaxel is an active drug (50% response rate), well tolerated in paclitaxel-pretreated advanced breast cancer patients.

1312 PUBLICATION

Tolerance and efficacy of high dose doxorubicin in a sequential neoadjuvant regimen for locally advanced breast carcinoma (LABC): Preliminary results of a phase II trial

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Background: Treatment of LABC requires more efficient systemic treatments for better disease control. Sequential dose intense regimens are new strategies developed trying to improve current response rates and survival.

Purpose: To evaluate the efficacy and tolerance of High Dose Doxorubicin followed by a combination of Cyclophosphamide and 5-Fluoruracil in a sequential intense neoadjuvant regimen in a prospective phase II trial. We presented an interim analysis of toxicity and efficacy data for the first 44 pts. who received the intensified Doxorubicin treatment.

Methods: Treatment plan consisted of 3 to 4 courses of Doxorubicin 90 mg/sqm divided in 3 days (iv push) every 3 weeks followed by 3 or 4 courses of Cyclophosphamide 1 gr/sqm on day 1 iv push and 5 Fluoruracil 1 gr/sqm daily for 3 consecutive days as 2 hours iv infusion. No hematopoyetic growth factors or cardioprotector agents were allowed. After primary treatment, responsive patients underwent surgery or locoregional radiotherapy.

Results: From June 1996 to June 1997, 44/48 pts. are evaluable. Median age was 47.2 years (32–69), with 61.3% of premenopausal; 42 pts. completed 3 courses of therapy and 12 pts underwent a 4th course. Objective response after Doxorubicin treatment was 79% (IC 95% 68.3–91.4%) with complete response in 23.2% and partial in 55.8%. The relative dose intensity was 0.87 (26.2 mg/sqm/week). Grade 3–4 hematological toxicity occurs in 19 pts. (47.5%) but only 5 cases of febrile neutropenia. One pt. was off study due to severe toxicity but no treatment related deaths or significant cardiotoxicity was observed.

Conclusion: Our data shows that High dose Doxorubicin is a safe and well tolerated regimen with moderate hematologic toxicity and no cardiac toxicity in spite of the dose intensity of the treatment with also impressive high antitumor activity. Further evaluation of the full regimen will clarify the impact of this sequential dose intense strategy in LABC.

1313 PUBLICATION

Post-irradiation sarcoma (PIS) in patients treated for breast cancer: A retrospective study of the BCNIRTOG-Italy

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Purpose: There are several reports in the literature on the development of sarcomas after irradiation for breast cancer (BC). Moreover, an increase of the risk of developing a soft tissue sarcoma in BC patients is reported. The aim of this retrospective study is to quantify the risk of developing a PIS in a population of patients treated in the Centers collaborating at the Breast Cancer North Italy Radiation Therapy Oncology Group (BCNIRTOG).

Methods: All the PIS registered in the 23 Radiation Oncology Depts. collaborating at the BCNIRTOG, annually treating about 3000 patients with BC, were collected.

Results: 17 cases were observed, 12 arising after breast conservation and 5 in the chest wall for an incidence of less than 0.1%. The histology was: angiosarcoma, 10; fibrosarcoma 2; malignant histiocytofibrosarcoma, 2; sarcoma nos, 2; condrosarcoma, 1. Age at diagnosis ranged between 25 and 76 years (median 48 years). The PIS developed 18–324 (median 120) months after irradiation (range 25–60.25 Gy, median 54 Gy). All the patients treated conservatively for the first tumor had a mastectomy: 11 are alive without disease, one developed a local recurrence and lung metastases and is dead. The 5 mastectomized patients had a local complete excision of the second tumor, one had a local recurrence (lost at follow-up) and one distant metastases.

Conclusion: In our experience the development of a PIS are BC is an extremely rare occurrence. In this series the poor prognosis of PIS is not confirmed. Surgery played an important role m the outcome of these patients.

1314 PUBLICATION

Cytokines in anticancer therapy in advanced and metastatic breast cancer

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Purpose: It is known, advanced and metastatic breast cancer is treated without significant positive results. Therefore we tried to use cytokine TNF-α and IFN reducer ds-RNA in breast cancer therapy.

Methods: TNF-α was used in complex therapy in 9 pts with advanced and metastatic breast cancer. All pts had metastases in bones, 4 pts (44.4%) had also metastases in lung, skin, lymph nodes and opposite mammary gland. TNF-α was used i.v. in dose n + 0.5 $\times$ 10^6 IU/daily (n = 10^6IU). The daily dose was escalated till 3 $\times$ 10^6IU. The total course dose of TNF-α was 3-x10^6IU. IFN inducer ds-RNA ("Ridostin") was used in dose 8 mg i.m. every other day (the total course dose was 48 mg). There were from 3 to 6 courses.

Results: Pr- 3 pts (33.3%); SD-6 (66.7%). Morphological examination of minor tissue from mamma gland and regional lymph nodes has shown extensive multiple necrosis in cancer tissue. Sorrounded tissue was infitrated with lymphocytes and neutrophils. In peripheral blood we have observed positive changes.

Conclusion: We conclude that using of cytokines in breast cancer therapy is effective. We can recommend to use TNF-α and interferon inducer in advanced and metastatic breast cancer treatment.

1315 PUBLICATION

Weekly combination of taxol, 5-fluorouracil and leucovorin (TFL) in advanced pretreated breast cancer patients

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The activity of TFL combination every 3 weeks has been demonstrated in an our previous study with a response rate of 47.5% (Nisticò, 9th International Congress on Anticancer Treatment '99) as well as the feasibility and safety of weekly 1-hour infusion of Taxol (Seidman, Seminars Oncology '97). With the frequent administration of shorter infusions there may be cytokinetic advantages to the dose-dense scheduling by reducing the interval between cycles. Since May 1998 24 advanced pretreated breast cancer patients were treated with taxol 80 mg/sqm/wk as 1-hour infusion, 5-fluorouracil 300 mg/sqm/wk plus 1-folinic acid 10 mg/sqm/wk for 24 consecutive weeks in the absence of progression. G-CSF was included in treatment schedule on days 2 and 4 to allow the full delivery of a dose-dense weekly schedule. Patient data: median age 54 years (range 39–70; PS 0–1/2–3: 21/3 pts; pre/postmenopausal status 1/23 pts; ER+/– 16/6 pts, 2 unknown. Metastatic site: bone 7 pts, soft tissue 8, viscera 9. All patients had received previous anthracyclines. TFL was delivered as first line metastatic treatment in 6 patients, as second line in 12 and as third line in 6 patients.

Results: toxicity (WHO) was evaluated in 257 courses (c): anemia G2 12 c (3 pts); no other hematological toxicity was observed; vomiting (G3) 1 c, stomatitis (G2) 1 c, severe asthenia 6 c (2 pts). No patient experienced peripheral neuropathy, diarrhea or cardiac toxicity; one patient had an hypersensitivity reaction. Seventeen pts are evaluable for response to now. A complete response was observed in 1/17 (6%), partial responses in 10/17 (59%), stable disease in 2/17 (11.5%) and progression in 4/17 (23.5%) for an objective response rate of 65%.

Conclusion: the excellent toxicity profile and the good activity in this group of unfavourable prognosis patients warrant further extension of this weekly experience.