450

SECOND LINE HORMONE THERAPY WITH AMINOGLUTETHIMIDE VERSUS MEDROXYPROGESTERONE ACETATE IN METASTATIC BREAST CANCER

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Patients (pts.) with metastatic breast cancer, progressing after an initial response to tamoxifen frequently respond to further endocrine treatment. In this study the clinical response and toxicity of medroxyprogesterone acetate (MPA) and aminoglutethimide (AG) as second-line treatment in pts. with metastatic breast cancer was compared. Eighteen pts. received AG at a dose of 500 mg/day and 18 pts. MPA at a dose of 1000 mg/day. All pts. were postmenopausal and previously treated with tamoxifen. The two groups did not differ with regard to prognostic factors. Objective response rate for the AG and MPA group were 56% and 50% respectively and media duration of response was 7 and 8 months respectively. Stable disease was 22% in both groups. No difference was observed in survival. Toxicity was light in AG group (lethargy and giddiness in 7 pts.) and hight in MPA group (metrorrhagia in 4 pts. and thrombophlebitis in 2 pts.). In conclusion significant differences regard to efficacy was not found, while side effects were small in AG group.

451

MODULATION OF ORAL TEGAFUR (T) BY ORAL FOLINIC ACID (FA) IN PATIENTS WITH PRETREATED METASTATIC BREAST CANCER (MBC): A PHASE II STUDY

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The combination of fluorouracil (FU) and FA is active in pretreated MBC. Tegafur is a slow release form of FU, with the advantage of oral administration. We have conducted a Phase II trial to assess the effect of oral FA in the activity and toxicity of T in patients (pt) with pretreated MBC.

PATIENTS AND SCHEDULE: From October 1992 to February 1993, 28 pt with MBC previously treated with chemotherapy regimens were included. The schedule was T 750 mg/m2/day and FA 45 mg/day, both given orally for 21 days, recycling at day 28, until progression. To date, there are 22 evaluable pt. (6 excluded from analysis; 4 too early, 2 inadequate inclusion), with the following characteristics: mean age 54 y. (37-71); median KPS 80 (60-100); mean number of prior chemotherapy 2.5 (1-6). Sites of disease: soft tissue 13, bone 9, lung 5, liver 3, pleura 2, pericardium 1.

RESULTS: The average number of administered cycles was 3.2 (1-5), and the total number 70. Responses: partial 7 (32%; 22-42%, CI 95%) (3-5+ months), no change 10 (45%) (2-5+ months), progression 5 (23%). Responses were seen in lymph node, chest wall sites, bone and lung. Toxicity: % of courses with toxicity;

Grade (WHO)	0	1	2	3	4
Mucositis	74.6%	6%	10%	8%	1.4%
Diarrhea	66.6%	14%	10%	8%	1.4%
Vomiting	87.2%	8.6%	2.8%	1.4%	0

Also, there were; grade 1-2 myelosuppression 2.8%; grade 1 thrombocytopenia 1.4%; hand-foot syndrome 1 patient; no alopecia or neurological toxicity occurred.

CONCLUSION: This trial suggests that biochemical modulation of oral tegafur by oral folinic acid is active in patients with prior chemotherapy for MBC and is well tolerated.

452

A PHASE II TRIAL WITH D-Trp-6(DECAPEPTYL) IN PREMENOPAUSAL RH+, HORMONAL UNTREATED ADVANCED BREAST CANCER PATIENTS.

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LHRH analogues are suitable first-line agents for the treatment of premenopausal breast cancer patients because their efficacy is comparable with that of surgical castration and because they lack serious side effects. D-Trp-6 is an analogue LHRH which inhibits breast cancer cell growth by several direct and indirect mechanisms.
In a trial including 33 patients treated with I.M. injection of 3,75mg (each 28th day) of D-Trp-6 for 3 to 35 months, no important side-effects occured with the exception of those caused by the intented hypogonadism, especially hot flushes. A few patients had more or less short-term urticarial skin irritation which did not cause pain not discomfort. 33 patients were assessable for toxicity and 31 for response. Twenty one (67%) objective responses have been obtained with first line D-Trp-6 : 6 CR (19%), 15 PR (48%), 4 (13%) stable disease, 6 patients (19%) progressed. Patients received chemotherapy at the moment of hormonal treatment failure. Time to progression was 20 months and median of the overall survival was not reached at 74 months.
In conclusion, D-Trp-6 is non toxic and clinically active inhibitor of breast tumor proliferation of premenopausal RH + patients.

453

RESULTS OF PHASE II STUDY OF HIGH DOSE EPIRUBICIN(EPI) WITH CYCLOPHOSPHAMIDE(CPH) IN UNTREATED DISSEMINATED BREAST CANCER(BC).

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In phase II trial between April 1990 and October 1991, 35 previously untreated pts(median age 45,3,range 29-67 yrs) with disseminated BC received EPI 120 mg/m^2+CPH 600 mg/m^2 i.v. q. 3 weeks.Overall 190 cycles of CT were performed (average 5,4+2,3;range 2-10) with mean cumulative dose of EPI 655,1+289,9 mg/m^2(range 230-1100 mg/m^2). Three pts(8,6%) had CR,15(42,8%) PR, 1 pts(2,9%) was considered stable. The mean duration of response was 10,8 months.Only in 2 pts treatment was terminated because of toxicity.Side effects observed were grade III-IV leucopenia(59,6%),grade III vomiting(28,6%), febrile neutropenia(7 pts),alopecia(all pts). Decrease of LVEF(mean - 2,8%) was up to 22% in 1 pts.Congestive heart failure developed in 1 pts after 1100 mg/m^2 cumulative dose of EPI.It can be concluded that combination CT with high dose EPI and CPH in untreated disseminated BC has moderate efficacy and toxicity.

454

A CROSSOVER COMPARATIVE STUDY OF AMINOGLUTETHIMIDE VS TRILOSTANE IN ADVANCED POSTMENOPAUSAL BREAST CANCER.

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Trilostane (T) produces a 3,4 beta hydroxysteroid blockade preventing the metabolism of dehydroxyandrostenedrone and thence to estrone. In contrast Aminoglutethimide (AG) is active through its inhibitory action on the aromatase system though it does also have demolase 11, and 21 oxidase inhibitory actions. Both are given with a corticosteroid. Open studies of T have suggested a similar degree of effectiveness to AG. This randomised trial with crossover was designed to confirm this and test for cross resistance. All patients were postmenopausal and had measurable or evaluable advanced or recurrent breast carcinoma. Patients may have received prior hormones or adjuvant chemotherapy. Response criteria were those of the UICC. Patients were randomly allocated to receive aminoglutethimide D1-14 250mg bd, D15 onwards 250mg qid or Trilostane D1-3 120mg bd, D4-6 120mg qid, D7-9 240mg tid, D10 onwards 240mg qid. All patients received hydrocortisone (C) 20mg/d in divided doses. 130 patients in 12 hospitals were randomised (2:1 in one trial) and 120 are available for analysis. 71 received T, 33 crossing to AG. 49 received AG, 14 crossing to T. 1st line responses (CR, PR, & SD) were T 46%, AG 53%. Mean time to progression was 45 & 64 weeks respectively. For patients crossing over, 9 responded to both drugs, 5 responded to AG having not responded to T and 7 responded to T having failed AG. The rest did not respond to either (8) or had too little therapy for adequate assessment (18). Toxicities were similar in incidence (T 41%, AG 51%) but different in type. T caused principally upper and lower GI side effects (37) and AG sedation (18) and skin rash (14). T + C has a similar degree of activity to AG + C with a different pattern of side effects. The drugs are not cross resistant; 19% of all patients receiving both drugs responded to both.

455

PHASE II STUDY OF THE EORTC BREAST GROUP WITH VOROZOLE (R 83842), A NEW NON-STEROIDAL AROMATASE INHIBITOR IN METASTATIC BREAST CANCER (MBC) - PRELIMINARY RESULTS.

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Vorozole (R 83842), a new potent stereospecific inhibitor of the cytochrome P 450 - dependent aromatase enzyme was tested in an open multicenter phase II trial in postmenopausal patients (pts) with MBC. Eligibility called for progressive disease with measurable lesions, postmenopausal status, ECOG PS $\leq$ 3, ER or PR + or ? status with DFI $\geq$ 1 year, adequate bone marrow, liver and renal functions and informed consent. All pts had to have received one prior endocrine treatment modality as adjuvant and/or as first line treatment of advanced disease; prior adjuvant chemotherapy was also permitted provided a DFI $\geq$ 1 year. Treatment consisted of 1 tablet containing 2.5 mg R 83842, daily in the morning, for at least 2 months and pursued until progression; response evaluation was performed every second month. From December '91 to February '93, 27 pts were included; due to very short follow-up in several cases (median treatment duration 128 days, range 22 to 340 days) data on tolerance and response are only available for 21 and 19 pts respectively. Tolerance was excellent without significant changes of safety biology parameters; among toxicities quoted as probably drug related are hot flushes (3), mild anorexia (5) and mild facial oedema (1). Among 19 pts already evaluated for response there were 1 complete remission (skin lesions) and two partial responses (skin and lung), 9 stabilizations (response status may improve) and 7 failures. Preliminary conclusion : Vorozole is a very well tolerated and active second line hormonal agent in postmenopausal pts with MBC. True response rates and details on hormonal effects must await longer follow-up.