396

OVARIAN ABLATION (OO) VERSUS ZOLADEX (Z) ± TAMOXIFEN (T) IN PRE-PERIMENOPAUSAL PATIENTS (pts) WITH ADVANCED BREAST CANCER: RESULTS OF A MULTICENTRIC RANDOMIZED TRIAL.

E. Boccardo*, A. Rubagotti*, D. Amoroso*, A. De Matteis, A. Di Carlo, E. Galligioni, P. Gallotti, M. Lopez, P. Pacini, R. Petrioli, M. Sassi, P. Zola and others. *Istituto Nazionale per la Ricerca sul Cancro, Genova – Italy

OO is still considered the treatment of choice for premenopausal pts with advanced breast cancer and a not aggressive disease. LHRH analogs were shown to exert a similar therapeutic activity in pilot studies. So far no evidence of equefficacy from direct comparisons is available. No trial has prospectively investigated the possibility to ameliorate the results of OO or medical castration with the concurrent use of T. From June '88, 85 pre- perimenopausal pts with advanced breast cancer were randomly allocated to receive either OO or Z. Pts were also randomized to receive or not T treatment. The tumor ER status was either positive (49%) or unknown (51%). Objective responses (OR) were obtained in 25% of pts treated with OO(±T), and in 36% of pts receiving Z(±T) (NS). OR were achieved in 34% of pts treated with OO or Z alone, and in 29% of pts receiving gonadal ablation plus T (NS). Data concerning tumor progression and death are summarized below:

	OO(±T)		Z(±T)		OO/Z		OO/Z(+T)
n. of pts	37		48		42		43
n. of events	26		41		32		37
p=		0.16				0.53	
n. of deaths	16		20		19		17
p=		0.67				0.66	

Median S time was 38 mos in the OO (±T) arm and 36 mos in the Z (±T) arm. Median S time of pts treated with gonadal ablation was almost identical to that of pts treated with gonadal ablation + T (37 mos and 36 mos respectively). It is concluded that medical castration is equieffective to Z. The addition of T to gonadal ablation did not increase treatment toxicity but did not improve therapeutic results.

397

4-HYDROXYANDROSTENEDIONE (4-OHA) AS FIRST LINE TREATMENT IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER(ABC)

Zilembo N., Bajetta E., Noberasco C., Buzzoni R., Martinetti A., Ferrari L., Galante E*., Fariselli G*., Piromalli D*.

Division of Medical Oncology B, * Division of Surgical Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

4-hydroxyandrostenedione, a new selective aromatase inhibitor devoid of severe side-effects, has been demonstrated to be active in pts with ABC. Between June '89 and October '91, 143 consecutive postmenopausal pts pretreated or not for ABC, entered a randomized trial to evaluate the endocrine and clinical effects of 2 fortnightly 4-OHA i.m. doses, 250mg(A) or 500mg(B). 52 /143 pts (median age 59 yrs) received 4-OHA as first line treatment (24A, 28B). All pts had PS≤ 1 (ECOG), 34 pts (65%) had DFI ≥ 2 yrs, 21 pts (40%) both ER+/PgR+. Hormonal adjuvant treatment was given to 20 pts while adjuvant chemotherapy (CMF) to 14 pts. Sites of metastatic disease were as follow: soft tissues 60%, viscera 44% and bone 60%; 15 pts had multiple sites. After a median treatment time of 8 mos, clinical responses were:

	250 mg (24 pts)	500 mg (28 pts)
CR	4	6
CR+PR	8 (33%)	13 (46%)
SD	2	2

Median response duration was 8 mos in both groups, while time to progression was 5 mos on A and 10 mos on B. Considering sites of disease, A and B provided similar responses in soft tissues. Better results were obtained in B on viscera (7/14) and bone (6/16). E2 serum levels significantly ($p<0.001$) decreased, more than 40% from baseline value in both groups after 1 mo of treatment and remained unchanged thereafter. LH and FSH levels remained practically unchanged, SHBG levels decreased only during the first 3 mos. No pts complained of severe side-effects. Local tolerability was satisfactory. In order to confirm these encouraging results with 4-OHA as first line, a multicentre study coordinated by Italian Trials in Medical Oncology Group (I.T.M.O.) is ongoing.

398

A RANDOMIZED, MULTICENTRE TRIAL EVALUATING AREDIA IN BREAST CANCER PATIENTS WITH BONE METASTASES.

Conte P.F., Latreille J., Mauriac L., Koliren L., Calabresi F. and *Ford J.M. On behalf of the Aredia Multinational Cooperative Group and *Ciba-Geigy, Switzerland.

To evaluate the efficacy and tolerability of Aredia 295 breast cancer patients (pts) with lytic or mixed bone metastases (BM) were randomized to receive Aredia 45 mg i.v. every 3 weeks plus standard chemotherapy or chemotherapy alone. 35 Centres participated in 7 Countries.

The primary end-point of the trial was time to progression of disease (PD) in bone on serial X-rays and bone scans. To minimise bias the end-point was determined by blinded observers during "extra-mural review" (EMR) of the trial data. Secondary end-points included the complications of BM - pain, analgesic and radiotherapy requirements, pathological fracture and hypercalcaemia. An analysis of time to PD in bone has been performed on all data collected until 15.5.92 and is shown in the following table.

	Aredia	Control
No. of Pts randomised	142	153
No. of Pts evaluated by EMR	116	115
No. of Pts with PD in bone	67	75
Median time to PD in bone (days)	249	192

The difference between the groups is statistically significant ($p = 0.05$ Wilcoxon test). Aredia was well tolerated with no major toxicities reported. A complete and final analysis will be presented (both primary and secondary end-points) and will include data collected until 31st January, 1993.

399

EFFECT OF TAMOXIFEN ON LUMBAR SPINE BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN AFTER FIVE YEARS.

Love RR, Barden HS, Maness RB, Chappell RJ, Depts of Human Oncology, Medical Physics & Biostatistics, University of Wisconsin, Madison, WI USA

Because adjuvant tamoxifen is given for long periods, it is important to know how it affects risk factors for osteoporotic bone fractures, particularly since rates of bone fracture increase rapidly with age in postmenopausal women. In a 2-year randomized placebo-controlled toxicity 140-subject study, we demonstrated that tamoxifen was associated with preservation of bone mineral density (BMD), a major risk factor for fractures in the lumbar spine. Five years after entry on this study we re-examined 61 of the original subjects. These were women available for study because they had not suffered major illnesses and had continued on (1) tamoxifen or (2) no tamoxifen they had originally been randomized to receive, for the entire 5 years.

For lumbar spine BMD at baseline, the 30 long-term tamoxifen subjects and the 31 long-term no tamoxifen subjects were not significantly different ($p=0.26$).

During the first two years of follow-up, the 30 long-term tamoxifen subjects showed the same BMD pattern as the entire 70 patient tamoxifen cohort and similarly the 31 long term no-tamoxifen subjects showed the same pattern as the entire 70 patient placebo cohort, suggesting no sample bias. Five year mean BMD measurements for each long term follow-up group showed no significant changes from their respective two year levels. Five year BMD measurements between the two groups differed (tamoxifen group +0.8%; placebo group -0.7%) ($p=0.06$). We conclude that tamoxifen preserves BMD in the lumbar spine over 5 years of treatment.

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400

SHORT VERSUS LONG TERM TREATMENT WITH CMF IN POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER; AN EORTC BREAST CANCER CO-OPERATIVE GROUP PHASE III TRIAL (10852). Nooy M.A., Beex L.V.A.M., de Haes J.C.J.M., Wildiers J., Klijn J.C.M., Engelsman E., Jassem J., Mignolet F. and Sahmoud T. (University Hospital Leiden, Clinical Oncology, P.O. Box 9600, 2300 RC LEIDEN. The Netherlands)

The classical CMF (Cyclophosfamide orally, methotrexate, 5 Fluorouracil) was used as first line cytostatic treatment in postmenopausal patients with measurable and/or evaluable advanced breast cancer, to compare 6 months treatment with treatment till progression. Four hundred and fourty-two patients were registered in the study, 204 patients with no evidence of progression were randomized after 6 cycles of CMF. The overall respons rate after 6 cycles was 4% CR, 32% PR and 37% NC. Provisional analysis demonstrates that the mean time to progression for the continuous arm was 5.3 months, for the short treatment arm 3.7 months (P.0.286) both calculated from randomization. Median survival for the continuous and short treatment was 14 months, (p.0.422) also from the moment of randomization.

We conclude that although continuous treatment with classical CMF might be better in terms of progression free survival it does not lead to improved survival. As a result the disadvantages of longer CMF treatment have to be weighted against a small gain in time to progression. Consequently, an adopted Q-Twistmodel was used to compare both treatments in terms of quality and duration of life. Continuous treatment turns out to result in 8.5 and short treatment 7.6 months of quality adjusted survival. The difference, thus, is again minor.

401

Fluorouracil (F) , with and without high-dose folinic acid (HDFA) plus Epirubicin (E) and Cyclophosphamide (C) : FEC versus HDFA-FEC plus or minus Thymostimulin (TS) in metastatic breast cancer : results of a multicenter study.

L.Pavesi , on behalf of an Italian Cooperative Trials Group *

Rationale : HDFA-FEC has been claimed (Proc.ASCO,7:68,1988) as an highly effective regimen in metastatic breast cancer (MBC) . TS has been reported effective in reducing chemotherapy-induced fever and cytopenia(Anticancer Res. 9: 193,1989).Purpose : To compare therapeutic efficacy and tolerability of HDFA-FEC versus conventional FEC regimen and to ascertain the potential protective effect of TS on chemotherapy-induced febrile episodes and cytopenia.Patients and Methods : From Jan.1990 to Dec .1992 , 296 pre & postemonopausal women with histologically proven, progressive MBC were enrolled by partecipating Institutions and randomly allocated over the phone to one of the following treatment arms : A. FEC (F : 500 mg/m^2 + E :75 mg/m^2 + C: 500 mg/m^2 , all drugs given iv. on day one , q. 3 weeks). B. FEC + TS (1 mg/kg/day im. concurrently with chemotherapy and 3 times a week thereafter until progression or withdrawal). C.HDFA-FEC (FA : 200 mg/m^2 in 60' infusion, followed by F : 370 mg/m^2 days 1 to 5 +E: 75 mg/m^2 and C: 500 mg/m^2 on day one , all drugs administered iv. ,q.3 weeks).D. HDFA-FEC + TS. The four groups were well balanced in terms of pretreatment characteristics. Results: in 245 fully evaluable pts. no significant difference in overall response rate was observed : A (60.3%) vs.B (53.1%) vs.C (58.6%) vs. D (50.7%).The comparsion between the two chemotherapy regimens , irrispective of the TS treatment , showed no difference in terms of response rates : p =.420. . Likewise no significant differences were observed in terms of median time to progression (18 vs. 15 vs. 20 vs.15 months) and overall actuarial median survival (19 vs. 16 vs.23 vs.17 months).Toxicity : On a total of 1668 cycles of chemotherapy hematologcal toxicity , assessed as number of delayed / total number of administered cycles , was significantly lower in TS - treated subgroups of pts. (p= .0002), as well as by comparing chemotherapy alone and chemotherapy + TS - treated groups only (p=.0001) . No differences emerged from the analysis of the incidence of febrile episodes and other systemic toxicities. Conclusions : a) Modulation of FU with folinic acid did not improve results achievable with conventional FEC regimen ; b) The addition of TS to both tested regimens significantly reduced delays , for hematological toxicity, in administering chemotherapy; c) This documented effect of TS has a favourable effect on quality of life , but no impact on disease outcome.

* *T.Battelli (Ancona), M.Baroni (Milano), A.Farris (Sassari) , G.Marini (Brescia), L.Pavesi (Pavia), , A.Ravaioli (Rimini), A.Beni (Roma), G.Mustacchi (Trieste) , B.Massidda (Cagliari). M.Narcisi (Pinerolo), A.Contu (Sassari), C.Lameo (Potenza), C.Scoponi (Macerata).*