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G-CSF mobilised granulocyte transfusions in 32 paediatric patients with neutropenic sepsis

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Abstract *Introduction:* In this retrospective, uncontrolled, observational study, the effect of granulocyte colony-stimulating factor (G-CSF)-stimulated granulocyte transfusions (GTX) in neutropenic paediatric patients with sepsis was evaluated. *Patients and methods:* Granulocytes were collected from unrelated, ABO group-matched and cytomegalic-antibody compatible donors. For neutrophil mobilization, donors received a single subcutaneous dose of glycosylated G-CSF (Lenograstim, Chugai Pharma, Japan) plus oral dexamethasone (8 mg). In total, 168 (range 1–19 per patient) GTX were transfused in 32 children with a median age of 7.4 (0.25 to 16) years. *Results:* The underlying diseases comprised predominantly haematooncological malignancies (31 children). In 15 of 32 patients, neutropenia was related to allogeneic stem cell transplantation. All children suffered from sepsis based on international criteria (fever, tachycardia, respiratory rate >2 SD above normal in the context of a suspected or proven infection). In ten children bacteria were isolated, in six children a fungal infection was diagnosed and four sepsis episodes were caused by viral infections. GTX contained a median neutrophil number of 6.3 (range 1.9–13.9)$\times 10^{10}$ per transfusion and obtained a sustained haematological response after GTX. Nineteen out of 32 children survived the neutropenic sepsis, particularly nine out of 11 patients with bacterial sepsis. *Discussion:* In contrast to the non-survivors, we observed a significant decrease in the C-reactive protein levels shortly after initiation of the GTX treatment in the surviving patients. A clear-cut benefit of GTX for children with neutropenic sepsis cannot be concluded from these data, but in children with (severe) bacterial sepsis refractory to antibiotic treatment, GTX were feasible, safe and could reduce mortality rates in this subgroup of patients.

Keywords Sepsis · Neutropenia · Granulocyte transfusion · G-CSF

Introduction

Patients with prolonged neutropenia after chemotherapy are prone to serious infections. Despite appropriate antibiotic and antimycotic treatment, mortality is considerable [2]. Approximately 6% of paediatric oncological patients develop a septic shock, and about 5% of these patients die despite intensive care treatment. In children who have undergone haematopoietic stem cell transplantation (SCT), mortality increases to 40% [2]. Given the generally improved prognosis for the treatment of childhood cancer, infections are of major concern to oncologists. Response rates in treating bacterial, fungal or viral infections during neutropenia remain unsatisfying [9, 23]. The success of sepsis therapy is based on multiple factors and is related to the recovery from neutropenia, even though morbidity and mortality are not only linked to the duration of neutropenia but also depend on comorbidity [8, 15]. Reconstitution of the host defence system may improve the outcome during neutropenia-associated infections. Transfusions of recombinant granulocyte-stimulating factor (rhG-CSF) mobilised granulocytes (GTX) are a supportive measure that are controversially discussed for patients with severe infections. Data that confirm the value of GTX are limited, and results of the studies are heterogeneous and inconclusive [3–5, 7, 20–22].

With the introduction of recombinant G-CSF and improved apheresis techniques, it became possible to collect considerably higher numbers of leucocytes during apheresis, and a sustained increase in the peripheral blood neutrophil count in the recipients was achievable, particularly in children [12, 19, 21]. Our report is based on data collected from 2000 to 2003, on 32 neutropenic children receiving 168 GTX for treatment of neutropenic sepsis.

The primary objective of this study was to analyse the potential effect of GTX with special regard to outcome of sepsis. The authors aimed at evaluating risk factors for death—especially duration of neutropenia, type of infection and comorbidity—and at determining the potential influence of GTX on any of these risk factors and outcome.

Materials and methods

Patients and sepsis criteria

We reviewed the medical records of all neutropenic children who received GTX between April 2000 and December 2003.

Thirty-one children received GTX during neutropenia after chemotherapy for haematological malignancy or as conditioning chemotherapy before haematopoietic SCT. One child was treated for sepsis with respiratory failure during neutropenia of unknown aetiology. The decision to initiate GTX was made on an individual basis when antibiotic and antimycotic therapy failed to resolve a proven or suspected infection. All children were neutropenic (absolute neutrophil count <500/μl), at least 3 days before the first GTX, and were expected not to resolve from neutropenia within the next 5 days. All children were febrile (body temperature above 38.5°C) and showed increasing C-reactive protein (CRP) levels with additional clinical signs of an uncontrolled infection, e.g. respiratory deterioration (accelerated respiratory rate or additional oxygen requirement) and/ or hypotension (blood pressure <fifth percentile for age) (Table 2). Hence, all patients included in the analysis were suffering from sepsis or even severe sepsis or septic shock according to the definitions specified by Goldstein et al. and the Members of the International Consensus Conference on Pediatric Sepsis [6], as shown in the list below:

1. *Systemic inflammatory response syndrome* (*SIRS*) Presence of 2 of the following criteria
   - 1.1. Core temperature >38.5°C or <36°C
   - 1.2. Tachycardia (for definitions, see Goldstein et al.)
   - 1.3. Mean respiratory rate >2 SD above normal or mechanical ventilation
   - 1.4. Leucocyte count elevated or depressed (not secondary to chemotherapy)
2. *Sepsis* SIRS in the presence or as a result of a suspected or proven infection
3. *Severe sepsis* Sepsis plus one of the following:
   - 3.1. cardiovascular dysfunction or
   - 3.2. acute respiratory distress syndrome or
   - 3.3. two or more other organ dysfunctions
4. *Septic shock* Sepsis and cardiovascular dysfunction

Definitions of infections

A patient was regarded to have a fungal infection when fungi were isolated from tissue biopsy. All bacterial infections were diagnosed from blood cultures taken from central venous catheter, except for one patient with a pyogenic abscess that was surgically drained. Viral infections were diagnosed from blood (diagnosis based on polymerase chain reaction for adenovirus) or bronchoalveolar lavage (respiratory syncytial virus, parainfluenza, adenovirus).

Data collection

Clinical, radiological and medical records were reviewed in detail, as were the microbiological data, during the period of GTX and for a follow-up period of at least 30 days after the last GTX. Autopsy data were also included when available.

Any death >30 days after the last GTX was regarded to be out of the context of the initial sepsis episode.

Statistical analysis

To compare baseline characteristics of the patients according to the treatment outcome, the Mann–Whitney *U* test and Fisher's exact test were applied using the SPSS statistical data analysis program.

Method of granulocyte apheresis and application of GTX

Granulocytes were collected from unrelated, healthy, ABO blood group and cytomegalic antibody compatible volunteers. All donors were enrolled into an institutional protocol that was approved by the Ethics Committee of the Hannover Medical School. Informed consent was obtained from all participants before inclusion into the study protocol. To be included in the study, the donors had to fulfil the criteria of the German Medical Association and the German Society for Transfusion Medicine for haemapheresis donors. The granulocyte mobilisation and collection schedule has been previously described [11]. Briefly, the donors were given glycosylated G-CSF (Lenograstim, Chugai Pharma, Japan) as a single subcutaneous injection plus oral dexamethasone (DXM; Fortecortin, Merck, Germany). Lenograstim is commercially available as Granocyte13 (=105 μg Lenograstim) or Granocyte34 (=263 μg Lenograstim). The substance was administered at different total doses of either 526 μg [=2 ampoules Granocyte34 (*n*=52)], or 263 μg [=1 ampoule Granocyte34 (*n*=73)] or at 105 μg [=1 ampoule Granocyte13 (*n*=43)]. For a specific donor, these regimen resulted in a median dose per kilogram donor body weight of 6 (4.3–7.9) μg/kg Lenograstim for patients (=recipients) with a body weight >60 kg, a median dose of 3 (2.4–4.1) μg/kg Lenograstim for patients with a body weight ranging from 20 to 60 kg, and a median dose of 1.5 (1.0–2.3) μg/kg Lenograstim (*n*=43) for patients with a body weight below 20 kg. Additionally, all donors received 8 mg oral DXM. Both Lenograstim and DXM were given simultaneously 16 (13–19) hours before polymorphonuclear (PMN) apheresis. Leukapheresis was performed on the blood cell separator (Cobe Spectra) using the single stage WBC cytapheresis set and the PMN program of the Spectra software version 4.7. We followed a standard procedure that has been previously described [11]. The final product was tested for complete blood count and irradiated with 30 Gy. The Granulocytes were transfused on the same day, usually 3–6 h after the apheresis. The transfusion regimen differed slightly from one patient to the other; in general, we attempted an every other day schedule (=three GTX per week), which proved to be the easiest strategy to circumvent organisational difficulties.

Preventive measures taken before GTX consisted of a premedication with pethidine and clemastine intravenously until September 2001. Afterwards, only clemastine was given as premedication. Monitoring during GTX included continuous registration of oxygen saturation and measurement of the blood pressure, respiratory rate and heartbeat every 15 min. GTX were transfused over 1–4 h. The minimum interval between GTX and the last Amphotericin B infusion was 4 h. In our cohort, only one patient received steroid medication after GTX.

GTX were discontinued when resolution of neutropenia occurred or because of the death of the patient.

Results

Clinical characteristics

The clinical and haematological data of the children are summarised in Table 1. Most children received chemotherapy for acute leukaemia (acute lymphoblastic leukaemia, acute myeloid leukaemia). The remainders were treated for other haematooncological malignancies. One-third (11/32) of the patients were in ≥ second remission. Nearly one-half of the children (15/32) underwent haematopoietic SCT.

Three children suffered from post-transplant lymphoproliferative disorder (PTLD), one patient after SCT and the remaining patients after liver transplantation.

Infections

Microbiologically documented bacterial infections occurred in 11 patients. In six children, Gram-positive bacilli were isolated from the blood. In five children, the infection persisted despite removal of the catheter.

Proven invasive fungal infections (fungi detected from normally sterile site) were diagnosed in six children receiving GTX, while another patient was found to have a double infection with adenovirus and *Candida* after SCT.

Table 1 Demographic data of 32 GTX recipients

	Total	Survivors	Non-survivors
Number of children	32	19	13
Age (years, median, min/max)	7.4 (0.25–16)	8 (0.25–16)	6.6 (0.9–15)
F:M ratio	13:19	8:11	5:8
SCT	15	8	7
Weight (kg, median, min/max)	19.3 (6–110)	20 (6–110)	17.3 (6.9–60)
Acute leukaemia (ALL, AML), lymphoma, PTLD	26 (81%)	18 (95%)	8 (61%)

SCT Stem cell transplantation, *ALL* acute lymphoblastic leukaemia, *AML* acute myeloid leukaemia, *F* female, *M* male, *PTLD* post-transplant lymphoproliferative disorder

Table 2 Infective organisms, sepsis category, comorbidity and outcome in 32 children

Patient no.	Infection	Comorbidity	Category[a]	SCT (yes/no)	Outcome[b]
1	*Streptococcus mitis*	–	1	Y	Alive
2	Fever	MV[c]	1	Y	Alive
3	Pneumococci	–	1	N	Alive
4	*Aspergillus*	–	1	N	Alive
5	*Mucor*	IS, BP, RF	2	Y	Alive
6	*Stenotrophomonas maltophilia*	RF	1	Y	Alive
7	Fusobacteria	MV	2	N	Alive
8	*Candida albicans*, adenovirus	RF, BP	2	Y	Dead
9	*Aspergillus*	RF, IS, BP	2	Y	Alive
10	Fusariosis	RF, IS, MV	2	Y	Dead
11	*Enterococcus faecalis*	IS, MV, DIA, VOD	3	Y	Dead
12	Fever	–	1	Y	Alive
13	Adenovirus	RF, IS, MV	2	Y	Alive
14	*C. albicans*	–	1	N	Alive
15	Fever	–	1	N	Alive
16	Parainfluenza virus	IS, MV, ARDS, RF	3	N	Dead
17i	*Escherichia coli*	–	1	N	Alive
18	Fever	–	1	N	Alive
19	Fever	LF, RF	1	Y	Dead
20	RS virus	MV, IS, RF	2	N	Dead
21	*Aspergillus flavus*	MV, IS, RF	2	N	Dead
22	*Streptococcus oralis*	IS, MV, DIA, LF	2	Y	Dead
23	Fever	–	1	N	Alive
24	Fever	–	1	N	Alive
25	*Stomatococcus mucilaginosus*	IS, MV, ARDS, RF	2	N	Dead
26	Fever	IS, MV	2	N	Dead
27	*Bacillus cereus*, *E. coli*	MV, IS,	2	N	Alive
28	*Staphylococcus aureus*	RF	1	Y	Alive
29	Adenovirus	IS, MV, RF, ARDS	2	Y	Dead
30	*Staphylococcus hominis*	RF	1	N	Alive
31	Fever	IS, MV, DIA, LF, VOD	3	Y	Dead
32	Fever	IS, MV	3	N	Dead

IS Inotropic support, *MV* mechanical ventilation, *BP* BiPAP, *DIA* dialysis, *RF* renal failure, *LF* liver failure, *RS* respiratory syncytial virus
[a]Category (1=sepsis, 2=severe sepsis, 3=septic shock; for definitions, see "Materials and methods" section)
[b]Three months after last GTX
[c]After resuscitation following cardiac arrest

In ten children, the causative organism could not be isolated. These children with sepsis with suspected infection were considered for GTX due to their critical clinical situation (high fever, increasing CRP levels despite antimicrobial treatment). For a detailed description of the types of infections see Table 2.

Side effects of granulocyte transfusions

During 114 of 168 GTX side effects were analysed in detail. In general, side effects (fever, allergic reactions) were seen only to a limited extent (Table 3).

Fifteen children were on ventilator support due to respiratory failure in the context of pulmonary infections and/or pulmonary toxicity after chemotherapy or SCT. During or shortly after GTX, a minor increase of the ventilator support was necessary, which could be reduced within the next 2 h (data not shown). However, in two children with viral pneumonia (#20, #29), a deterioration of pulmonary symptoms was seen during the regeneration of the leucocytes. Patient #32 developed progressive respiratory failure during GTX. All three children with GTX-associated increase in ventilatory support were suffering from concomitant renal failure and fluid overload that was further accentuated by GTX. A differentiation whether volume overload or genuine GTX-associated side effects caused the increase in ventilatory support was not possible.

Table 3 Side effects of GTX (as recorded in 114 of 168 GTX)

Total	17 (14.9%)
Fever	11 (9.6%)
Respiratory deterioration[a]	6 (5.3%)
Hypotension[b]	2 (1.8%)
Erythema	1 (0.8%)

[a]More than 5% increase in oxygen requirement during/after GTX
[b]New or increasing inotropic support during/after GTX

Haematological data

A total number of 168 GTX was given to 32 children (median five GTX per patient, range 1–19). The median granulocyte-number per transfusion was 6.35×10^{10} ($1.9–13.9\times10^{10}$). At the onset of GTX, the children were neutropenic for a median of 16 days (range 3–85) and for a median total duration of 25 days (range 5–99). In three children, after stem cell transplantation, no haematological reconstitution was seen ("non-engraftment"). These children died during their prolonged neutropenia shortly after their last GTX due to viral infections (n=2) and SCT-associated toxicity (n=1). The children showed profound neutropenia before receiving their first GTX, with a median increase of the leucocyte count to 2,200/µl (range 580–18,300/µl), 1 h after GTX. Due to the great variability and the comparably low number of children included in the study, the differences between the children surviving their sepsis episode and those who died were not statistically significant (Table 4).

Outcome analysis

Fatal outcome

The deaths of all patients with fatal outcome (n=13; 41%) were reviewed individually by an independent doctor to define the cause of death. Five of 13 deaths occurred due to non-infectious causes (progression of the underlying malignant disease, bleeding, venoocclusive disease). In 8/13 children with a fatal outcome, death occurred secondary to the underlying infection (two fungal infections, two bacterial infection, four viral infections) after prolonged intensive care treatment, respiratory and circulatory failure. Only 3/15 children, who were on ventilator support during GTX, survived.

CRP-values before and after GTX

In the total study population, the median CRP values 24 h before initiating GTX were 171 mg/l (range 43–350), then dropped to a median of 140 mg/l (range 9–520) 48 h after the last GTX. When we compared the survivors (median CRP after GTX=119 mg/l; range 9–255) and the non-survivors (median CRP after GTX=187 mg/l; range 57–520), we saw a significant difference. This difference in CRP values between survivors and non-survivors was already clear-cut after the second GTX (data not shown), which provides the opportunity to see an early effect of GTX.

Discussion

Despite modern anti-infective treatment and achievements made in intensive care management, mortality in paediatric cancer patients with (severe) sepsis is still unacceptably high [2, 16, 25], ranging from 40 to 80% depending on the underlying diseases. This holds especially true for pulmonary failure after SCT, where the outcome is extremely poor [8, 13, 25]. Therefore, additional supportive measures to enhance survival seem justified, which provided the rationale to transfuse G-CSF stimulated granulocyte transfusions at our institution in the last years.

Due to the high variation and the relatively small number of patients in our study, we were not able to demonstrate a significant benefit for an early initiation of GTX. With regard to the prophylactic use of GTX, however, Kerr et al. performed in 2003 a case control study in adults during allogeneic stem cell transplant recipients at high risk of invasive aspergillosis [14]. According to their data, prophylactic granulocyte transfusions were feasible and resulted in a significant reduction in the period of post-transplant neutropenia. This reduction in neutropenia was associated with a reduction in the incidence of fever, the

Table 4 Haematological data before and after GTX (n=168)

	Total	Survivors (n=19)	Non-survivors (n=13)
GTX-transfused	168	103	65
Median no. of GTX/patient (range)	3 (1–19)	3 (1–19)	3 (1–13)
Median leucocyte count before GTX (range)	480/µl (0–1,300)	350/µl (0–1,300)	566/µl (100–850)
Median leucocyte count 1 h after GTX (range)	2,200/µl (580–18,300)	1,800/µl (580–9,400)*	2,700/µl (1,283–18,300)*
Median leucocyte count on the morning after GTX (range)	1,400/µl (300–13,200)	1,400/µl (300–8,306)	900/µl (475–18,200)

GTX Granulocyte transfusion
*Differences not statistically significant (p>0.05)

number of days of fever, the maximum CRP and the use of total parenteral nutrition and opiates for mucositis.

In a prospective study done by Peters et al., 30 paediatric patients received either G-CSF or prednisone-stimulated leucocyte transfusions for therapy of bacterial or fungal infection [21]. They demonstrated that GTX are valuable and safe tools in combating bacterial infections, with 14 out of 17 patients with bacterial infections surviving on day 100 after the first GTX. Price et al. could show that transfusion of neutrophils harvested from donors stimulated with G-CSF plus dexamethasone could restore a severely neutropenic patient and was effective as adjunctive therapy: the infection resolved in eight of 11 patients with invasive bacterial infections or candidemia [22].

In addition to the good results of GTX for bacterial infections that are strongly supported by our data, we present here the finding that the CRP levels may serve as one prognostic factor for the outcome of children with sepsis, which is supported by the data of paediatric SCT patients requiring intensive care treatment [24].

The outcome of children with malignancies admitted to the intensive care unit in the context of fungal infections is unfavourable in most instances [13]. Whether GTX are of additional value for patients with fungal infections remains a matter of debate [1, 3, 4, 18, 20]. Hester et al. reported that 60% of their adult patients (n=15) with invasive fungal infections showed a favourable response to GTX collected from G-CSF stimulated donors [10]. In their study, 7/15 patients suffered from an *Aspergillus* infection, and the early institution of GTX was associated with a better outcome. In the study done by Peters et al. [21], treatment of patients with fungal infections was much less effective. According to their data, infection control was achieved only in 38% of these children. A study recently published by Lee et al. [17] demonstrated favourable results in neutropenic patients with fungal infections, yet detailed information on the type of fungal infection was limited in this report. In our study, 4/6 children with documented invasive fungal infection survived; however, the information on this group of patients is still somewhat limited and requires further studies.

All five children suffering from a viral infection (that was diagnosed after completion of GTX) died. The relatively high number of non-survivors among the children without documented infection (four out of ten patients) is highly suspicious of unidentified viral infections in these patients. GTX appear to be ineffective in viral infections. However, in the critically ill, oncological SIRS or sepsis patient not responding to anti-infective therapy, the role of G-CSF and GTX remain to be determined.

In any case, besides the neutrophil recovery that can be achieved via GTX, the comorbidity of the patients is extremely relevant with regard to outcome. Once the patient is suffering from single or multiple organ failure, the case fatality rate rises considerably. With regard to the low incidence of adverse reactions to GTX, GTX should be considered as an additional supportive care measure of potential use.

In our study, GTX were given to pulmonary-compromised patients, including those receiving mechanical ventilation: The general outcome in ventilated patients was poor, although artificial ventilation should not be a per se contradiction for GTX. In most patients of our report, no severe pulmonary complications were noticed, but special attendance should be provided. As the safety data on GTX is convincing, we recommend that premedication should not include steroids to circumvent possible drawbacks in controlling infections. Steroids should be restricted to severe allergic reaction.

The optimal strategy for the use of GTX remains to be determined. With our three times per week schedule, a leucocyte count above 500/µl could be maintained for the majority of patients, and the balancing act between continuation of chemotherapy for haematological malignancy and abatement of underlying infections was possible. Four out of six children with a fungal infection and nine out of 11 with a bacterial infection surviving both infection and malignancy illustrate the success of this approach. However, due to the dose–response relation in GTX, similar results might not be automatically achievable in adults [10, 26].

Donor issues have systematically been evaluated by Heuft et al. [11]. According to their extensive data, the vast majority of donors experience side effects, but up to a dosage of 6 µg/kg, these side effects are acceptable with good results regarding the PMN harvest.

Although our study is limited by the retrospective approach, the heterogeneity of the patients and the individual decision about the initiation of GTX, several new and interesting conclusions can be drawn from the data presented: GTX seem beneficial to children with severe sepsis during neutropenia with regard to safety and control of bacterial and fungal infection. GTX are of value to maintain leucocyte counts above 500/µl, and there is good evidence that a decrease of the CRP levels indicates a positive course of the infection. However, the value of GTX is limited in viral infections where the mortality is still very high.

The results of the presented study led to a standardised protocol for neutropenic children with fever (fever of unknown origin or proven infection): An empirical antibiotic treatment is started at presentation. After 72 h, antibiotic therapy is switched (or immediately according to microbiological results). Galactomannan antigen testing is initiated in all febrile patients and repeated twice per week until defervescence. In all patients with persistent fever after 5 days, antimycotic therapy will be started. In children with persistent fever and neutropenia after 10 days expected not to resolve within ≥4 days and with any clinical or laboratory sign for deterioration (supplementary oxygen, clinical or radiological signs of pneumonia, inotropic support, increasing CRP-levels), GTX will be initiated. A secondary prophylaxis with GTX is initiated at our institution in all children with severe sepsis (e.g. fungal or soft-tissue infections) during previous neutropenic episodes.

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