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G-CSF-intensified chemotherapy in metastatic breast cancer (MBC)

L. Pavesi[1], A. Martini[2], A.M. Capotorto[3], G. Lelli[3], A. Zamagni[2], A. Farris[4], B. Massidda[5], G. Robustelli della Cuna[1]. [1]*Division of Medical Oncology in Pavia;* [2]*Bologna;* [3]*S. Giovanni Rotondo;* [4]*Sassari;* [5]*Cagliari, Italy*

From Aug 93 to Aug. 96, 131 women with previously untreated MBC were randomly assigned to receive FEC (5FU 500 mg/m^2, Epi 75 mg/m^2, CTX 500 mg/m^2 q 3 weeks) or FEC-G (same q 2 weeks + G-CSF 5 μg/kg sc day 2–12) or MMM-G (Mitoxantrone 10 mg/m^2 and MTX 35 mg/m^2 q 2 weeks, Mit-C 7 mg/m^2 q 4 weeks + G-CSF 5 μg/kg sc day 2–12). At Feb. 99, 125 pts. were evaluate (6 lost), 43, 41 and 41 had received FEC, FEC-G, MMM-G respectively. Statistically significant differences in response rate were observed: 70% (CI 28–56) in FEC-G group vs 56% (CI 41–71) in MMM-G group vs 42% (CI 28–56) in FEC group (p 0.029): in detail FEC vs FEC-G p = 0.008, FEC vs MMM-G p = 0.192. A mean of 5.33 (FEC-G), 5.05 (MMM-G), 5.54 (FEC) cycles for pts. were administred. Thrombocytopenia was the major side effect in patients receiving intensified tratments (11.9 and 11.6% in FEC-G and MMM-G groups respectively), and occurred in only 2% of FEC treated pts. Neutropenia was more frequent in antracycline-based schemes (FEC: 12.3%, FEC-G:6.7%) as compared to MMM-G (3.05%). No significant cardiac, renal, pulmonary or liver toxicity were observed. Time to treatment failure and overall survival were not statistically significantly different in the 3 groups: 11 mo (9–13) and 18 mo (15–28) for FEC-G, 9 mo (7–15) and 23 mo (15–26) for MMM-G, 11 mo (7–14) and 21 mo (16–26) for FEC.

Conclusion: a) intesified regimens are associated with a significantly increased response rate, b) no benefit was found in time to failure and overall survival c) toxicity was modest and all treatments were well tolerated.

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Preliminary data of a phase II randomized trial of taxotere (TXT) and doxorubicin (DOX) given simultaneously or sequentially as 1st line chemotherapy (CT) for metastatic breast cancer (MBC)

I. Koroleva[1], M. Wojtukiewicz[2], J. Zaluski[3], L. Korytova[4], M. Biakhov[5], N. Gadel-Mawla[6], Y. Gouda[7], V. Krishtopin[8], C. Dubois[9], C. Blanc[10]. [1]*City Oncology Hosp., Chemo Dpt, N. Novgorod, Russian Federation;* [2]*Oncology Centre, Chemo Dpt, Bialystok;* [3]*Oncology Centre, Chemo Dpt, Poznan, Poland;* [4]*Roentgoenoradiological Inst., Chemo Dpt, St Petersburg;* [5]*Moscow Hosp. 33, Chemo Dpt, Moscow, Russian Federation;* [6]*Cairo;* [7]*Alexandria, Egypt;* [8]*Stavropol, Russian Federation;* [9]*Brussels, Belgium;* [10]*Antony, France*

The study aim is to evaluate the response rate (RR) of TXT + DOX as 1st line CT in pts with MBC, with dose & schedule assigned randomly: Group A: TXT 75 mg/m^2 + DOX 50 mg/m^2 for 8 cycles (cy); GpB: TXT 60 mg/m^2 + DOX 60 mg/m^2 for 8 cy; GpC: TXT 100 mg/m^2 (4 cy) then DOX 75 mg/m^2 (4 cy). 124 pts were included up to Feb. 99. Data are available for 90 pts: med. age = 54 y (24–69), med. PS = 0 (0–1), 42% pts received adj/neoadjuvant CT without anthracyclines. Pt characteristics are balanced in each group.

Median No. of cycles received: 6 (1–8)

Response Rate (as per investig. evaluation) in pts with 3 cycles or more:

Evaluable Pts: A = 26, B = 27, C = 25, All = 78;

Complete Resp.: A = 12%, B = 19%, C = 12%, All = 14%;

Partial Resp.: A = 46%, B = 52%, C = 44%, All = 47%;

Overall Resp. Rate: A = 58%, B = 71%, C = 56%, All = 61%;

Overall safety (90 pts, 488 cycles): Gr3–4 neutropenia: 64%/cy; Gr3 vomiting 1%/cy; Gr3 stomatitis: 0%/cy; Febrile neutrop.: 2%/cy; Gr3 neurosensory 2%/pt; Gr2 edema 1%/pt; no cardiotoxicity has been observed; no difference in safety were observed between each goup. Overall efficacy and safety profiles are in the range of what has been reported with TXT + DOX in the same indication. It is too early to compare the results between each groups. Study is still ongoing. Almost final results will be presented at the congress.

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Phase II randomized study of paclitaxel and paclitaxel + PSC 833 for advanced breast cancer

Darcy V. Spicer[1], Susan Groshen[2], James H. Doroshow[3], Tim Synold[3], David Gandara[4], Christy Russell[1], Franco Muggia[5]. [1]*USC/Norris Cancer Center, Medical Oncology, Los Angeles;* [2]*USC/Norris Cancer Center, Preventive Medicine, Los Angeles;* [3]*City of Hope, Medical Oncology, Duarte;* [4]*UC Davis, Medical Oncology, Davis;* [5]*NYU, Medical Oncology, New York, United States*

PSC 833 is a potent analogue of cyclosporine; preclinical studies with PSC 833 indicate reversal of MDR mediated resistance. This randomized phase II study was performed to evaluate the response rate and time to treatment failure of paclitaxel without and with PSC 833. Patients (pts) with evaluable or measurable metastatic breast cancer, who had received prior anthracycline-based chemotherapy as adjuvant and recurred within 2 years or who failed one prior anthracycline-based chemotherapeutic regimen for advanced disease were entered. Pts randomized to arm I received paclitaxel 175 mg per square meter by 3-hr IV infusion d1 every 21 days. Those randomized to arm II received PSC 833 at 5 mg per kg po qid for 12 doses beginning d 1 plus paclitaxel 70 mg per square meter by 3-hr IV infusion d 2 every 21 days. Thirty-three female pts have been randomized 15 to arm I and 18 to arm II; the median (range) age was 47 (29–68). The median (range) number of courses received was 4 (1–14). Arm I responses were complete response (CR) 0 partial response (PR) 4, and overall response rate 27% (95% confidence interval 19%, 67%); arm II responses were CR 2, PR 7, and overall response rate 52% (95% confidence interval 28%, 75%). The median time to progression for arm 1 was 96 d (14 have progressed) and for arm II 93 d (16 have progressed). The median survival for arm 1 is 23 months (7 have died), and for arm II 29 months (7 have died). During cycles 1 and 2, grade 3 or 4 WBC toxicity occurred in 4/15 pts on arm I and in 9/17 pts on arm II. Any neurologic grade 3 or 4 toxicity (during cycles 1 and 2) occurred in 3 PSC 833 treated pts. Cerebellar toxicity of any grade occurred in 5 PSC 833 treated pts. Paclitaxel pharmacokinetic data will be presented. These results are compatible with the hypothesis that paclitaxel + PSC 833 will be effective in the treatment of anthracycline resistant breast cancer. Prevention or reversal of drug resistance with PSC 833 warrants continued investigation.

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Phase I/II study of gemcitabine plus mitoxantrone in advanced breast cancer (ABC)

V. Lorusso, A. Catino, S. Mancarella, C. D'Amico, A. Latrorre, M. Guida, D. Sambiasi, M. De Lena. *Oncology Institute Via Amendola 209 70126 Bari, Italy*

Purpose: To determine the maximum tolerated dose (MTD) of Gemcitabine (GEM) and Mitoxantrone (MXT) and to evaluate activity and toxicity of this combination in treatment of patients affected by ABC.

Methods: patients (pts) less than 70 yrs were eligible if they have measurable disease, good PS (ECOG 0–1), normal cardiac ejection fraction and normal bone marrow reserve. All pts must have had previous treatment with anthracycline or taxanes and may have also received mote than one chemotherapy regimen for advanced disease unless containing GEM or MXT. MXT was given at a starting dose of 10 mg/m^2 on day 1 and GEM at a starting dose of 600 mg/m^2 on days 1 and 8 every 3 weeks. The doses of both drugs were escalated until G4 toxicity, according to WHO, developed in 3 pts treated at a given dose level. In particular, if dose limiting toxicity (DLT) occurred in 3 of 3, 4 or 5 pts, previous dose level was the MTD.

Results: The phase I study, performed on 22 pts, concluded that MXT at 10 mg/^{2} and GEM at 1000 mg/m^2 were dosages suitable for the phase II study and that higher doses would induce G4 leukopenia (DLT) in more than 50% of cases. Actually, out of 16 pts treated in the phase II study, 2 (12.5%) achieved CR and 5 (31.25%) PR respectively. Stable disease was observed in 6 (37.5%) pts. Responses were observed in soft tissue as well as in bone and liver lesions. Treatment was very tolerable, with negligible haematological and extrahaematological toxicity (nausea vomiting and alopecia practically absent).

Conclusions: These exciting preliminary results warrant further accrual in phase II study and future investigations in chemotherapy naive patients.