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STUDY OF 2 DOSES OF GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) : PE 2601 IN PATIENTS (PTS) WITH ADVANCED BREAST CARCINOMA (ABC) TREATED BY INTENSIVE CHEMOTHERAPY

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Twenty patients were included in a phase II trial of a first line chemotherapy regimen FEC 100 (Epirubicin : 100 mg/m^2 - 5FU : 500 mg/m^2 - CPM : 500 mg/m^2) every 2 weeks with the adjunct of G-CSF (PE 2601) 1 µg/kg/d or 4 µg/kg/d from day 4 to day 11, for 4 cycles.
The aim was to assess the feasibility of this regimen every 2 weeks and the dose-effect of 2 doses of PE 2601. The major inclusion criteria were : measurable lesion, pts previously untreated for ABC, WHO PS ≤ 2, normal hematological, renal and hepatic functions. Pts were randomized to receive either G-CSF at 1 µg/kg/d (n = 10) or 4 µg/kg/d (n = 10). The 2 groups were well balanced for all baseline characteristics. Mean age was 48.8 y (29-61), median PS (ECOG) = 1 (0-2). Results are summarized below (for all cycles) :

	G-CSF 1 µg/kg/d	G-CSF 4 µg/kg/d	
N° of cycles	40	35	Kruskal-wallis test
N° delayed cycles	5	6	
Mean nadir PNN (10^9/L)	1.365 (0-4.52)	0.714 (0-2.58)	p = 0.0018
Mean nadir Platelets (10^9/L)	168.25 (26-238)	89.45 (9-191)	p = 0.0001
Mean duration in days			
PNN < 500	1.95 (0-22)	3.26 (0-21)	p = 0.03
PNN < 1000	0.73 (0-8)	1.94 (0-8)	p = 0.004
N° of hospitalisation for infections episodes	2	6	Fisher test p = 0.04
N° of episodes of °C > 38°C / total cycles	4 (10%)	11 (31%)	

Six objective responses were observed in both groups. We would point out that there was no dose-effect relationship, 4 µg/kg/d of G-CSF appears paradoxically less effective than a dose of 1 µg/kg/d for biological and clinical parameters.

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HIGH DOSE CHEMOTHERAPY (HDCT) WITH MITOXANTRONE, CYCLOPHOSPHAMIDE, VINBLASTINE OR CARBOPLATIN WITH BONE MARROW SUPPORT IN METASTATIC BREAST CANCER (MBC): ROLE OF AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT) AND CYTOKINES. Nabholtz J.M.(2), Gluck S.(1); (1) Northeastern Ontario Regional Cancer Centre, Sudbury, Ontario, Canada (2)Cross Cancer Institute, Edmonton, Alberta, Canada.

Two prospective phase I and II trials were conducted by our group for evaluation of toxicity and efficacy of HDCT with bone marrow support in MBC. The first trial was a phase I study of HDCT combining Mitoxantrone (MTX) (63 mg/m2), Cyclophosphamide (CTX) (120 mg/kg) and Vinblastine (0.3 mg/kg) with Autologous Bone Marrow Transplantation in refractory MBC. Twenty Pts were accrued, mean age: 43 years. The mean durations of grade 4 neutropenia and thrombocytopenia were respectively 29 and 23 days. Other toxicities were mild except 1 toxic death (cardiac grade 4). Major response rate was 57.9% (Complete response (CR):10.5%). Median survival was 9 months. The second trial was a phase II of induction chemotherapy (IC) combining 5FluoroUracil (750 mg/m2), Epirubicin (100 mg/m2) and CTX (750 mg/m2) with GM-CSF followed by HDCT combining MTX (64 mg/m2), CTX (6 gm/m2) and Carboplatin (800 mg/m2) with PBSCT and GM-CSF in first line therapy of MBC. Nineteen Pts were treated, mean age: 43 years. The mean durations of grade 4 neutropenia and thrombocytopenia were both 12 days. Other toxicities were mild. No toxic death was observed. Major response rates were 73.6% (CR=31%) after IC and 100% (CR=58%) after HDCT. Median survival is not reached yet. HDCT with PBSCT and GM-CSF, without bone marrow backup, is feasible with significant decrease of hematologic toxicity, but its role remains to be proven in the management of MBC.

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EFFICACY OF HIGH DOSE CHEMOTHERAPY WITH/WITHOUT BCNU FOR AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN BREAST CANCER

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We assessed the efficacy of high dose combination chemotherapy with and without BCNU with reinfusion of purged BM in women with breast cancer either with responsive metastatic disease or in stage II, with 10≥ axillary LN involved, following adjuvant chemotherapy. Twelve female patients (PTS) age 38 (31-51) year, six with metastatic disease (Group A) and six in stage II (Group B) were included in the study. Pts in Group A received Carboplatin 1,500 mg/m^2, Etoposide 800 mg/m^2, Melphalan 120 mg/m^2, thiotepa 30 mg/m^2, BCNU 300 mg/m^2 and Group B received Carboplatin 800 mg/m^2, Etoposide 600 mg/m^2, Melphalan 120 mg/m^2, Thiotepa 180 mg/m^2 (except one patient who received the protocol given to Group A). All BM were purged with SBA. All pts engrafted, satisfactorily. Predominant side effects were myelossupressive, gastrointestinal and hepatic, mainly for Group A with one toxic death in group B (patient who received chemotherapy of Group A).
Three (50%) of the six pts of Group A who showed PR after conventional chemotherapy achieved CR after AMBT and two pts further improved their previous PR status. One patient of Group A who was in CR pre BMT continued being in CR post ABMT. Three of the Group A pts remained with median time to progression 8.3 (4-14) months, and two pts died (18 and 7 months, post BMT respectively. Median survival for all pts in Group A is 14.5 months (7-23). All pts in Group B except one who died from sepsis 10 days post BMT are in CR with a median follow up of 4.5 (3-12) months.
This study indicates that this dose intense regimen can be safely administered especially without BCNU and with high response rate in women with responsive metastatic breast cancer. The value for high risk pts in stage II following adjuvant chemotherapy has to be tested.

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HIGH-DOSE TAXOL (HDT) WITH G-CSF IN PATIENTS WITH ADVANCED BREAST CANCER (ABC) REFRACTORY TO ANTHRACYCLINE (ANT) THERAPY. Vermorken JB, Huizing MT, Liefting AJM, Postma TJ, Depauw L*, Ten Bokkel Huinink WW, for the European Cancer Center, Amsterdam and Bristol-Myers Squibb, PRI, Brussels*

Previous studies suggested activity of 24-hr infusions of Taxol (T) in patients (pts) with ABC, resistant to ANT. We started a phase II study in such pts, using 3-hr infusions of 250 mg/m^2 (with escalation to 300 mg/m^2) and G-CSF support (5 ug/kg sc, days 2-19, depending on neutrophils) every 3 weeks. So far, 17 pts with a median age of 51 yrs (range 33-71) and a WHO performance status of 1 (0-2) were treated. All had progressed during doxorubicin (9) or epirubicin (8) containing regimens, 4-12 weeks before starting T. A total of 57 cycles were given; median 4 per patient (range 1-7). Doses were escalated in 7 pts; they were reduced in 7 and stopped in 1 (7/8 for neurotoxicity). The median dose per cycle and per patient was 250 mg/m^2. One patient received a 24-hr infusion after an initial hypersensitivity reaction. Leukopenia (and neutropenia) occurred in 5 of the other 16 pts (2 grade 2, 2 grade 3, 1 grade 4), thrombocytopenia in 4 (2 grade 1, 2 grade 2). Nonhematologic toxicity included: mild hypotension (3pts), nausea/vomiting (2), diarrhea (1), neurotoxicity (13: 1 grade 1, 6 grade 2, 6 grade 3), myalgia (11), arthralgia (10), bone pain (2), facial flushing (4), fatigue (4), apathy and drowsiness (1). Three pts died early, 5 showed PD, 6 had NC, 1 had a PR and 2 showed > 50% tumor regression in indicator lesions. In conclusion, the antitumor activity of the 3-hour HDT regimen in ANT-resistant ABC pts has to be further defined, but neurotoxicity appears to be the dose-limiting factor.

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L-FOLINIC ACID (FA), FLUOROURACIL (F), EPIRUBICIN (E), CYCLOPHOSPHAMIDE (C) AND G-CSF IN ADVANCED BREAST CANCER (ABC).

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From may 1992, to increase the dose intensity, untreated patients (pts) with ABC were treated in a multicentric study (prot. GOIM no. 9201) with modified FEC regimen (F-FEC), including biochemical modulation of F with FA, escalating doses of E, and G-CSF. F-FEC regimen included (mg/m2): FA 100 iv d1-3, F 375 iv d1-3, E 90 iv d1, C 600 iv d1. G-CSF was given at a dose of 0.5 ug/Kg as a daily subcutaneous injection from day 5 to 15. Dose for E was increased of 10 mg/m2 according to toxicities. Time interval between the cycles was 3 weeks. Forty-three pts were enrolled in the study and 27 are actually evaluable for response and toxicity. The main characteristics of the evaluable pts were: median age 49 yrs; dominant site of disease: viscera 14, bone 6, soft tissue 7; multiple sites of disease: 20 pts; metastatic disease (MD): 22 pts; locally advanced disease (LAD): 5 pts. Results: 6 CR (22%), 16 PR (59%), 4 SD (15%), 1 PD (4%); pts with MD achieved 6 CR (27%), 11 PR (50%), 4 SD (18%), 1 PD (5%). All pts with LAD achieved a response and underwent to the surgery. The median duration of response for pts with MD was 6+ mos. In 79/151 (52%) cycles the dose of E was increased, and in 40 (26%) cycles the time interval between the cycles was reduced. Toxicity was mild with only few cases of grade III-IV (nausea/vomiting 5 pts, mucositis 2 pts, anemia 4 pts) and leukopenia (grade I) in 7% of cases. Conclusion: Preliminary conclusions of this ongoing study indicate that the addition of G-CSF allows the safety and the efficacy of the F-FEC chemotherapy, producing high response rate and acceptable toxicity in ABC.

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PHASE II STUDY OF TAXOTERE IN REFRACTORY METASTATIC BREAST CANCER (RMBC). V. Valero, R. Walters, R. Theriault, L. Esparza, G. Fraschini, F. Holmes, A. Buzdar, R. Bellet, M. Bayssas, G. Hortobagyi. M. D. Anderson Cancer Center, Houston, Texas 77030, USA and Rhone-Poulenc Rorer, Collegeville, PA 19426, USA

Eighteen patients (pts) with RMBC who had ≤ 2 prior chemotherapy regimens (CT) and had primary (P) or secondary (S) resistance to doxorubicin were treated with Taxotere 100 mg/m^2 every 21 days. **Pts characteristics (18):** median (med) age, 51 yrs (range 27-65); med Zubrod PS, 1 (0-2); med # sites 3 (1-6); disease sites: visceral 13/18, bone 5/18, soft tissue 15/18, breast 8/18; med # of prior CT was 1.5 (1-2). 6/18 had prior adjuvant, 7/18 neoadjuvant, 15/18 metastatic CT, with P resistance in 11 pts and S in 7. **Results:** 15 pts were evaluable for response, 1 pt had an early treatment-related death (day 7, due to gram (-) sepsis while severely neutropenic) and 2 pts were too early. **Responses:** 9 PR (60%), 2 NC and 4 PD. **Toxicity:** to date, 18 pts received 64 evaluable courses. med nadir granulocytes (x10^3)/dl: 0.3 (0.1-1.1), med nadir platelet count (x10^3)/dl: 165,000 (78-462,000). **Other toxicity (grade 2 o greater) by # pts:** alopecia 13, diarrhea 5, hypersensitivity reaction 2 (grade 2), fatigue 9, chills 1, myalgias 12, skin rash 7 (grade 3 1), nausea/vomiting 3, stomatitis 4, conjunctivitis 2, fluid retention 6. **Conclusion:** The preliminary data of this ongoing trial showed that Taxotere has significant antitumor activity in doxorubicin resistant pts. The main toxicities were reversible myelosuppression, skin toxicity, and fluid retention of uncertain etiology.