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Prospective and Randomized Comparison of Early Versus Delayed Prophylactic Administration of Granulocyte Colony-Stimulating Factor (Filgrastim) in Children With Cancer

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Background. The prophylactic use of hematopoietic growth factors has been shown to reduce the duration of neutropenia and related complications encountered after anticancer chemotherapy. However, the optimal timing for initiation of granulocyte colony-stimulating factor (G-CSF) has not been established. ***Procedure.*** We evaluated the clinical parameters of the early versus delayed start (+1 day vs. +5 days postchemotherapy) of filgrastim (G-CSF; 5 μg/kg) after 36 courses of anticancer chemotherapy in 18 children with cancer in randomized fashion. Each child received two identical anticancer chemotherapeutic courses followed by one early (group 1) and one delayed (group 2) administration of G-CSF. Filgrastim was administered until absolute neutrophil count (ANC) exceeded 1.0×10^9/l. ***Results.*** The mean duration of G-CSF therapy was 8.6 (range, 5–14) days in group 1 and 5.4 (range, 3–10) days in group 2 ($P = 0.001$). The mean duration of neutropenia (ANC < 1.0×10^9/l) did not differ between the study groups (7.8 vs. 8.2 days). Seven infection episodes occurred in group 1 and eight in group 2, respectively. The mean number of hospital days on broad-spectrum antibiotics was 2.3 (range, 0–8) in group 1 and 3.3 (range, 0–11) in group 2 (ns). ***Conclusions.*** We conclude that the delayed start of filgrastim reduced the costs of this treatment, but was not followed by more prolonged neutropenia or febrile neutropenias. Med. Pediatr. Oncol. 32: 326–330, 1999.

Key words: G-CSF; filgrastim; cancer; children; neutropenia; infection; chemotherapy

INTRODUCTION

Pediatric solid tumors are usually highly chemosensitive and conventional-dose chemotherapy has improved survival rates for the majority of pediatric patients. Children receiving intensive chemotherapy are at high risk of suffering infectious complications during neutropenic episodes. The incidence and severity of infections are directly influenced by both the severity and the duration of neutropenia. Prompt empirical therapy with broad-spectrum antibiotics administered at the appearance of fever or at the first sign of infection has also decreased the mortality rate of children with cancer [1–3].

There are several reports of the use of hematopoietic growth factors in pediatric cancer patients [4–7]. The prophylactic use of these factors after anticancer chemotherapy has been demonstrated to reduce the duration of neutropenia and related complications, infections, and hospitalizations [8,9]. The clinical practice has been to start administration of G-CSF on +1 day postchemotherapy, but the optimal timing for starting G-CSF has not been clearly established in prospective trials [4–7].

The purpose of this trial was to evaluate the clinical parameters of early vs. delayed start of filgrastim (G-CSF) therapy in children with cancer. We determined the duration and severity of neutropenia, incidence of febrile neutropenia, duration of hospitalization, use of broad-spectrum antibiotics, and the related costs.

MATERIALS AND METHODS

The study was carried out in Kuopio University Hospital, Department of Pediatrics, University of Kuopio, Finland, between October 1995 and May 1997. The study protocol was approved by the institutional ethics committee. Informed written consent was obtained from every parent/guardian and age-appropriate patient according to institutional guidelines.

Patients

The series comprised of 18 children, 6 boys and 12 girls. The clinical characteristics of the patients are shown in Table I. None of the patients had major organ impairments. The time from initial diagnosis to onset of the trial was in median 0.4 years (range, 2 weeks to 11 months). All children had central venous catheters.

The patients were treated according to international cancer protocols. There were various conventional multiagent chemotherapy regimens in use depending on the

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TABLE I. Characteristics of Patients

Characteristics	Patients
Number of patients	18
Age in years, mean (range)	8.7 (1–15)
Male/female ratio	6/12
Underlying disease	
Lymphoma	4 (21%)
Teratoma	3 (17%)
Osteosarcoma	3 (17%)
CNS tumor	3 (17%)
PNET	2 (10%)
ALL	1 (6%)
Rhabdomyosarcoma	1 (6%)
Ewing sarcoma	1 (6%)
Central venous catheter	18 (100%)
Trimethoprim-sulfamethoxazole prophylaxis	17 (95%)
Antifungal (fluconazole) prophylaxis	10 (53%)

diagnoses of the children. Patients with non-Hodgkin lymphoma (NHL) were treated with the LBM-89 and BFM-90 protocols [10,11] and children with malignant teratomas with cyclophosphamide, doxorubicin, and cisplatin plus vinblastine and bleomycin [12]. Patients with osteosarcoma were treated with neoadjuvant chemotherapy with methotrexate and cisplatin and postoperative chemotherapy consisted of adriamycin, bleomycin, cisplatin, and methotrexate [13]. Chemotherapy of CNS (central nervous system) tumors comprised vincristin, CCNU and prednisolone [14]. Patients with primitive neuroectodermal tumor (PNET) and Ewing sarcoma were treated with ifosfamide and etoposide [15]. Acute lymphoblastic leukemia (ALL) patients were treated according to the protocols of Nordic Society of Pediatric Hematology and Oncology (NOPHO) [16] and patients with rhabdomyosarcoma according to the protocol of IRS III [17]. The patients chosen for the study were receiving chemotherapy regimens expected to lead to absolute neutrophil count (ANC) nadirs below 0.1×10^9/l of several days duration. The requirement for starting the subsequent chemotherapy course was an ANC of at least 1.0×10^9/l and platelet count of 50×10^9/l.

Procedure

The clinical parameters after two identical courses of chemotherapy were prospectively compared, one with G-CSF starting +1 day postchemotherapy (group 1), the other with G-CSF starting on +5 days postchemotherapy (group 2) in randomized fashion (randomization concerning the timing of the G-CSF). Based on the diagnoses each child received two identical anticancer chemotherapeutic courses followed by one early and one delayed administration of G-CSF and served as his or her own control. During G-CSF administration complete blood counts with differential and C-reactive protein (CRP) levels were taken three times a week on an outpatient basis and daily when the children were hospitalized. Neutropenia was defined as an ANC of $<1.0 \times 10^9$/l and severe neutropenia as an ANC of $<0.1 \times 10^9$/l. The durations of G-CSF therapy, neutropenia, hospitalization due to infections and incidence, and site of infections as well as side effects of G-CSF were evaluated.

Administration of G-CSF

The nonglycosylated recombinant human G-CSF (filgrastim) used in this study was produced by Amgen-Roche (Basel, Switzerland). The dosage of filgrastim was 5 μg/kg daily given subcutaneously (s.c.) starting on +1 day or on +5 days postchemotherapy. In both groups, G-CSF was administrated until ANC increased after its nadir to above 1.0×10^9/l. G-CSF was generally administered at home by the parents.

Treatment of Infections

Patients with fever (>38.0C) and neutropenia were hospitalized and empiric intravenous broad-spectrum antibiotics were started promptly. The admission work-up included a physical examination, complete blood counts with differential, CRP level, blood cultures from peripheral vein, and each of the lumens of a central venous catheter, with other examinations as indicated clinically. Antibiotic treatment was discontinued and patients were discharged when they had been afebrile for at least 48 hr, the CRP concentration had been normal for at least 2 days, and neutrophils had recovered. The minimum duration of antibiotic therapy was 5 days, as is customary in our institute.

The infections were afterwards categorized as a bacteremia, as a clinically defined focal infection, or as a fever of undetermined origin (FUO). Bacteremia was documented by one or more blood cultures being positive for some organism. Clinically defined focal infections included bacterial pneumonia defined as a new radiographically documented infiltrate, urinary tract infection caused by a single-organism, soft-tissue infections (cellulitis and severe oral mucositis). FUO comprised those cases in which clinical and microbiologic evaluation failed to reveal a site of infection or an isolate responsible, but fever subsided in response to the antimicrobial treatment or defervesced with recovery of neutropenia [18]. Seventeen (95%) patients received trimethoprim-sulfamethoxazole as a prophylaxis of *Pneumocystis carinii* and 10 (53%) of patients received fluconazole as an antifungal prophylaxis.

Statistical Analysis

Student *t*-test was performed to examine differences between groups in outcome events as the number of days

of G-CSF, varying levels of ANC counts, and hospitalization, and the chi-square test was used to assess the statistical significance of frequency of bacteremias and febrile neutropenias. A P value of >0.05 was considered nonsignificant (ns).

RESULTS

The study comprised a total of 36 administrations of G-CSF. In 18 courses G-CSF was started on +1 day postchemotherapy (group 1) and in 18 courses G-CSF was started on +5 days postchemotherapy (group 2).

Administration of G-CSF

The mean duration of G-CSF therapy in group 1 was 8.6 (range, 5–14) days and in group 2 it was 5.4 (range, 3–10) days ($P = 0.001$). The total days of G-CSF administration were 154 days in group 1 and 98 days in group 2. Severe neutropenia (ANC $<0.1 \times 10^9$/l) lasted for a mean of 6.2 days (range, 3–12) in group 1 and for 6.4 days (range, 3–12) in group 2 (ns) and the mean durations of neutropenia (ANC $< 1.0 \times 10^9$/l) were 7.8 days (range, 4–14) and 8.2 days (range, 5–14), respectively (ns; Table II). No side effects related to G-CSF administration were observed.

Infection Episodes

No bacteremia was documented in group 1 and three bacteremias were found in group 2. Five organisms were isolated from blood cultures (*Micrococcus luteus, Staphylococcus epidermidis, Enterococcus casseliflavum, Xanthomonas maltophilia, Corynebacterium spp.*). Multietiology was documented in one patient with primitive neuroectodermal tumor (PNET). The mean number of hospital days on broad-spectrum antibiotics did not differ between the groups; in group 1 it was 2.3 days, with a total of 42 days, the corresponding figures in group 2 being 3.3 days, total 60 days (ns). Seven episodes of FUO were observed in group 1 and five in group 2. No clinically defined focal infections occurred. There was no infection-related mortality.

Costs

In group 1, patients received G-CSF therapy for a total of 154 days and in group 2 the total was 98 days. The daily cost of G-CSF (0.3 mg) was U.S. $100. The total cost of the G-CSF therapy was U.S. $15,400 in group 1 and U.S. $9,800 in group 2. Accordingly, the total saving by delaying the start of G-CSF on +5 days postchemotherapy was U.S. $5,600.

TABLE II. Clinical Parameters Compared After the Early (Group 1) Versus Delayed Start (Group 2) of Prophylactic Granulocyte Colony-Stimulating Factor

	Group 1[a]	Group 2[b]	P
Courses	18	18	NS
Time from diagnosis (years)	0.4	0.5	NS
G-CSF (days)	8.6 (5–14)[c]	5.4 (3–10)[c]	0.001
ANC $< 1.0 \times 10^9$/l (days)	7.8 (4–14)[c]	8.2 (5–14)[c]	NS[c]
ANC $< 0.5 \times 10^9$/l (days)	6.8 (3–13)[c]	7.4 (4–14)[c]	NS
ANC $< 0.1 \times 10^9$/l (days)	6.2 (3–12)[c]	6.4 (3–12)[c]	NS
Bacteremias	0	3	NS
Febrile neutropenias	7	5	NS
Hospitalization (days)	2.3 (0–8)[c]	3.3 (0–11)[c]	NS

[a]Early start (+1 day postchemotherapy) of G-CSF therapy.
[b]Delayed start (+5 days postchemotherapy) of G-CSF therapy.
[c]Mean (range).

DISCUSSION

The prophylactic use of hematopoietic growth factors has been shown to reduce the incidence of neutropenia and infectious complications occurring after chemotherapy. The purpose of this trial was to evaluate the clinical effectiveness of early versus delayed start of filgrastim in children with cancer. Early administration of G-CSF offered no advantage when compared to delayed start. No differences in the duration of neutropenia or in the incidence of febrile neutropenias were observed between the groups. However, the delayed start of G-CSF reduced the costs associated with the treatment.

Based on the literature review the American Society of Clinical Oncology recommended the primary use of hematopoietic colony-stimulating factors, when febrile neutropenia is likely to occur in 40% or more of the patients [19–21]. In our previous study we evaluated the use of G-CSF as an adjunct to courses of conventional chemotherapy in children with cancer [6]. We found that the use of G-CSF (+1 day postchemotherapy) facilitated myeloid recovery significantly and reduced the number of infectious complications and hospital days due to febrile neutropenia. The use of G-CSF could prevent profound neutropenia in 55% of chemotherapy episodes. However, there are studies showing that the prophylactic use of hematopoietic growth factors has not led to clinical benefits, either in reducing febrile events or in increasing chemotherapy dose intensity [22–24].

In the present trial, the study protocol was to start the delayed G-CSF on +5 days postchemotherapy, because the neutrophil nadir is anticipated to occur between +7 and +10 days postchemotherapy [7]. We feel that with a delayed start of G-CSF we were able to maintain the benefits of the prophylactic administration of G-CSF and to reduce the number of days of G-CSF treatment.

Only a few trials have been carried out to define the optimal timing of the initiation of the hematopoietic

growth factors [25–28]. In many centers, the clinical practice has been to start prophylactic G-CSF on +1 day postchemotherapy, but prospective trials have failed to reveal clinical benefit from this practice when compared to a more delayed start of colony-stimulating factors. Gomez et al. [25] investigated the optimal timing of G-CSF administration after bone marrow transplantation (BMT) in children and adolescents with a variety of hematological diseases. They reported that the use of G-CSF immediately after BMT was unnecessary and more expensive, offering no clear advantage over delayed (+7 days after BMT) administration [25]. Similar findings were shown by Elonen et al. [26] with adult patients. Their results suggest that an early start (+2 days postchemotherapy) of G-CSF (lenograstim) was no more effective in preventing neutropenia or infections than a delayed start (+9 days postchemotherapy) during the induction therapy of acute lymphoblastic leukemia. The above findings are in accord with our study.

In conclusion, the delayed start of prophylactic G-CSF was not followed by more prolonged neutropenias or any increase in the incidence of febrile neutropenias in our patients. The possibility to safely delay the start of G-CSF may reduce the costs of the treatment and increase the quality of life in children with cancer.

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