Eur J Cancer, Vol. 29A, No. 6, p. 924, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00


# Side-effects of GM-CSF Treatment in Advanced Testicular Cancer

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WITH THE increasing use of haematopoetic growth factors the benefits and the risks of these drugs need to be further determined. The biology and clinical applications of granulocyte (G) and granulocyte–macrophage (GM) colony-stimulating factor (CSF) have been described in many reviews [1, 2]. However, different frequencies of side-effects have been reported. In a recent phase I study, using subcutaneous application of bacterially synthesised GM-CSF in patients with different malignancies, the GM-CSF-related toxicity was regarded as minimal [3].

In a phase I/II study at Hannover University Medical School (Hannover, Germany) 59 patients with newly diagnosed metastatic advanced germ cell tumours were treated by dose-intensified chemotherapy with the platinum/etoposide/ifosfamide regimen (PEI). The 5-day regimen of PEI chemotherapy was repeated every 22 days for a total of four cycles, followed by subcutaneous GM-CSF (Shering Plough, Kenilworth, U.S.A.) starting the first day after chemotherapy (day 6) for 10 consecutive days. The first 38 patients received GM-CSF at a dose of 10 μg/kg bodyweight daily; the next 21 patients were treated with a lower dose of 5 μg/kg of GM-CSF. The incidence of side-effects of GM-CSF therapy is shown in Table 1. An interim analysis of the study results is given elsewhere [4].

Overall, 8 of 59 patients (13.5%) had to discontinue GM-CSF due to side-effects. In 1 patient with anaphylactic type reaction, who suffered from a prolonged phase of neutropenia after his fourth cycle of chemotherapy, GM-CSF was reinstituted with concomitant application of prednisolone (100 mg/day) which was well tolerated. Neither the frequency nor the severity of the anaphylactic type reactions in our patients was dependent upon the dose of GM-CSF used, either 10 or 5 μg/kg. In 3 patients with particularly severe reactions (two anaphylactic type, one cutaneous), who were further evaluated for plasma IgE levels and GM-CSF antibodies, no abnormalities were found. Biopsies from cutaneous reactions at the site of GM-CSF injection showed oedema of all skin layers and interstitial infiltration with lymphocytes and eosinophils, resembling the histological picture of skin eruptions in 3 patients with leukaemia receiving continuous systemic treatment with GM-CSF [5]. Overall, the incidence of skin reactions in patients with testicular cancer was low. In a placebo-controlled trial using GM-CSF for dose-intensive chemotherapy in patients with inflammatory breast cancer, all 7 patients randomised into the GM-CSF arm developed skin infiltrates at the site of injections [6].

The side-effects of GM-CSF treatment may not only be related to the underlying neoplastic disease but also to the type of cytostatic treatment used and its immunosuppressive potential. Further data on the side-effects of haematopoetic growth factors are clearly needed.

*Table 1. GM-CSF-related side-effects in 59 testicular cancer patients treated with intensified PEI chemotherapy*

| Side-effects | Number of patients | | |
|---|---|---|---|
| | 5 μg/kg | 10 μg/kg | Total |
| Anaphylactic type reaction (bronchospasm, myalgia, fever, skin reaction) | 2 | 3 | 5 (8.4%) |
| Fever (without infection) | 0 | 3 | 3 (5.1%) |
| Cutaneous reaction alone | 1 | 1 | 2 (3.4%) |

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Received 28 Oct. 1992; accepted 20 Nov. 1992.

Eur J Cancer, Vol. 29A, No. 6, pp. 924–925, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00


# Papillomavirus, p53 Alteration and Primary Carcinoma of the Vulva

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RECENT MOLECULAR studies on the role of human papilloma virus (HPV) in the genesis of genital carcinomas indicate as a

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Received 25 Sep. 1992; accepted 5 Oct. 1992.