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Use of Granulocyte Growth Factors in Solid Tumours

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INTRODUCTION

RECOMBINANT GRANULOCYTE colony-stimulating factor (rHuG-CSF) is a glycoprotein hormone which has been produced in mammalian cells through recombinant DNA technology. It stimulates proliferation, differentiation and activation of committed progenitor cells of the neutrophil–granulocyte lineage, and has been investigated as therapy for patients with various neutropenic conditions, both iatrogenic and disease-related.

Major usage of rHuG-CSF currently is in amelioration of neutropenia which follows cytoreductive chemotherapy: rHuG-CSF accelerates neutrophil recovery after chemotherapy, leading to a reduction in duration of the neutropenic phase and, consequently, antibiotics usage and duration of hospitalisation. rHuG-CSF may allow increased dose intensity and stricter adherence to chemotherapy schedules, which is of interest when treating chemosensitive tumours.

Several studies have indicated that rHuG-CSF enhances neutrophil recovery after various chemotherapy regimens, including those which are anthracycline or platinum based. Fifty per cent of the patients with granulocyte counts less than 500/mm^3 will develop severe infections, particularly when the neutropenia lasts for more than 3–5 days. Indeed, infection remains one of the most common causes of death in chemotherapy patients. Decreasing or preventing the period of neutropenia with rHuG-CSF therapy offers the potential to reduce morbidity, cost and even mortality associated with chemotherapy.

The three main therapeutic uses for rHuG-CSF in cancer patients undergoing myelosuppressive chemotherapy are: (1) prophylactic: all patients receive rHuG-CSF after chemotherapy; (2) pre-emptive: given to patients at high risk of becoming neutropenic in order to prevent infections; and (3) interventional: treatment of patients with neutropenic fever.

PROPHYLACTIC USE

Growth factors are currently used prophylactically following the first cycle of myelosuppressive chemotherapy in the treatment of chemosensitive tumours. Solid tumours should be defined as chemosensitive when: (a) overall patient response is > 50%; (b) 10–20% complete response can be achieved with standard therapy; and (c) chemotherapy treatment improves survival.

Results of clinical trials for a number of cancers, including small cell lung cancer (SCLC), bladder carcinoma, breast carcinoma and sarcomas, using rHuG-CSF prophylactically, are available in recent literature.

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SCLC treatment is the most actively studied in terms of myelosuppression. The first published study [1] tested the effect of rHuG-CSF given to each patient for 14 days on alternate cycles only of AIE chemotherapy (doxorubicin, ifosfamide and etoposide) so that each patient acted as his own control. Cycles supported by rHuG-CSF had shorter and less severe episodes of neutropenia and also fewer febrile episodes.

The results of the first randomised, placebo-controlled trial were published in 1991 [2]. In this study of 199 evaluable patients receiving up to six cycles of chemotherapy (CAE: cyclophosphamide, doxorubicin, etoposide) for SCLC, the incidence of severe (grade IV) neutropenia was reduced, relative to placebo, in rHuG-CSF recipients (98 versus 84%), as was the median duration of episodes (6 versus 1 day across all cycles). A 50% reduction in the frequency of infection, as manifested by fever with neutropenia, was produced; decreases in the rate of culture-confirmed infections, mean number of days of hospitalisation and of intravenous antibiotic use were of a similar magnitude. This prospective effect persisted during the six cycles of chemotherapy. The percentage of patients who qualified to receive the next planned cycle of chemotherapy was significantly increased, although complete responses and overall survival were the same with or without rHuG-CSF.

The third trial in SCLC was presented at the American Society of Clinical Oncology Meeting 1992 [3]. Patients were randomised to receive either CODE alone (cisplatin, vincristine, doxorubicin and etoposide) or CODE plus rHuG-CSF. Febrile episodes were significantly reduced and dose intensity increased, but total response did not improve in patients receiving rHuG-CSF. Although these preliminary results suggest that CODE plus rHuG-CSF improved the clinical outcome, the follow-up period was too short and the number of patients too few to reach a conclusion.

Finally, the European G-CSF Lung Cancer Study Group [4] has conducted a randomised study comparing CAE plus rHuG-CSF with CAE plus placebo in 130 patients with SCLC. The results were consistent with previous studies: febrile neutropenia and antibiotic use were reduced in the rHuG-CSF group, treatment delays occurred more frequently in the placebo group, but responses and survival were similar.

In conclusion, while prophylactic use of rHuG-CSF in SCLC reduces neutropenia and allows dose escalation, studies reported thus far have not shown a significant increase in terms of response and survival. Similar studies in breast cancer [5, 6], bladder carcinoma [7–9] and sarcomas [10] have only reported myelosuppression as an endpoint, response and overall survival were not included (Table 1).

In prophylactic administration protocols of rHuG-CSF, the following points should be considered:

Table 1. Randomised studies investigating the role of rHuG-CSF in small cell lung cancer treatment: results for chemotherapy plus rHuG-CSF as compared to the control group

Study	No. of patients	Dose intensity	Febrile episodes	Response (CR + PR)	Overall survival
Trillet-Lenoir 1993 [4]	130	Higher	Less	NS	NS
Crawford 1991 [2]	207	Higher	Less	NS	NS
Fukuoka 1992 [3]	64	Higher	Less	NS	$^*P < 0.05$

* Compared to control treatment group. CR, complete response, PR, partial response; NS, non-significant.

Drug dosage. The recommended starting dose of rHuG-CSF is 5 μg/kg/day subcutaneously. Although the increase in neutrophil counts appears to be dose-proportional, the effective dose of rHuG-CSF may have individual variation.

Initiation and duration of therapy. Prophylactic rHuG-CSF administration usually begins 24 h postchemotherapy in order to allow elimination of cytotoxic compounds and their metabolites. The period of administration varies in practice, however; day 18–21 or until the neutrophil count is in excess of 10 000/mm^3 is feasible. Early discontinuation of therapy should be avoided as a 50% decrease of granulocytes will be expected to occur after 24 h.

Activity. A study performed by Crawford [2] suggests that a similar efficacy can be expected when rHuG-CSF is administered from the first cycle to the sixth; median duration of neutropenia in the rHuG-CSF group was consistently 1 day.

Safety. There are insufficient data to draw any conclusions regarding the effect of rHuG-CSF on tumour growth. Because of the concerns that it may stimulate proliferation of malignant leukaemic cells in acute myeloid leukaemic patients undergoing chemotherapy, the therapeutic use of rHuG-CSF in these patients is speculative and currently under investigation.

Adverse effects. rHuG-CSF is generally well tolerated. Mild or moderate bone pain, the main adverse effect occurring in about 20% of patients, is alleviated with acetaminophen. Patients with inflammatory or cutaneous disease may have exacerbation of symptoms which resolve after discontinuation of rHuG-CSF administration. A rise in serum levels of lactic dehydrogenase (LDH), alkaline phosphatase and uric acid occurs during treatment, particularly with higher doses of rHuG-CSF.

Cost/benefit analysis. This should be incorporated in all study protocols of growth factors.

PRE-EMPTIVE USE

Pre-emptive use of rHuG-CSF indicates introduction from the second cycle of high dose chemotherapy to those patients recognised to be at high risk of infection, either when the previous granulocyte nadir was < 500/mm^3 or in order to avoid treatment delays in patients with < 1000/mm^3 granulocytes at day 1 of chemotherapy. Patients in the high risk category include those in whom: (a) cytostatic chemotherapy has induced a neutropenia of < 500/mm^3; (b) Karnofsky index < 70; (c) age is > 70 years old; (d) cancer-related AIDS is diagnosed; (e) patients with poor bone marrow medullary function.

Only one study comparing prophylactic use of rHuG-CSF with pre-emptive use is available to date [11]. 40 patients with non-small cell lung cancer (NSCLC) receiving chemotherapy (cisplatin, mitomycin C and vindesine), were randomised to receive 2 μg/kg/day rHuG-CSF, on four schedules: (1) control group: no rHuG-CSF; (2) group A: rHuG-CSF days 2–15; (3) group B: rHuG-CSF days 8–21; and (4) group C: rHuG-CSF when neutrophil count was < 1000/mm^3. The results indicated that chemotherapy with prophylactic administration of rHuG-CSF (groups A and B) was more beneficial than therapeutic administration (group C). However, larger numbers of patients and longer follow-up periods are required to draw definitive conclusions.

INTERVENTIONAL USE

Clinical trial data indicate that the administration of rHuG-CSF to patients with severe neutropenia may result in a reduction of antibiotic use, together with a reduction in hospitalisation periods. Only two randomised trials have explored the potential ability of rHuG-CSF to reduce the duration of neutropenia, which is the main prognostic factor in patients with neutropenic fever. In the first study, by Maher and colleagues [12], 216 patients with neutropenic fever (temperature > 38°C, granulocytes count < 1000/mm^3), were randomised to receive rHuG-CSF or placebo. rHuG-CSF administration reduced days of neutropenia, fever and febrile neutropenia. In the second study, by Mayordomo and colleagues [13], 83 patients with neutropenic fever (temperature > 38°C, granulocytes count < 500/mm^3), were randomised to receive placebo, rHuG-CSF or granulocyte–macrophage (GM)-CSF. Preliminary results show that the addition of rHuG-CSF or GM-CSF shortened the duration of severe neutropenia and the duration of hospitalisation. Indeed, this approach was cost-effective and further randomised studies are ongoing.

CONCLUSIONS

The prophylactic use of rHuG-CSF appears to reduce the frequency, intensity and duration of neutropenia with fewer febrile episodes and infections. These benefits allow dose optimisation and dose intensification in chemosensitive tumours. However, the real value of rHuG-CSF in terms of increased response rate and overall survival does require evaluation. Clinical trials are required to compare the prophylactic and pre-emptive use of rHuG-CSF in order to define its optimal application. At present, the use of rHuG-CSF in the treatment of neutropenic fever needs additional clinical trials to determine the cost/benefit ratio.

In summary, there is no clear evidence supporting the use of rHuG-CSF in patients with solid tumours receiving standard chemotherapy, except to alleviate a few days of fever, and whether that is of practical relevance is debatable. To prove that the use of rHuG-CSF in standard clinical practice is worthwhile, it would be necessary to conduct additional randomised trials to look for a survival advantage.

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Dose Optimisation and Dose Intensification in Malignant Lymphoma

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INTRODUCTION

IT IS self evident that the response of malignant lymphomas to cytotoxic drugs is related to dose insofar as the adminstration of homeopathic dose does not effect remission. The issue, therefore, is whether steps to optimise the therapy given (full dose, on time) or to escalate the doses above that in standard protocols will improve the remission and survival rates.

The work of Skipper and colleagues [1,2] certainly provides a theoretical rationale for the belief that modest increments in cytotoxic drug delivery could effect greater responses: in a number of animal tumour cell lines, there was a log linear relationship between tumour cell kill and administered dose. It must be borne in mind, however, that there are a number of limitations in extrapolating from this type of data to the clinical setting. It can, for instance, be argued that animal tumour models poorly reflect human tumours. The original model used by Skipper assumes that the growth rate of tumours is exponential, which is not the case at all times; this is well illustrated by a consideration of the growth kinetics in multiple myeloma. This same model also assumes that cure is brought about by the elimination of all tumour cells by the cytotoxic agents, not taking into account any host anti-tumour mechanisms.

DOSE OPTIMISATION

There is no feasible replacement for good clinical data, but, unfortunately, the availability of this type of data is limited. Several lymphoma studies have shown that those patients who do not receive full dose therapy [3, 4] have a lower response rate and survival, and it has been suggested that optimising such therapy with haematopoietic growth factors will improve the response rates. However, it should also be taken into account that failure to give planned therapy is related to the age of the patient, stage of the disease (e.g. marrow involvement) and overall performance status, all of which might predict, independently of drug delivery, for a poor outcome. Definite evidence of the benefits of dose optimisation cannot, therefore, be obtained from retrospective analyses. One randomised trial has been performed in ovarian carcinoma where patients were deliberately given half dose therapy, albeit for twice as long [5]. The responses and overall survival were reduced in the low dose

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