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LOW DOSE WEEKLY ANTHRACYCLNES FOR ADVANCED BREAST CANCER: IS TOLERANCE IMPROVED?

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From 1985 to 1989 102 eligible patients, 91 post- and 11 premenopausal, with advanced breast cancer were included into a trial studying the efficacy and tolerance of weekly low-dose antracyclines (adriamycin-A- or epirubicin-E- 20 mg/m^2). At progression the dose of both drugs was increased to 30 mg/m^2.

Results with 20 mg/m^2: Patients treated with A reached in 28% of the cases an objective response (CR+PR), whereas those receiving E had remissions in 17% of the cases (p=0.24). After dose escalation to 30 mg/m^2 at progression only patients treated with E showed second remissions (29%). Time to treatment failure was 9.6 ms for patients treated with A and 7.0 ms for those receiving E (p=0.37). Hematologic toxicity (WBC nadir diff. p=0.016) and alopecia (p=0.06) were significantly inferior for pts treated with E at 20 mg/m^2. At 30 mg/m^2 stomatitis and finger nail changes were significantly inferior for E whereas WBC nadirs and alopecia were similar for both compounds.

Conclusions. Adriamycin and Epirubicin weekly showed a similar overall response rate, lower than expected in this not heavily pretreated population. After dose escalation at progression only patients receiving epirubicin reached additional responses. Toxicity of epirubicin was less pronounced, especially hematologic, alopecia, and mucositis.

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PHASE I TRIAL OF ADRIAMYCIN (A) + TAXOL (T) IN METASTATIC BREAST CANCER (MBC). Sledge GW, Robert N, Goldstein LJ, Sparano J, Cobleigh M, Baughman C, Neuberg D, Rowinsky E. Indiana University, Indianapolis, IN USA.

Between 8/92 and 12/92, we entered 12 patients (pts) with MBC on a Phase I trial combining T with A. Pts were eligible if they had received ≤ 1 prior non-anthracycline, non-taxane-containing regimen, either as adjuvant or metastatic chemotherapy. Alternating pts received initial therapy with either A IV push followed 4 hours later by T by CI over 24 hours, or with T followed by A. The order of administration (A- >T or T- > A) was alternated with each cycle for individual pts. All pts received G-CSF 5 μg/kg days 3-12. Six pts received A 50 mg/m^2 and T 150 mg/m^2 initially, and 6 pts received A 60 mg/m^2 and T 175 mg/m^2 initially. Dose reductions were performed for neutropenic fever or infection, and for Grade 3/4 non-hematologic toxicity. Neutropenic fevers or infections complicated 6/34 cycles (17.6%) and 3/10 cycles (30%) with lower and higher doses respectively. Grade 3/4 neutropenia/leukopenia was seen in 7/7 cycles (100%) of A+T at 60/175, 13/20 cycles (65%) at 50/150, and 4/8 cycles (50%) at 45/131 mg/m^2. There were 4 episodes of Grade 3/4 mucositis (in 3 pts), all occurring in pts entered at the second dose level and receiving T prior to A. Clinically significant cardiac rhythm disturbances and peripheral neuropathy have not been experienced. The combination of A+T results in dose-limiting mucositis at doses of 60 & 175 mg/m^2. The occurrence of mucositis appears dependent upon the order of administration.

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PHASE II STUDY IN PATIENTS (PTS) WITH METASTATIC BREAST CANCER (MBC) **Giacomi N., Pascual M., García J., Stagnaro A., Chirino M., Algarniz C., Escudero M., Ponce W., Nievas O. R., Lattman A., Morante S., Salvadori M., Santarelli M., Luchina A. Centro Oncológico Excelencia, La Plata, Argentina.**

Anthracyclines (ANTH) in second line therapy are effective in MBC, Mitoxantrone (MIT), methotrexate (MTX) and cyclophosphamide (CPM) had demonstrated clinical activity as monodrug in MBC, then MIT was adopted due to a low cardiotoxicity (CATX). 76 eligible pts with MBC previously treated with ANTH and normal cardiac function had received: MIT 10 mg/m^2, MTX 40 mg/m^2, CPM 600 mg/m^2 IV day 1 and prednisone 40 mg/m^2 OP days 1 to 5 in a 21-28 treatment cycle. Features at diagnosis were: median age 51 (range 32-70), postmenopausal 67%, performance-status ≤1 74%. Objective Response (CR+PR) was achieved in 29/76 pts (38%), initial progression was 30% and stable disease 32%. Median duration of response is 11.5 mo, median time to progression is 3 mo and median overall survival is 10 mo. Toxicity was mainly myelosuppression with 25% (grade 3-4) and 1 pt experience CATX (grade 4). The combination of MMCP at this dose and schedule was a reasonably well tolerated regimen with a promising activity in MBC and a low CATX.

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REFRACTORY BREAST CANCER TREATMENT WITH TAXOL: CORRELATIONS WITH BASELINE IMMUNO HISTOCHEMISTRY FOR P-GLYCOPROTEIN (Pgp). B Uziely, E Delaflor-Weiss, C Russell, G Leichman, R Hanisch, D Spicer, F Muggia, M Press.
Department of Oncology, Kenneth Norris, Jr. Comprehensive Cancer Center at the Univ. of So. Calif., Los Angeles, CA., U.S.A.

Advanced breast cancer patients (pts) were treated with Taxol following failure of 1 or more prior regimens. All had baseline biopsies for Pgp determination. Taxol dose was 135 mg/m^2 q3w by 24h infusion; response was assessed every 3 courses by standard SWOG criteria. Pgp was assessed by double staining with monoclonal antibodies C219 and JSB-1 and compared with the staining intensity of known plasma cell lines (donated by T. Grogen, Univ. Arizona). Wild-type lines and sublines over expressing Pgp 6x and 40x yielded negative, slight, and strong positivity, respectively. In addition, normal tissue immunostains were performed for comparison (kidney tubles, adrenals). From October 1992-February 1993, 22 pts have been entered; 20 were refractory to doxorubicin. 19 pts are evaluable for response: 3 PR, 1 MR, 8 stable, 5 inevaluable pts including 2 too early to evaluate; 1 intercurrent death; 1 refusing further treatment. Toxicity has been primarily myelosuppression. Pgp immunohistochemistry shows 4 negative, 4 slightly positive, and 5 moderately to strongly positive. A focus of the analysis will be whether prior therapy with doxorubicin and vinca alkaloids leads to over-expression of Pgp. Correlation of response with baseline Pgp expression will be performed blinded at study completion.

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NAVELBINE (NVB) AS A SALVAGE TREATMENT FOR ADVANCED BREAST CANCER REFRACTORY TO ANTHRACYCLINES

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Navelbine (vinorelbine) a new vinca-alcaloid is an active agent in breast cancer (BC). In our study, 109 heavily pre-treated patients (pts) with advanced and/or metastatic BC received NVB at the dose of 30 mg/m2/weekly as a 20-min. i.v. infusion. All pts had previously received at least one chemotherapy regimen including an anthracycline for advanced disease. Median age was 55 years (29-79), PS : 1 (0-3), number of metastatic sites : 2 (1-5). All 109 pts were evaluable for toxicity and 92 pts for response. The main toxicities (WHO gr ≥ 3) were neutropenia and anemia, in 55 % and 9 % of pts, respectively. Thrombocytopenia, nausea/vomiting, constipation, peripheral neuropathy and alopecia were rare and mild. There were 1 CR (soft tissue) and 18 PR (soft tissue, lymph nodes and visceral metastases). Overall objective RR was 21 % (95 % CI : 12-30) and median duration of response 20 weeks (11-74). Responses were not related to dose-intensity, whose mean value was 19 mg/m2/week (9-30), ie, 63 % of the theoretical value. There was no significant difference in RR whether pts responded previously to anthracycline or not. Similarly neither menopause or simultaneous hormonal therapy had any effect on the RR. Conclusion: NVB is an active drug in advanced BC, particulary in soft tissue, with no apparent cross resistance with anthracyclines.

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CISPLATIN (CDP) + MITOMYCIN C (MIT-C) + VINDESINE (VDS) AS A SALVAGE TREATMENT IN ADVANCED BREAST CANCER (ABC) PATIENTS (PTS):

Leonardi V., Palmeri S. Russo A., Meli M., Rausa L. Oncologia Medica, Università, Policlinico "P.Giaccone", via Del Vespro 129, Palermo, Italy.

Failure after first line treatment of ABC is quite the rule during the medical treatment of this disease. At present there is not an established chemotherapy for this difficult clinical situation. 21 pretreated ABC pts were treated as follows: CDP 80 mg/m2 i.v.(d 1) + Mit-C 8 mg/m2 i.v.(d 1) + VDS 3 mg/m2 i.v.(d 1 and 15) q 4 wks. The main accrual criteria were: histologically proven ABC, age < 75 yrs, life expectancy > 2 months, K.I. > 60, measurable disease, good liver, renal, cardiac and bone marrow function. The main characteristics of the 21 included pts were: mean age 57 yrs (range 42-68); mean K.I. 84 (range 70-100). 20 pts (95%) had received Surgery, 21 pts (100%) I line Chemotherapy, 2 pts (9%) II line, 9 pts (42%) Radiotherapy and 13 pts (61%) Hormonotherapy. The sites of disease were: bone 71%, lymph nodes 38%, liver 19%, lung 14%, skin 9%, pleura 9%, breast 5%. WHO criteria were used for both clinical respons and toxicity evaluation. At present 18 pts are evaluable for response (3 too early). There were 3 PR (16%), 7 MC (38%) with a mean duration of 4,3 and 4,3+ months respectively. 8(44%) pts did not respond at all. The mean survival are 12,5 (RP), 8,6+ (MC) and 12,5 (PD) months, while the overall survival is 11 + months. 14 pts (66%) had grade (G) 3-4 nausea and vomiting, 16 pts (76%) G 2-3 leukopenia, 4 pts (18%) G 2-3 thrombocytopenia, 3 pts G 1-2 Hb, 1 pt (4%) G 2 neurotoxicity, 6 pts Hair G 2-3. Renal toxicity was seen only occasionally. In conclusion we think that this protocol is poorly active in this setting of pts. Further studies are needed in order to evaluate toxicity and activity of different drugs and association.