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The effect of recombinant human granulocyte macrophage colony stimulating factor after chemotherapy of various tumors

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Recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) has been successfully used in different clinical settings. We evaluated the tolerability of rhGM-CSF treatment in addition to its efficacy in preventing myelosuppression and reducing infectious complications after standard-dose chemotherapy of various tumors. Of the patient group analyzed ($n = 308$), 75% had solid tumors and 25% had hematological malignancies. In 27.9% of these patients an infection occurred after the first cycle of chemotherapy and between 8.2 and 19.0% in later cycles with a mean duration of fever (above 38.5°C) of 3.6 days. Treatment with rhGM-CSF was well-tolerated. After the completion of treatment, the investigators assessed the efficacy of rhGM-CSF in 83.7% of the patients as 'very good' or 'good', and as 'moderate' or 'bad' in only 11.5% of patients as well as the tolerability as 'very good' or 'good' in 87.0% of the patients and in 9.4% 'moderate' or 'bad'. We conclude that rhGM-CSF proved to be an effective and well-tolerated tool in preventing myelosuppression and infectious complications after standard-dose chemotherapy of various tumors.

Key words: Cancer, chemotherapy-induced neutropenia, infections, rhGM-CSF.

Introduction

Neutropenia and infection are major dose-limiting side effects of chemotherapy. The magnitude of neutropenia is dependent on the intensity of the chemotherapy regimen. The risk of initial infection and subsequent complications is directly related to the severity and duration of neutropenia.[1] As fever may be the first and often the only manifestation of infection, standard practice for all patients who present with fever in the setting of neutropenia is to receive broad-spectrum antibiotics.[2–4] In addition to the impact on quality of life for the patient, episodes of febrile neutropenia may result in subsequent chemotherapy delays or dose reductions. Reducing the degree of myelosuppression may therefore have the advantage of decreasing morbidity as well as improving disease control. Common therapeutic agents that cause myelosuppression include cyclophospamide, carboplatin, etoposide, cytarabine and doxorubicin.

Granulocyte macrophage colony stimulating factor (GM-CSF) is an endogenous protein which stimulates the proliferation and differentiation of myeloid cells, thus leading to increased granulocyte and monocyte numbers.[5] In addition, recombinant human GM-CSF (rhGM-CSF) enhances the functional activity of these cells, i.e. phagocytosis and antibody-dependent cellular cytotoxicity.[6–9] The cloning and purification of human hematopoietic growth factors like rhGM-CSF and granulocyte colony stimulationg factor (rhG-CSF) has established a new tool to manage chemotherapy-induced myelosuppression. Several studies showed that colony stimulating factors are beneficial after administration with standard-dose chemotherapy.[10,11]

This paper describes a multicenter, open-label study that was performed in order to collect further data on the efficacy and tolerability of rhGM-CSF in daily hematology/oncology practice. Mean outcome measures used were the increase in leucocyte counts and the reduction in infectious complications after standard-dose chemotherapy of various tumors.

Materials and methods

Patients

Between May 1993 and January 1995, 308 patients received rhGM-CSF after chemotherapy of various tumors in 160 institutions in Germany.

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Treatment design

Standard-dose chemotherapy regimens were given with combinations of cyclophosphamide 330–1750 mg/m^2, ifosphamide 1000–2500 mg/m^2/day, carboplatin 388–662 mg/m^2, cisplatin 30–144 mg/m^2, vincristine 1–2 mg/m^2, vinblastine 6–10 mg/m^2, doxorubicin 40–200 mg/m^2, etoposide 150–250 mg/m^2, epirubucin 30–105 mg/m^2, cytarabine 40 mg/m^2/day, bleomycin 15–30 mg/m^2 and/or methotrexate 40–65 mg/m^2. A minimum of one and a maximum of six chemotherapy cycles per patient were analyzed. Unglycosylated rhGM-CSF produced in *Escherichia coli* (LEUCOMAX®; Sandoz/Essex) was administered subcutaneously at a dose of 5.0–10.0 μg/kg/day. The rhGM-CSF treatment started 24 h after the last chemotherapy cycle and was administered daily for 7–10 days. The analysis was performed retrospectively in order to retrieve data on tolerability and hematologic parameters. At the end of treatment a clinical assessment of the overall efficacy and tolerability of rhGM-CSF was made by the treating physician using a scale: very good, good, moderate, bad or very bad.

Diagnostic procedures

Baseline data collected prior to commencing therapy included diagnosis of clinical condition, disease history and tumor staging. Physical examination, blood chemistry and complete blood count was assessed at baseline and at each cycle. Any adverse events, all concomitant medications, fever, antibiotic therapy, the type and severity of infection, organisms involved, and administration of study drug were recorded.

Safety analysis

All changes in physical findings, laboratory values and patient observations (graded according to the WHO system) were included in the safety analysis.

Results

A population of 308 patients including 75% with solid tumors and 25% with hematologic malignancies were treated with GM-CSF. In 76% of the patients a primary tumor was diagnosed and in 24% a recurrence was treated during the course of this study. The detailed patient characteristics are shown in Table 1. A total of 746 chemotherapy cycles were studied, resulting in a mean number of 2.4 chemotherapy cycles per patient. All patients had enhanced leucocyte recovery that was mainly due to neutrophil recovery. However, the monocyte and eosinophil counts were also enhanced. The leukocyte recovery after rhGM-CSF application was more pronounced in chemotherapy cycles 1–3 in comparison to later cycles (Figure 1).

In a total of 80 patients (26.0%) 132 infectious episodes occurred and in 27.9% of these patients an infection occurred after the first cycle of chemotherapy. The incidence of infection was between 8.2 and 19.0% during cycles 2–6. Causative organisms were bacteria (36.4%), fungi (12.1%), viruses (2.3%) and 49.2% of infections were of unknown origin. The mean duration of fever (above 38.5°C) was 3.6 days and 88.6% of infectious episodes were treated with antibiotics for a median duration of 8.0 days. A subpopulation of 50.7% of patients was hospitalized for infection for a median duration of 18 days.

The investigators assessment of efficacy was 'very good' or 'good' in 83.7% of patients and 'moderate' or 'bad' in 11.5%. In 4.7% of patients the assessment was missing (Figure 2). Tolerability was assessed in all patients and rhGM-CSF was well tolerated. Table 2 lists the frequency of adverse events graded according to the WHO score. A of total 81/414 adverse events (19.6%) occurring in 42 patients (13.6%) were assigned to be possibly related to rhGM-CSF. Most frequently these adverse events were cutaneous reactions, pain and allergy. Only 2.7% of the patients showed adverse events of WHO grade III or IV assessed as possibly related to rhGM-CSF. All other adverse events were consistent with the toxicity pattern to be expected during chemotherapy. The investigators assessment of tolerability of rhGM-CSF treatment was 'very good' or 'good' in 87.0% of patients, 'moderate' or 'bad' in 9.4%, and 'very bad' in 1.3% of patients. In 2.3% the final assessment of tolerability was missing (Figure 3).

Discussion

A significant number of treatment-related deaths in cancer patients are caused by bacterial and fungal infections as a function of both the duration and severity of myelosuppression. Despite advances in patient isolation, prophylactic antibiotics and new antimicrobial agents, the duration of granulocytopenia remains the major risk factor for infection.[12,13]

The results of this report are consistent with other observations. Whereas the myelosuppression was

Table 1. Baseline characteristics of 308 patients in the intent-to-treat population

Background Information		
Male	42.3%	
Female	57.7%	
Median age	52 years	
Hematologic malignancies	25%	
Solid tumors	75.0%	
Diagnoses	**No. of patients**	**%**
Non-Hodgkin's lymphoma	49	15.9
Multiple myeloma	8	2.6
Hodgkin's disease	6	1.9
Myelodysplastic syndrome	2	0.6
Leukemias	8	2.6
Testicular carcinoma	38	12.3
Breast cancer	47	15.3
Ovarian cancer	52	16.9
Lung cancer	17	5.5
Sarcoma	7	2.3
Colorectal carcinoma	14	4.5
Bladder cancer	15	4.9
Tumours of unknown origin	10	3.2
Cervix/uterus	9	2.9
Stomach cancer	6	1.9
Malignant melanoma	5	1.6
Other tumors	15	3.8
Intent-to-treat population	308 patients	

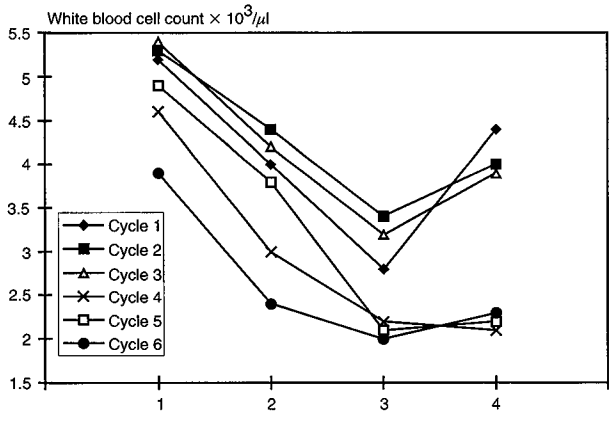

Figure 1. Median white blood cell counts before start of each chemotherapy cycle (1) and after application of rhGM-CSF (2–4).

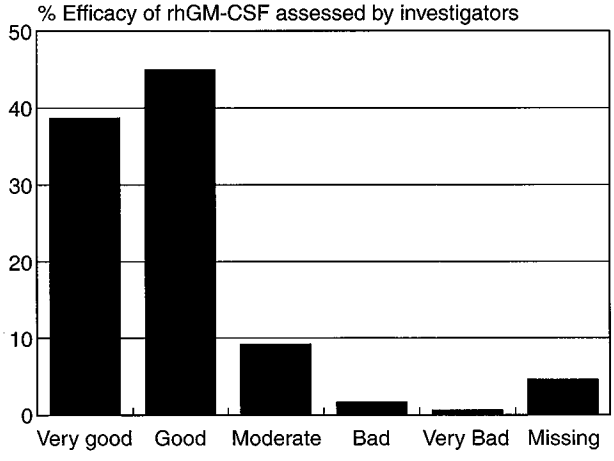

Figure 2. Assessment of the efficacy of rhGM-CSF after completing treatment in one patient.

alleviated with hemopoietic growth factors in all studies, only a few demonstrate a reduction in the frequency of neutropenic fever or the incidence of infection.

Some of these discrepancies might be due to differences in treatment protocols. The reduction in the incidence of infection and neutropenic fever was observed after prophylactic treatment with growth factors. The potentially favorable clinical effects of rhGM-CSF were investigated in patients suffering from non-Hodgkin's lymphoma. In this study the use of prophylactic rhGM-CSF resulted in a

Table 2. Investigator's assessment of causality of 414 adverse events reported during 746 chemotherapy cycles in 308 patients

Events	Investigator's assessment of cause			
	rhGM-CSF		Other	
	Any grade	WHO III + IV	Any grade	WHO III + IV
Hemorrhage	–	–	18	2
Mucous membranes	1	–	39	6
Nausea/voimiting	7	1	77	14
Diarrhea	2	–	14	4
Constipation	2	–	14	1
Hematuria	–	–	5	–
Cardiac functions	2	–	12	4
Pulmonary events	–	–	6	1
Allergy	7	1	11	1
Injection site reaction	24	4	14	1
Consciousness	–	–	6	1
Peripheral neuropathy	1	–	18	2
Pain	16	4	40	3
Other	19	1	59	24
No. of events: 414	81		333	

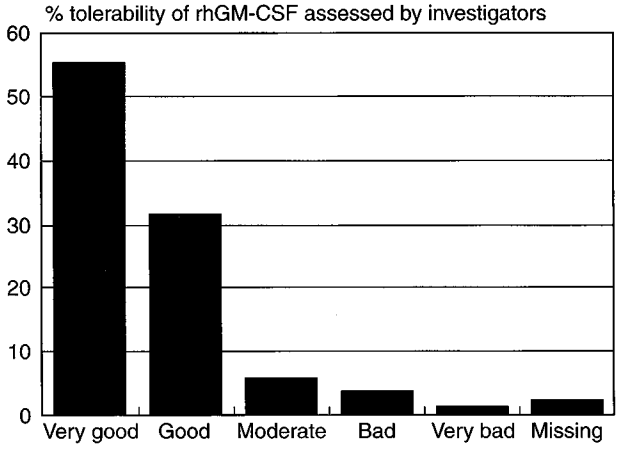

Figure 3. Assessment of tolerability of rhGM-CSF after completing treatment in one patient.

decreased incidence of infections and reduced time of hospitalization.[11] A study using rhGM-CSF in different dosages in patients with lung cancer showed that those who received 10 μg/kg/day rhGM-CSF had a decreased use of antibiotics after the first chemotherapy cycle.[14] A controlled trial in patients with testicular cancer reduced infection rates after the first cycle of chemotherapy in the rhGM-CSF group.[15] In a fourth study, acute myelogenous leukemia (AML) patients receiving induction chemotherapy who were given rhGM-CSF support showed a reduced incidence of serious infections and more prolonged survival in comparison to the placebo-treated controls.[16] By contrast, in two randomized studies with patients receiving AraC–daunorubicin for treatment of primary AML, rhGM-CSF did not decrease the severe myelosuppressive consequences of initial chemotherapy.[17,18]

In trials giving hematopoietic growth factors interventionally in case of neutropenic fever the results regarding clinical benefits are even more conflicting. Some trials show a reduced antibiotic requirement and reduced time of hospitalization,[19,20] whereas in other studies no clinical benefit was observed.[21,22] With interventional treatment of febrile neutropenia, the outcome is dependent on tumor type, pretreatment and severity of myelosuppression. In contrast to other studies investigating the therapeutic use of growth factors, in our study the prophylactic use of antibiotics was not excluded. Despite this fact the majority of infections still occurred during the first chemotherapy cycle.

This observation supports the use of rhGM-CSF during the first cycle of therapy. As compared to other trials the mean duration of febrile neutropenia was relatively short (3.6 days), a fact that also demonstrates the advantage of early prophylactic

rhGM-CSF application, even in standard-dose regimens.

Conclusion

Results from this report confirm the therapeutic value of rhGM-CSF in the prevention of chemotherapy-induced myelosuppression in a relatively large group of patients with various tumors in daily hematology/oncology practice. The incidence of adverse events was low in this patient group and similar to that reported in placebo-controlled trials. Further impact of rhGM-CSF therapy maybe related to the functional activation of monocytes and macrophages leading to enhanced anti-infective properties, potential anti-tumor effects and immunostimulation.[23–25]

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