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HIGH-DOSE EPIRUBICIN (HD-E)IN A 2-WEEK (W) SCHEDULE IN ADVANCED BREAST CANCER (ABC).

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Over 3 years we performed 3 feasability studies with HD-E in a 2 W schedule at different doses of E, with and without hemopoetic-colony stimulating factors(CSFs),in patients(pts)with advanced malignancies.Among 58 pts included,25 pts had evaluable or measurable,non-anthracycline pretreated ABC. These pts were evaluated separately for response to HD-E.At a dose of 12o mg/m2/2W (without CSF),2/13 had complete remission (CR),8/13 partial remission(PR) and 3/13 no change(NC).At HD-E 14o-18o mg/m2/2W with GM-CSF all 6 pts included had PR(3 pts at 14o,2 pts at 16o and 1 pt at 18o mg/m2/2W).At HD-E 14o mg/m2/2W with G-CSF (ongoing study)2/6 pts have CR, 3/6 PR and 1/6 NC.The overall response rate for HD-E/2W is 84% (CR+PP)with 4/25 pts achieving CR.With CSFs an increase of HD-E dose intensity per week of about 33% can be achieved with acceptable toxicity.

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THE PROGNOSTIC ROLE OF HISTOLOGICAL GRADE AND c-erbB-2 ONCOGENE AMPLIFICATION IN PRIMARY TUMORS OF METASTATIC BREAST CANCER.

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In a previous study (Proc. ASCO vol 11, 74 1992) it was shown that in patients with metastatic breast cancer the outcome of cytotoxic treatment was dependent on scheduling of drug administration. Two randomized groups of patients received the same monthly dose of 5-fluorouracil (500 mg/m^2), epirubicin (60 mg/m^2) and cyclophosphamide (500 mg/m^2) either on a once a week or once a month basis. 158 patients were evaluable for response. Survival was significantly longer in the group treated once a month. Assesment of histological specimens from primary tumors revealed that low grade correlated with prolonged survival (p <0.05). Amplification of c-erbB-2 gene by polymerase chain reaction and c-erbB-2 oncoprotein positivity as determined by immunoperoxidase stain were most often observed in the same samples (p <0.005, F-test.) These factors predicted favorable treatment response in patients receiving chemotherapy on a weekly basis (p <0.05)
The results indicate that favorable response to epirubicin containing combination therapy correlates best with low histological grade. The detection of c-erbB-2 gene amplification and oncoprotein in the primary tumor may identify groups of patients who after development of metastases demonstrate improved response to selected chemotherapy regimens.

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ENDOCRINE AND CLINICAL EVALUATION OF 4-HYDROXY-ANDROSTENEDIONE IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER (BC)

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Estrogens are considered responsible for the onset of breast cancer in 1/3 of postmenopausal women. Aromatase inhibitors, such as AG, can reduce the synthesis of estrogens but they are not selective nor well tolerated. New aromatase inhibitors, such as 4-OHA, appear to be selective and much better tolerated. Preliminary Phase II studies have demonstrated a response rate of 24-35%. Between May '89 and August '91, 26 pts (mean age 56.5 yrs) heavily pretreated for BC and suitable for endocrine treatment received 4-OHA 250 i.m. fortnightly. Their characteristics include:46% ER+, 54% ER unknown, DFI>5 yrs. No CRs have been observed:
- PR 4 (36m+,4m,24m,12m)
- SD 8 (6m,6m,12m,14m,19m,24m,20m,23m)
Estradiol(E2) serum levels decreased more than 50% from baseline values during the first month of therapy (from 19.4±7.4 to 9.1±3.1 pg/ml). LH and FSH serum levels slightly increased during the first months, remaining constant thereafter. 4-OHA was well tolerated and no patient complained of severe side-effects. In conclusion, this trial confirms the efficacy of 4-OHA 250 mg i.m. in pts with advanced BC, especially when the long duration of response is considered.

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COMBINATION CHEMOTHERAPY OF METASTATIC BREAST CANCER WITH MITOXANTRONE, LEUCOVORIN AND 5FLUOROURACIL.

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Chemotherapy (CT) in metastatic breast cancer refractory to anthracycline-containing Iline therapy is still a challenge. The aim of this study was to assess the efficacy and safety of the new combination of Mitoxantrone 10 mg/m2 d1, 5Fluorouracil 350 mg/m2 d1+8 and Leucovorin 200 mg d1+8 given every 4 weeks. We treated 20 pts with metastatic breast ca - meanage 58 (35-74 yrs), 7 pts pre- and 13 pts post-menopausal, mean rating on Karnofsky scale 90, 5 pts with 1 site of involvement and 15 with multiple sites (all measurable). All pts received prior I-line CT with anthracycline. Pts received 1-8 CT cycles (median 5). Tolerance was good in most pts. Results:- CR 2 pts, PR 8 pts (RR 10+40%), NC 6 pts, PD 4 pts. Median duration 32 weeks overall. We concluded that this combination is effective in pts refractory to anthracyclines and is well tolerated.

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VINORELBINE AS SECOND LINE TREATMENT IN ANTHRACYCLINE PRE-TREATED ADVANCED BREAST CANCER PATIENTS: A PHASE II STUDY.

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From April 1992 to February 1993 48 advanced breast cancer patients (pts) entered a phase II study aimed to evaluate the toxicity and activity of Vinorelbine (VNB) (Eunades, Farmitalia Carlo Erba, Milan) as a second line treatment after an anthracycline based first line chemotherapy (FEC, 16 pts; Epirubicin, 120 mg/m2, 32 pts). Their median age was 52 yrs. (35- 75) and P.S. 1 (0-3, ECOG). 20 pts had multiple site metastases, 19 pure visceral, 5 soft tissues and 4 bone metastases. 30 mg/m2 VNB were administered i.v. over 10 min day 1 and 8 every 21 days. 44 pts received at least 2 courses of therapy and are evaluable for response. Overall, 137 courses of VNB have been administered (median 3, range 2-8). One patient showed a C.R., 8 pts P.R. (21%); 4 showed a minimal response (11%); 23 N.C. (50.5%) and 8 P.D. (19%). 46 pts are evaluable for toxicity. Overall, treatment was well tolerated and major toxicity included: leucopenia grade III in 8 pts (16%) and grade IV in 1 pt (2%); trombocytopenia grade III in 1 pt (2%); fatigue, grade III, in 5 pts (10%); local pain in 6 pts (11%); mucositis, grade III, in 1 pt (2%); reversable constipation grade IV in 3 pts (6%).
In conclusion, our data show that VNB is a quite well tolerated and moderately active drug in antracycline pre-treated patients.

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FEASIBILITY AND TOXICITY OF HIGH-DOSE CHEMOTHERAPY WITH/WITHOUT BCNU FOR AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN BREAST CARCINOMA P Drakos, A Nagler, R Or, E Naparstek, J Kapelushnik, S Slavin. BMT Dept, Hadassah Univ Hospital, Jerusalem, Israel.

A phase II study was conducted between 1.90-12.92 to determine feasibility and toxicity of a new preparative ABMT regimen with/without BCNU, in 12 female patients, (PTS) age 38 (31-51) yr. Six were with responsive metastatic disease and six in stage II with ≥10 axillary LN involvement. Six pts were conditioned with BCNU (300 mg/m^2) carboplatin 800-1500 mg/m^2, etoposide 600-800 mg/m^2, melphalan 120 mg/m^2, thiotepa 30 to 180 mg/m^2 (group A). Six pts received an identical protocol w/o BCNU (group B). Major toxicity was bone marrow suppression, which was markedly shorter in group A. (PNM ≥500/mm^3 +14 and +10, and PLT's ≥20,000/mm^3 +24 and ±26 post BMT for Group A and B respectively). Febrile neutropenia was also longer for the BCNU treated pts 17 (8-36 vs 9 (5-14) days for Group B. Non-hematologic toxicities (grade 2 and 3, NCI criteria for ABMT) are shown below. We conclude that BCNU free regimen with bone marrow was well tolerated with no serious organ toxicity.

Toxicity	Group A	Group B
N&V	2	0
Mucositis	6	2
Diarrhea	5	0
Hepatic	1	2
Renal	3	2
Pulmonary	1	1
CNS	1	0
Paralytic ileus	2	0
Bacteremias	2	0
Toxic death (sepsis)	1	0