456

INTERFERON (IFN) AND TAMOXIFEN (TAM) FOR PATIENTS WITH ADVANCED BREAST CANCER AND NEGATIVE ESTROGEN RECEPTORS (ER)*

T. Peretz, L. Baider, R. Catane, V. Barak, R. Isacson, A. Hubert and A. Kaplan, Depts of Oncology and Psychiatry, Hadassah Medical Center, Jerusalem, Israel.

Animal and human studies suggest that IFN may increase the response to hormonal agents in breast cancer. Sixteen evaluable ER negative breast cancer patients received the combination of natural IFN-β , recombinant IFN-γ and tamoxifen. By 3 months 38% of patients had an objective tumor response and 31% progressed. Side effects were mild (fever and flew like syndrome in 6 patients-33%). These preliminary results suggest an increased responsiveness to TAM in ER negative breast cancer patients by the addition of IFN.

* Supported by RENCHLER company, Laupheim, Germany.

458

PRELIMINARY RESULTS OF A RANDOMIZED TRIAL COMPARING SHORT VS PROLONGED CHEMOTHERAPY IN METASTATIC BREAST CANCER. Mauriac L, Toulouse C, Durand M, Chauvergne J, Fondation Bergonié, 33076 Bordeaux, France.

Metastatic breast carcinomas are never cured despite improvement and intensification of chemotherapy. Optimal response is usually obtained after the first courses of chemotherapy and to protract such a treatment rarely improves the therapeutic benefit. So this randomized trial has been carried out to compare efficiency of the same first line chemotherapeutic regimen applied for metastatic disease either on a short (6 courses) or a prolonged schedule (11 courses). End point of the trial is overall survival. Eligible patients have obtained either a stabilization or an objective response of their metastatic disease after 6 courses of EVM (Epirubicin 75 mg/m^2, Vincristin 1 mg/m^2, Methotrexate 20 mg/m^2), each of them delivered every 21 days. After randomization the patients either carry on with the same chemotherapy up to an Epirubicin cumulative dosage of 825 mg/m^2 (prolonged treatment) or discontinue it (short treatment). From January 1988 to December 1992, 82 patients were randomized. Fortytwo in the prolonged and 40 in the short treatment. Paticnt characteristics are equivalent in the two treatment groups. Response rates after the six treatment courses performed before randomization are also well balanced, indicating identical chemosensitivity in the two groups with a 34 month median follow up the survival curves are identical. In the short treatment group renewed clinical evolution of the disease required a new palliative treatment for 30 patients either by chemotherapy in 27 cases or by hormonal treatment in 3 cases. The mean time without any specific treatment is short, 5 months, with a maximum time of 14 months. Inclusions are still going on.

460

SALVAGE CHEMOTHERAPY (CT) WITH COMBINATION OF CARBOPLATIN (CBDCA) AND VINORELBINE (VRB) IN ADVANCED BREAST CANCER (ABC).

IAFFAIOLI R.V., TORTORIELLO A.*, FACCHINI G.*, DE MATTEIS A.**
Cattedra di Oncologia Clinica Univ. di Cagliari, *Oncologia Medica II Policlinico Napoli, ** Endocrinologia Oncologica Istituto Tumori Napoli

Introduction: most metastatic breast cancer patients require combination chemotherapy with drugs such as anthracycline plus alkylating agents or antimetabolite and alkylating agents containing combinations. Sequential use of non-cross reagents drugs as second-line therapy still represents the main option to improve in survival duration.
Patients and treatment: to aim to evaluate the safety and efficacy of a second line schedule containig CBDCA (300 mg/m^2 e.v. day 1) and VRB (30 mg/m^2 on day 1 and 8), repeated every 4 weeks, 26 pts, who failed to adjuvant or metastatic CT from October '91 to February '93 were treated. The median age was 57 years (26-75), 7 had locally advanced disease, 11 only skeletal/soft tissues involvement and 8 visceral localization.
Toxicity: a total of 82 courses have been performed up to now. Grade 3-4 myelotoxicity occurred in 15 pts (38 courses, 46.3 %), CT administration was delayed in 14 pts (25 courses, 30.5 %) and in 13 courses (15.8 %) the second VRB dose was elided. Neurotoxicity never caused treatment discontinuation. The most important VRB side effect was vascular toxicity in the site of drug injection (40 courses 48.8 %).
Results: 9 major responses (45 %), 2 CR and 7 PR, were achieved in 20 evaluable pts. At a median follow up of 6 (1-14) months 4 deaths and 3 PD have been observed.
Conclusions: this new combined treatment seems to be a quite well tolerated and highly effetive approach to chemoresistant breast cancer.

457

NEGATIVE PHASE II WITH 5-FLUOROURACIL (5-FU) PLUS LOW DOSES OF LEUCOVORIN (LV) IN REFRACTORY BREAST CARCINOMA(RBC). *Palacio I, Fernández Y, Peláez I, Cueva J, Esteban E, Estrada E, Buesa JM and Lacave AJ. Department of Medical Oncology. Hospital General de Asturias. 33006 Oviedo. Spain.*

Since Dec 1990 till Jan 1993 18 pts with RBC were treated with LV (20 mg/sqm in a 2-4 h. infusion) followed by 5FU (425 mg/sqm iv push) for 4 days q 4 wk. 16 pts were fully evaluable and 2 evaluable for toxicity (1 too early, 1 refused treatment after 1 cycle). Pt characteristics: median age 59 y (40-70); KI 60% (60-80); previous chemotherapy: 1 line 16, 2 lines 2 (all pts had progressed to anthracycline therapy); major sites of disease: soft tissues 2, bone 2, viscera 14, (liver 7). A total of 52 cycles of treatment were administered, median 3 (1-10). There was 1 PR in a patient with liver metastases and continues therapy after 24 wks, 5 NC, and 10 PD (1 rapid progression, 1 early death). The median time to progression was 13 wks (2-36+) and survival was 13 wks (2-52). Toxicity observed was (WHO grade >2, maximal toxicity per patient, n pts): leukopenia 4, granulocytopenia 5, mucositis 5; there was 2 episodes of febril neutropenia associated with mucositis G3. At this moment 3 pts are alive and 15 have died due to tumor progression.
In contrast with previous reports of 5FU plus higher LV doses, we conclude that this schedule has not significant activity as a second line therapy in breast cancer.

459

LONIDAMINE, ALPHA 2B INTERFERON AND HIGH-DOSE EPIRUBICIN IN ADVANCED BREAST CANCER.

IAFFAIOLI R.V., TORTORIELLO A.°, FACCHINI G.°, GESUE' G.*, PEZZULLO L^, PERSICO G.*
Oncologia Medica Università di Cagliari, *Div. Chirugia Ospedale Loreto Mare - Napoli, °IV Div. Chirurgia e ^VII Div. Chirurgia II Facoltà di Medicina - Napoli

Previous studies showed that lonidamine and α 2B IFN can potentiate antitumor activity of chemoterapy in advanced breast cancer patients. High-dose epirubicin (120-180 mg/m^2) can achieve a high response-rate in these patients. In view of these consideration , in July 1991 we started a phase II clinical trial employing a combination of epirubicin (130 mg/m^2), α 2B IFN (3 Mil.I.U./m^2 s. c. daily d-4-0) and lonidamine (600 mg/m^2 p.o.daily d 1-5), in women with advanced breast cancer. All pts received also G-CSF (30 Mil.U. s.c. d 15-18). A maximum of 6 courses were planned. To date 30 women, median age 53 (36-70), have been enrolled. 4 pts had locally advanced disease, 20 only skeletal-soft tissue involvement and 13 visceral localization. A total of 141 courses have been performed up to now. Grade 3-4 myelotoxicity occurred in 13 pts (36 courses) CT administration was delayed in 9 pts. (13 courses) and in additional 8 courses epirubicin dose was reduced. Epirubicin mean dose-intensity delivered was 40.7 mg/m^2 week, which rapresented 94% of planned dose-intesity. Fever, flu-like syndrome and malaise frequently occurred, but never caused discontinuation of IFN-treatment. Myalgia was observed in 10 pts..20 major responses (10 CR 10 PR) were achieved in 24 evaluable pts., for 83% overall response rate. At a median follow-up of 11 (2-10) months 2 deaths (1 for cardiac failure) and only 2 relapses have been observed. This new combined treatment seems to be a quite well tolerated and highly effective. These preliminary data seem encourage a larger phase III trial.

461

A COMPARISON OF AROMATASE INHIBITORS BY DIRECT ISOTOPIC MEASUREMENT OF AROMATISATION

S Jacobs[1], FA MacNeill[1], AL Jones[1], PE Lonning[2] & M Dowsett[1]
1 Acad Dept of Biochem, Dept of Med Royal Marsden Hosp, England. 2 Dept of Oncology, Haukland Univ Hosp Norway.

The conversion of androstenedione (A) to oestrone (E) by aromatase is the major source of oestrogen production in postmenopausal women. The use of aromatase inhibitors in postmenopausal breast cancer patients has been shown to be clinically effective. We have measured the effectiveness of several inhibitors using an isotopic urinary technique *in vivo*. Also measured in each of the patients were serum oestradiol, oestrone and oestrone sulphate. The results for aromatase and oestradiol are summarised here.

	Dose	% Suppression Aromatase	Oestradiol
CGS 16949A	2mg b.d.	92.6	73.1
	1mg b.d.	82.3	61.4
Aminoglutethimide	250mg qds	90.5	75.7
4-hydroxy-A (i.m.)	500mg 2wkly	91.8	60.8
	250mg 2wkly	84.8	46.4
4-hydroxy-A (oral)	250mg o.d.	58.6	N/A
Rogletimide	800mg b.d.	73.8	57.6
4-hydroxy-A (i.m.) +Aminoglutethimide	500mg 2wkly+ 250mg qds	94.9	78.5

Nearly all the inhibitors suppress peripheral aromatase activity by over 90% but oestradiol does not fall to the same extent. There does appear to be some relationship between degree of aromatase inhibition and oestrogen suppression. Work is currently progressing to determine whether greater inhibition can be achieved with triazole inhibitors (such as CGS20267) and whether this is associated with increased clinical benefit.