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Original Paper

Febrile Neutropenia: Prophylactic and Therapeutic Use of GM-CSF

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THE RELATIONSHIP between the severity of neutropenia and risk of serious infection has been well recognised [1]. The duration of granulocytopenia is also important as it increases the risk of second or multiple infections including invasive fungal infections. Neutropenia is subdivided into four grades depending on the absolute granulocyte level, Grade I: $>1.0\times10^9$/l; Grade II: $0.5–1.0\times10^9$/l; Grade III: $0.1–0.5\times10^9$/l and Grade IV: $<0.1\times10^9$/l. The incidence of serious infections in grade III and IV neutropenia is approximately 80–100%. Other factors which enhance the incidence of febrile episodes in neutropenic patients are: alteration of patients' physical barriers including mucositis and indwelling intravenous (i.v.) catheters, status of patients' humoral and cellular immune system and impaired phagocytic, microcidal and tumouricidal function of neutrophils monocytes and macrophages [2, 3].

In recent years use of dose-intensive chemotherapy has improved the remission rates in some patients with cancer. This approach has also increased the severity and duration of neutropenia. Consequently, the risk of infections remains the commonest cause of morbidity and mortality in cancer patients receiving dose-intensive chemotherapy. Approaches to prevent infections in these patients have employed various measures including strict personal hygiene for the patient, reverse barrier nursing, filtered air with or without laminar air flow system and use of prophylactic antibiotics. Earlier reports suggest that chemotherapy patients treated within a protective environment and given prophylactic antibiotics have lower incidence of severe infections [2]. Recent data indicate that all these cumbersome measures may not be necessary in all patients receiving chemotherapy and risk of infection can be decreased further if the severity and duration of neutropenia is reduced [1, 3]. It is suggested that use of cytokines including granulocyte-colony stimulating factors (G-CSF), granulocyte macrophage-colony stimulating factors (GM-CSF) can ameliorate chemotherapy induced neutropenia [4, 5]. Various clinical trials have assessed the prophylactic and therapeutic role of GM-CSF in febrile neutropenia (temperature exceeding 38°C and absolute neutrophil count ANC $<0.5\times10^9$/l). Preclinical studies demonstrate that GM-CSF enhances myeloid recovery and reduces the duration of neutropenia. In addition it promotes the functional activation of neutrophils, eosinophils and macrophages. *In vitro* GM-CSF increases the phagocytic and fungicidal activity of neutrophils against *Candida albican* and *Torulopsis glabrata* and exposure of monocytes to GM-CSF *in vitro* results in increased killing of *C. albicans* and *Aspergillus fumigatus* [4, 5]. Taken together, improvement of neutropenia and host defence mechanisms by GM-CSF therapy could be beneficial in post-chemotherapy patients [6, 28]. To this end, various investigators have reported a possible role of GM-CSF in afebrile and febrile neutropenia.

Rowe and colleagues [7] conducted an Eastern Cooperative Oncology Group (ECOG) phase III prospective study of GM-CSF during induction therapy for elderly patients with acute myeloid leukaemia (AML) (aged >55 to 70 years). Patients were treated with daunorubicin 60 mg/m^2 i.v. for 3 days, and cytosine arabinoside 100 mg/m^2 i.v. for 7 days. A bone marrow examination was performed 3 days after completion of one or two cycles and if this was aplastic, yeast drived GM-CSF at a dose of 250 μg/m^2 or placebo was commenced on day 11 until neutrophil recovery to 1.5×10^9/l. A total of 124 patients were entered in this study. Neutrophil recovery was significantly shortened among patients receiving GM-CSF (P value 0.0015). There was no difference in the platelet or red cell recovery. Despite the theoretical risk of stimulation of leukaemia with GM-CSF therapy in cases with AML, the relapse rates were similar among all patients (GM-CSF and placebo group) who achieved complete remission. There were significant differences in the death rate from pneumonia and fungal infections. 99 patients were analysed for documented fungal infections (GM-CSF $n=52$, placebo $n=47$). ECOG data show reduced morbidity and mortality in patients receiving GM-CSF. The mortality from fungal infections, *aspergillus* and *candida* in the GM-CSF group was 1.9% compared with 19% among those receiving placebo ($P<0.001$). The overall mortality from fungal infections was 13% and 75% in patients receiving GM-CSF and placebo, respectively.

Other well-designed trials [8, 9] have used *Escherichia coli* derived GM-CSF (leucomax) after induction therapy in elderly patients with AML and show statistically significant difference with regards to neutrophil recovery time, however, there was no difference in the morbidity due to infections and median survival among GM-CSF and placebo group patients. Contrary to this, the largest G-CSF trial, reported

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by Heil and colleagues [10], showed an enhanced neutrophil recovery time was associated with significant reduction in morbidity and there was a decreased requirement for amphotericin-B in these patients. In a controlled trial, Mayordomo and colleagues [11] compared GM-CSF, G-CSF and placebo as an adjunct to antibiotics in neutropenic fever. Neutropenic fever was defined as a temperature exceeding 38°C and an absolute neutrophil count ANC $<0.5\times10^9$/l. 121 patients with neutropenic fever secondary to standard dose cancer chemotherapy were randomised to receive placebo or 5 μg/kg/day of GM-CSF or G-CSF in conjunction with antibiotics. Treatment was continued until 2 days after the temperature normalised and ANC recovered to $>1\times10^9$/l. Compared with placebo median duration of neutropenia and hospital stay were reduced with G-CSF or GM-CSF therapy ($P<0.001$), but the median duration of fever did not differ. Another trial [12] used GM-CSF (leucomax) (5 μg/kg/day) or placebo as an adjunct to antibiotic therapy in 134 patients with haematological malignancies or solid tumours who developed chemotherapy-related neutropenic fever. After 4–5 days GM-CSF therapy, accelerated neutrophil recovery was observed with significant difference from placebo ($P<0.001$). There was no difference in median duration of fever or hospital admissions.

Anaissie and colleagues [13] conducted a trial in 107 cancer patients with febrile neutropenia employing a lower dose of GM-CSF (leucomax, 3 μg/kg/day) as an adjunct to antibiotic therapy. It was suggested from this trial that routine use of GM-CSF is not recommended in neutropenic fever but GM-CSF therapy may be beneficial in a subgroup of patients with refractory infections and persistent profound neutropenia (ANC $<0.1\times10^9$/l). It has been suggested from various data that there is enhanced neutrophil recovery with GM-CSF, but conclusions about the resolution of fever, reduction in morbidity, duration of hospital stay and improved median survival continue to create contention among investigators (Table 1). These randomised trials emphasise the need to identify the group of patients who will clearly benefit from pre-emptive and therapeutic use of GM-CSF to prevent and treat febrile neutropenia. One important group is patients with presumed fungal infections.

PROPHYLACTIC AND THERAPEUTIC ROLE OF GM-CSF IN FUNGAL INFECTIONS

Disseminated fungal infections in postchemotherapy patients are a major cause of morbidity and mortality at all ages. They are difficult to diagnose, particularly early in the course of the disease when therapy may be most effective. Amphotericin, conventional or liposomomal, is the drug of choice for fungal infections. It is suggested from various pilot studies that adding GM-CSF to conventional amphotericin B accelerates the neutrophil and monocyte recovery and potentiates the antifungal activity of the monocytes/macrophages system [4, 6, 14]. Consequently, febrile neutropenic patients with presumed fungal infections respond more frequently to conventional amphotericin and the need for

Table 1. *Role of cytokines in febrile and afebrile neutropenia*

Cytokine/ placebo/ control	*n* of pts	Start day	Diagnosis	Reduction in neutropenia *P* value 0.05	Reduction in duration of fever/infections	Reduction in hospitalisation	Author [ref.]
GM-CSF/ placebo	41	D0	Autologous BMT recipients for lymphoma	Yes	Yes	NS	Nemunaitis and colleagues [25]
GM-CSF/ placebo	134	Neutropenic fever adjunct to antibiotics	Solid tumours and haematological malignancies	Yes	NS	NS	Vellenga and colleagues [12]
GM-CSF/ G-CSF/ placebo	124	Neutropenic fever adjunct to antibiotics	Poststandard dose chemotherapy for cancer patients	Yes	NS	Yes	Mayodomo and colleagues [11]
GM-CSF/ placebo	107	Neutropenic fever adjunct to antibiotics	Poststandard dose chemotherapy for cancer patients	Yes	NS	Yes but NS	Anaissie and colleagues [13]
GM-CSF/ placebo	117	D11	Postinduction chemotherapy for AML	Yes	Yes	NS	Rowe and colleagues [7]
GM-CSF/ control	316	D1–8	During induction chemotherapy for AML	Yes	NS	NS	Lowenberg and colleagues [9]
GM-CSF/ placebo	209	D1	During induction chemotherapy for AML	Yes	NS	NS	Witz and colleagues [26]
GM-CSF/ placebo	379	D8	Postinduction chemotherapy for AML	Yes	NS	NS	Stone and colleagues [8]
G-CSF/ placebo	521	D8	Postinduction chemotherapy for AML	Yes but NS	NS	NS	Heil and colleagues [10]
G-CSF/ placebo	138	Afebrile neutropenia (ANC $<0.5\times10^9$/l)	Poststandard chemotherapy solid tumours and lymphomas	Yes	NS	NS	Hartmann and colleagues [27]
G-CSF/ placebo	234	D11	Postinduction chemotherapy in elderly AML	Yes	Yes	NS	Godwin and colleagues [24]

ANC, absolute neutrophil count; NS, non-significant; AML, acute myeloid leukaemia; BMT, bone marrow transplant.

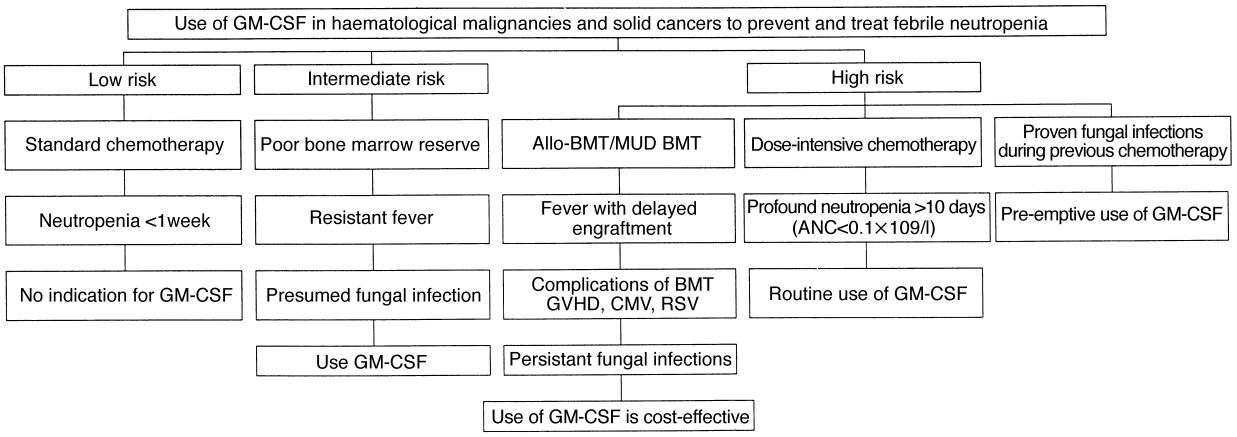

Figure 1. Algorithm for GM-CSF therapy. GM-CSF, granulocyte macrophage-colony stimulating factor; allo-BMT, ?-bone marrow transplant: MUD BMT, ? bone marrow transplant; ANC, absolute neutrophil count; MUD, match unrelated donor; BMT, bone marrow transplant; GVHD, graft versus host disease; CMV, cytomegalovirus; RSV, respiratory syncytial virus.

expensive liposomal/lipid complex amphotericin is reduced [15]. It is concluded from these pilot studies that GM-CSF therapy is cost-effective for prevention or treatment of presumed fungal infections [6, 15].

Pharmacoeconomics

The European School of Oncology (ESO) panel [16] and the American Society of Clinical Oncology (ASCO) [17, 18] panel recommended that if the rate of febrile neutropenia in postchemotherapy patients is less than 40% then use of haemopoietic growth factors will not reduce costs [19, 20]. Economic analysis on the use of GM-CSF in primary prophylaxis and secondary prophylaxis, i.e. before development of febrile neutropenia and after episode of febrile neutropenia respectively, has been performed. Cost-minimising studies performed in 1997 show that savings of US$16 000 can be made by using malgamostim (*E. coli* derived GM-CSF) in autologous bone marrow transplant (BMT) recipients [21]. Pharmacoeconomic data of sargramostim (yeast derived GM-CSF) use in autologous BMT showed cost savings of US$14 500 and US$12 513 in 1994 and 1996, respectively [21]. Contrary to this, Uyl-de Groot and colleagues [22] reported that GM-CSF as an adjunct to intensive therapy in elderly AML was not cost-effective and did not reduce neutropenic fevers and days in hospital. The overall cost of GM-CSF and chemotherapy in an EORTC trial was US$40 782 compared with US$34 465 with chemotherapy alone. It is suggested that starting GM-CSF at day +7 postchemotherapy rather then day 0 can save the cost of 7 days GM-CSF with no clinical detriment. In addition, use of low-dose GM-CSF in febrile neutropenia can also reduce overall cost and demonstrates the same efficacy as standard dose GM-CSF therapy [13, 23]. We have devised an algorithm for GM-CSF therapy in patients with cancer (Figure 1). Cases are divided into low risk, intermediate risk and high risk groups. There is no indication to use GM-CSF in low risk patients, i.e. patients receiving standard chemotherapy which may cause neutropenia of <1 week duration. In high risk patients, i.e. patients receiving dose-intensive chemotherapy which will lead to profound neutropenia (absolute neutrophil count (ANC $<0.1\times10^9$/l for >10 days) should receive routine GM-CSF at day +7 postchemotherapy. A pre-emptive use of GM-CSF is recommended in patients with proven fungal infection during previous chemotherapy. Use of GM-CSF in intermediate-risk patients with poor bone marrow reserve (hypoplastic AML or myelodysplastic syndrome (MDS) with profound cytopenia or relapsed AML with high risk of infection neutropenia) may be beneficial in reducing infection-related morbidity and mortality. Therapeutic use of GM-CSF in auto/allo/MUD (match unrelated donor) bone marrow transplant remains contentious. We suggest that GM-CSF therapy in cases with delayed engraftment, persistent fever or presumed fungal infection is cost-effective. Our approach is to use GM-CSF in these cases around days +10/+14 postchemotherapy (Figure 1).

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