European Journal of Cancer Vol. 30A, No. 5, p. 723, 1994.

0959-8049/94 $7.00 + 0.00

0959-8049(94)E0085-5

Dose Intensification in the Treatment of Patients With Testicular Germ Cell Tumours

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IN A RECENT edition of the *European Journal of Cancer*, Abrizzoni and colleagues reported the results of a study aimed at determining the feasibility of using granulocyte–macrophage colony stimulating factor (GM-CSF) to facilitate delivery of high dose intensity chemotherapy to patients with small cell lung cancer [1]. Their results demonstrate that, although the use of GM-CSF did allow some increase in delivered dose intensity, cumulative haematological toxicity (particularly thrombocytopenia) precluded the administration of more than a limited number of courses. Moreover, toxicities other than myelosuppression have also been reported to become dose limiting using this approach to dose intensification [2].

A recent review of the literature has supported the concept of dose intensification in the treatment of patients with testicular germ cell tumours [3]. We devised a high dose intensity weekly chemotherapy schedule comprising bleomycin 15 mg intramuscular (i.m.), etoposide 100 mg/m^2 intravenous (i.v.), vincristine 1.0 mg/m^2 i.v. (maximum 2 mg) and cisplatin 75 mg/m^2 i.v. (BEOP) for patients with resistant or relapsed germ cell tumours. In an initial cohort of 13 patients, treatment was given weekly provided that the white blood cell count (WBC) was $\geq 2.0 \times 10^9$/l and the platelet count was $\geq 50 \times 10^9$/l. If myelosuppression occurred, treatment was delayed until blood counts had recovered to these levels. Cisplatin dose was reduced if significant deterioration in renal function occurred. In a pilot study, all 9 patients who received four or more cycles of BEOP experienced treatment delays and/or dose reductions. There were a total of 14 delays in treatment either due to neutropenia ± thrombocytopenia ($n = 11$) or thrombocytopenia alone ($n = 3$). In addition, cisplatin dose was reduced in 40 (48%) courses. Having defined the toxicity of BEOP without colony stimulating factor support, we then treated a second cohort of patients using filgrastim (G-CSF), kindly supplied by Amgen, in conjunction with BEOP. Patients received weekly BEOP until the WBC was $<2.0 \times 10^9$/l. Treatment was then delayed until haematological recovery and patients subsequently received filgrastim 5 μg/kg subcutaneous daily for 5 days between cycles of BEOP.

17 patients entered this part of the study. 2 patients were withdrawn from study during weeks 1–4 due to renal failure and 1 patient died from an infection after course 3. The remaining 14 patients received a total of 115 cycles of BEOP. The median time to first treatment delay was 4 weeks (range 3–5) and this delay was due to neutropenia ± thrombocytopenia in 13/14 patients. Following haematological recovery, treatment with filgrastim was initiated between cycles of therapy. 4 patients did not experience further dose delays. However, the remaining 10 patients experienced 15 further dose delays: three delays were due to neutropenia alone, four to neutropenia and thrombocytopenia, six to thrombocytopenia alone and two to non-neutropenic sepsis. In addition, a reduction in cisplatin dose because of significant deterioration in renal function (i.e. glomerular filtration rate failing to <50 ml/min) was necessary in 33/115 (29%) courses. Thus, while filgrastim support allowed BEOP chemotherapy to be delivered with fewer treatment delays due to neutropenia, thrombocytopenia and nephrotoxicity continued to be major problems limiting the intensity of chemotherapy possible with this schedule. Although the use of currently available CSFs may abrogate chemotherapy-induced neutropenia, alternative toxicities (both haematological and non-haematological) may still preclude significant dose intensification.

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Received 7 Oct. 1993; accepted 11 Oct. 1993.

European Journal of Cancer Vol. 30A, No. 5, pp. 723–724, 1994.

0959-8049/94 $7.00 + 0.00

0959-8049(93)E0103-W

The Concomitant Expression of Oncogenes and Growth Factors in Human Breast Cancer

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TUMORIGENESIS HAS long been thought to be a multistep process [1]. Evidence from experiments with primary rodent cells, and also from studies on transgenic animals, indicate that the

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Received 4 Nov. 1993; accepted 11 Nov. 1993.

Table 1.

No. of positive parameters	% of positive cases	Combination
1	30.9	
Total	30.9	c-*myc*
2	18.1	c-*myc* + EGF R
	11.0	c-*myc* + c-*erb*B-2
	1.8	c-*myc* + TGF α
Total	30.9	
3	9.1	c-*myc* + EGF R + TGF α
	5.5	c-*myc* + EGF R + c-*erb*B-2
	1.8	c-*myc* + c-*erb*B-2 + c-H-*ras*
Total	16.4	
4	7.2	c-*myc* + EGF R + c-*erb*B-2 + TGF α
	1.8	c-*myc* + EGF R + c-*erb*B-2 + c-H-*ras*
	1.8	c-*myc* + EGF R + TGF α + c-H-*ras*
Total	10.8	
5	11.0	c-*myc* + EGF R + c-*erb*B-2 + TGF α
Total	11.0	+ c-H-*ras*

expression of two or more oncogenes is required for tumorigenic transformation [2, 3]. However, in spite of large numbers of studies, very few data are available from human cancer in support of this theory.

Recently we have reported an immunohistochemical study on expression of c-*myc*, c-*erb*B-2, c-H-*ras*, epidermal growth factor receptor (EGFR), transforming growth factor (TGF)-α, oestrogen and progesterone receptors in human breast lesions [4]. Closer examination of these cases (and also of additional cases analysed since then) revealed an interesting pattern of expression in those tumours that were positive for investigated parameters. We noticed, by parallel monitoring of the same areas of tumour, that the investigated parameters are overexpressed in a certain order, thus allowing sorting into groups (Table 1).

In our study, the samples in which only one parameter (c-*myc*) was positive showed weak immunoreaction. In contrast, in the tumours in which four and five parameters were positive concomitantly, there was strong immunoreaction. These multiple positive tumours also seemed to have higher metastatic potential, since all were staged as T2–4 and N1–3, while none of the patients bearing tumours with one or two positive parameters had confirmed positive lymph nodes, and most of the tumours (32/37) were staged as T1–2. Whether this finding indicates the cascade of events in the oncogenic transformation of breast cancer cells, or simply is the result of simultaneous independent events is unknown. Although it is possible that total accumulation of changes is responsible for determining the biological properties of the tumour, our results indicate that genetic alterations in breast cancer often occur according to a preferred sequence, and result in subsequent amplification and/or overexpression of nuclear oncogenes/transcription factors (presumably *myc*), membrane-associated G proteins (*ras* family), receptor and non-receptor protein tyrosine kinases (i.e. EGF-R, $p185^{erbB\text{-}2}$), and growth factors (i.e. EGF, TGF-α) [3]. Furthermore, our results are in agreement with the theory (also supported by numerous *in vitro* studies) according to which tumorigenic transformation occurs predominantly as a result of "cooperation" between oncoproteins from different subgroups (i.e. "nuclear" and membrane-associated).

Due to variations in approach and the factors analysed, comparison of these results directly with different studies is difficult. However, a comparable pattern of expression has been reported in one previous study [5]. The presented data suggest that simultaneous monitoring of various (potentially oncogenic) parameters in a larger number of patients would add to our better understanding of transformation processes, and bring us, eventually, one step closer to an aetiologically based classification of breast cancer.

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