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News

Germ Cell Tumour Conference III

The Yorkshire Regional Cancer Organisation will be holding the germ cell tumour conference III at the University of Leeds, U.K. on 8–10 September 1993. For further information contact P. Hodgins, Yorkshire Regional Cancer Organisation, Cookridge Hospital, Leeds LS16 6QB, U.K. Tel: 532 673411, exn. 402.

Cell Growth and Growth Hormone Forum

The Cell Growth and Growth Hormone Forum is holding a workshop on the superfamily of receptors for growth hormone, prolactin, erythropoietin and cytokines in Haifa, Israel on 7–11 November 1993. For further information contact Margalit Zur, Management and Organization of Congresses, P.O. Box 9095, Ramat Efal 52190, Israel. Tel: 972-3-6355038, Fax: 972-3-5351103, TLX: 371679 GIZU IL.

Anticancer Drug Development

A postgraduate course on anticancer drug development will be held on 8–12 September 1993 in Amsterdam, The Netherlands. The course is organised by the European Cancer Centre Amsterdam (ECC) and the European Society of Medical Oncology (ESMO) in cooperation with the EORTC New Drug Development Office Amsterdam. For further details, contact IKA c/o Robbert F.M. van Bokhoven, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands. Tel: 31-20-617 2903, Fax: 31-20-615 5904.

Monoclonal Antibody Immunoconjugates

The ninth international conference on monoclonal antibody immunoconjugates for cancer will be held on 3–5 March 1994 in San Diego, California, U.S.A. For further details contact Cass Jones, Professional Conference Management Inc., 7916 Convoy Court, San Diego, CA 92111, U.S.A. Tel: (619) 565-9921, Fax: (619) 565-9954.

Gene Therapy of Cancer

The second international conference on gene therapy of cancer will be held on 18–20 November 1993 in San Diego, California, U.S.A. For further details contact Cass Jones, Professional Conference Management Inc., 7916 Convoy Court, San Diego, CA 92111, U.S.A. Tel: (619) 565-9921, Fax: (619) 565-9954.

Letters

Hormone Priming in Breast Cancer: Oestrogen Priming Has a Detrimental Effect on Response in Oestrogen Receptor-negative Patients

Lesley Seymour, Karin Meyer and Werner R. Bezwoda

POTENTIAL THERAPEUTIC benefits from hormonal recruitment of neoplastic cells into the cell cycle has been suggested in a number of preclinical observations and has also been reported in clinical studies [1–4]. Results have, however, not been uniformly favourable [5, 6]. We undertook a randomised controlled trial comparing treatment with combination chemotherapy with or without diethylstilbestrol (DES) priming. Eligibility criteria included pre- and postmenopausal patients with histologically documented recurrent or progressive breast cancer with at least one measurable site of disease. Oestrogen receptor-positive (ER+) and oestrogen receptor-negative (ER−) patients were included in the study. Receptor status was determined at the start of the study by biopsy of accessible metastatic lesions (usually cutaneous), the determinations being carried out immunochemically using a commercially available kit (ER-ICA, Abbot Laboratories) according to the manufacturer's instructions. Additional histological material was utilised for determination of progesterone receptor, proliferative index (PI), assessed by fluorescence-activated cell sorter, and the expression of the proliferation-associated antigen Ki67 [7–9]. Patients with accessible tumour were rebiopsied at the end of oestrogen priming and again at the end of the first cycle of chemotherapy.

The chemotherapy regimen used in both arms of the study was identical and consisted of a combination of cyclophosphamide 600 mg/m^2, mitoxantrone 12 mg/m^2 and vincristine 1.4 mg/m^2 given intravenously (iv) once every 28 days (CNV). Patients randomised to the hormone priming arm (DES-CNV) received DES 5 mg orally daily for 5 days starting on day 1 of each chemotherapy cycle. Postmenopausal patients on the hormone priming arm received, in addition, aminoglutethimide 250 mg twice daily orally throughout the entire treatment period. Randomisation was by the random number closed envelope technique and all patients gave informed consent. The study was

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Table 1. Hormone priming in breast cancer. Patients' characteristics

	DES-CNV	CNV
No. patients entered	23	25
Mean age (range)	48 (29–69)	47 (28–71)
Inevaluable	4	5
Reason for inevaluability for response		
Death prior to initiation of treatment	1	2
Lost after 1st dose of treatment	3	3
Evaluable patients	19	20
Premenopausal	11/19	9/20
ER positive	5/19	5/20
ER negative	14/19	15/20
Metastatic sites		
Soft tissue only	3	6
Bone and local	3	6
Viscera and local	12	10
Inflammatory	5	3

Table 2. Hormone priming in breast cancer: response to treatment

	DES-CNV	CNV
Response rate	5 (26%)	11 (55%)
Complete response	2 (10%)	5 (25%)
Partial response	3 (16%)	6 (30%)
No response	14 (74%)	9 (30%)

approved by the Ethics Committee of the University of Witwatersrand and was carried out in accordance with the principles of the Declaration of Helsinki.

A total of 48 patients were eligible and randomised. 9 (19%) patients defaulted from treatment during the first course and were considerd to be unevaluable for response and time to treatment progression. Survival analysis, however, includes these patients up to the time of last follow-up. Further patient details are shown in Table 1.

Of the 19 evaluable patients who received DES-CNV, 5 (26%) achieved a response with 2 (11%) complete responses. In the CNV treatment arm the objective response rate was 11/20 (55%) with 5 (25%) complete responders (Table 2). This difference in overall response rate approached statistical significance ($P = 0.06$) and was significant for the subgroup of ER− patients ($P = 0.02$), with 8/15 (53%) of ER− patients responding to CNV alone vs. 2/14 (14%) responding to DES-CNV. Among the patients receiving CNV alone, there was no significant difference in response rate according to ER status. Premenopausal patients had a significantly higher response to CNV (7/9, 77%) than did postmenopausal patients (4/11, 36%) ($P = 0.05$).

Neither progesterone receptor, tumour ploidy or percentage positivity for the proliferation-associated antigen Ki67 had any impact on response rate. Both ER+ (4/6, 67%) as well as ER− (10/14, 71%) patients who were rebiopsied after DES priming showed an increase in PI and Ki67 expression.

Time to treatment failure (median 200 days for patients receiving DES-CNV, 300 days for patients receiving CNV), as well as overall survival (median 410 days, DES-CNV and 450 days, CNV), were not significantly different between the two treatment groups.

The present study showed a significantly lower response rate among ER− patients receiving DES-CNV. That this difference is due to the oestrogen priming is suggested by the lack of significant differences in response to chemotherapy alone when ER+ and ER− patients are compared.

Reasons for the adverse effect of oestrogen priming need to be considered. While the DES dose used was relatively large and the duration of oestrogen treatment (5 days) was somewhat longer than that described in other studies, it should be pointed out that one of the objects of oestrogen priming, namely recruitment of cells into the growth cycle, as evidenced by increase in PI and Ki67 expression, was in fact achieved with this regimen, irrespective of ER. A number of previous studies have shown that pharmacological doses of oestrogen can increase the proliferation of tumour cells even in the absence of specific receptor protein. It may well be the ability of oestrogen to stimulate ER− breast tumours that was responsible for the adverse effect on response rate since there is no evidence to suggest that oestrogens have any effect on chemotherapy drug uptake or efflux.

The results of this study suggest that hormonal recruitment is unlikely to play a major role in improving results of chemotherapy for advanced breast cancer and in ER− subgroups may well have a deleterious effect.

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