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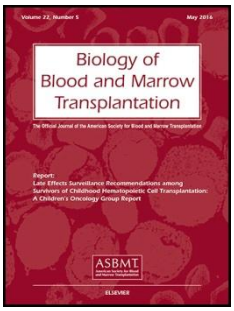


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# GRANULOCYTE TRANSFUSIONS: A CRITICAL REAPPRAISAL

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**HIGHLIGHTS**

- Granulocyte transfusions are employed as a life-saving therapy for neutropenic patients with severe infections.
- The GT efficacy has not definitely established in clinical trials and is still debated.
- Various factors might have weakened the evidence of GT advantages in past studies.
- This review aims to illustrate some unsettled issues that could deserve reconsideration in future clinical trials.

ABSTRACT

Granulocyte transfusions (GTs) are seldom used as a life-saving therapy for neutropenic patients with severe infections. Despite several compelling evidences of GT efficacy in retrospective and prospective case series, no study has been successful in demonstrating a definite advantage for recipients in controlled clinical trials. This review will critically revise some aspects emerging from the past experience which might have weakened the evidence of GT benefits. Some specific issues relevant to the efficacy of this therapeutic approach, such as the primary infection, the delivered doses and schedules, and the immunological effects of GTs, will be discussed. Importantly, the awareness of biological effects accompanying the transfusion of neutrophils might support their use at standardized doses, and may definitely convey significant advantages to the recipient patients.



**Keywords:** Granulocytes; infections; individualized medicine; personalized therapies

INTRODUCTION

Neutrophils play a pivotal role in the host defense against bacterial and fungal infections. They elicit their effects through different mechanisms: phagocytosis, degranulation, cytokine production, and neutrophil extracellular trap production [1]. Neutropenic patients exhibit an increased risk for infections that is proportional to the severity and the duration of neutropenia [2]. Pioneering studies indicated that repeated transfusions of granulocytes to neutropenic patients were effective in the clinical management of septicemia due to gram-negative bacteria [3]. Experimental data in neutropenic dogs demonstrated that a threshold dose of $2x10^8$/kg conveyed protection from an otherwise lethal *Pseudomonas* septicemia [4]. After the advent of granulocyte growth factor, adequate transfusion doses can be efficiently achieved by apheresis collection from donors mobilized with G-CSF [5]. Shortly after the G-CSF administration, several neutrophil phenotype modifications occur *in vivo*, with increased expression of CD16, CD14, CD66b and CD11b, and down-regulation of CD62L [6,7]. While these changes underlie neutrophil activation, likewise they reduce neutrophil-endothelial cell interaction [6,7]. Moreover, mobilization efficiency and collection yield can be amplified by adding dexamethasone to G-CSF [8]. The drug combination results in reduced neutrophil apoptosis and increased G-CSF half-life in comparison with the G-CSF alone [9,10]. Nowadays, the safety of the practice of administering G-CSF to donors has been consolidated by decades of donations of both allogeneic hematopoietic stem cells and granulocytes [11,12]. Since no HLA matching is usually required between granulocyte donors and recipients, volunteers can be recruited among community donors or patients' friends and relatives. Nevertheless transfusions from relatives candidate to hematopoietic stem cell donation should be avoided to prevent alloimmunization [13,14]. In alternative to apheresis granulocytes, equivalent products can be obtained by assembling granulocyte fractions isolated from multiple whole blood donations [15]. Regardless their collection, several studies provide evidence that neutrophils achieved through either G-CSF mobilized donors or whole blood processing are functional when assayed for bactericidal and fungicidal activities, and efficiently reach the sites of infection [15,16].

In the following sections, we will revise the key concepts emerging from the past experience on granulocyte transfusions (GTs), in the belief that the awareness of some crucial aspects might contribute to expand the critical utilization of this therapy, definitely conveying significant advantages to the recipient patients.

## THE PAST

In Table I and Table II the 20 retrospective and 13 prospective studies on GTs are illustrated. These studies include hematological patients with post-chemotherapy neutropenia or severe aplastic anemia and have been carried out subsequently to the advent of G-CSF. On the whole, case series and phase I/II studies suggested that GTs, provided they contain adequate amount of neutrophils (>$10x10^{10}$), could improve the outcome of severely neutropenic patients suffering from bacterial infections. In particular, the resolution/recovery from infection was reported as outcome in 17 studies, including overall 379 patients, and it varied from 36.7% to 92.6% [17-33]. The mortality attributable to infection (or comparable outcomes such as day-28 or day-30 survival, which allowed to indirectly estimate the mortality related to the infection) was reported in 12 studies including 594 patients, and ranged between 6.7 and 66.7% [34-45]. In contrast to the generally encouraging appraisal in bacterial infections, results in patients with fungal infections were more heterogeneous, with some studies reporting low efficacy [27,45] or even detrimental effects [46]. In general, the majority of studies observed a lower response rate to GTs among fungal as compared with bacterial infections [17,19,20,24,27,30,32,34,36-39,41-43], even though a high susceptibility was also reported [28,35,47]. Indeed, several authoritative reviews supported the use of GTs in severely neutropenic patients with either bacterial or fungal infections [48-53].

Disappointingly, no phase III trial succeeded in demonstrating whatsoever clinical advantage for patients who received GTs, nor the recently updated meta-analysis of data accrued in randomized controlled trials (RCT) identified any beneficial effect of transfusions in term of mortality (up to 30 days) or clinical reversal of infection [54-56]. Nonetheless, the recent meta-

analysis of 6 RCT (4 accomplished before and 2 after the advent of G-CSF) provided additional interesting information: first, it failed to demonstrate any differences between groups of patients receiving more or less than $10x10^{10}$ neutrophils per day; moreover, a slight decrease of all-cause 30-day-mortality was observed in studies performed before 2000, that were conducted prior to G-CSF licensing [56]. Altogether, these findings paradoxically suggest that improving apheresis collection of neutrophils and increasing transfusion doses did not translate in any clinical advantage for recipients [56].

Although the wide heterogeneity among studies in regard of patient populations, infection types, intervention parameters or outcome measures might have rendered their results scarcely comparable, the low rate of patient enrollment by participating centers is by far the most straightforward challenge for the informative efficacy of randomized controlled trials on GTs. This limitation has been experienced in an European trial started in 1999 and prematurely ended in 2005, with a 50% reduction of the expected sample size (from 90 subjects per arm to 40 and 39 patients in intervention and control groups, respectively) [54], as well as in the more recent RING (Resolving Infection in Neutropenia with Granulocytes) U.S.A. study, where the target sample size of 118 subjects per arm was reduced to 48 and 49 patients in the intervention and control groups, respectively [55]. It is noteworthy to emphasize that despite these figures are inconclusive to establish the superiority of GTs over standard treatments, they are even more inadequate to conclude for the "equivalence" between intervention and control arms.

THE PRESENT

In general, the practice of transfusing granulocyte concentrates is barely adopted among hematological centers. For example, among thirty-eight interviewed Italian hematological centers, only four (10.5%) declared to use GTs. Several factors contribute to the unpopularity of this therapeutic approach, including the difficulty to recruit and screen eventual donors in urgency conditions, the off-label use of G-CSF, the necessity of a tight cooperation between clinical

department and apheresis center. Moreover, both patients and physicians may hesitate to randomize in a life-threatening situation, especially if GTs are considered potentially life-saving, explaining the low enrollment rate in RCTs [54,55]. Although these concerns might be probably overcome by the uncontroversial clinical evidences of the efficacy of GTs, in the meantime they jeopardize the possibility to gather conclusive findings on the role of therapeutic GTs in life threating infections of neutropenic hematological patients. Presently, the results from a new planned study (GRANITE: Transfusion of granulocytes for patients with febrile neutropenia; German Clinical Trials Register number DRKS00000218 and EudraCT number 2009-010700-28) are wishfully awaited [57]. The GRANITE study is a randomized, German, multi-center trial for the treatment of febrile neutropenia without a response after 96 hours of standard therapy. This trial is addressed to both pediatrics and adults patients and includes all hematological diseases. The experimental arm provides the transfusion of granulocytes on every day/every other day in association with standard anti-infective therapy (antibiotics and antifungal); the control arm treats patients with standard-therapy without GTs. Primary outcome is the normalization of body temperature for 72 consecutive hours. A sample size of 100 patients has been anticipated and the enrollment is still ongoing [57].

In alternative to conventional GTs, a promising strategy has been attempted based on the use of myeloid progenitor cells (MPCs). In preclinical models, fully allogeneic MPCs were infused and the myeloid effector cells derived from them were able to prevent infection and bridge myelopoiesis following high-dose radiation exposure [58-60]. Following these studies, Cellerant Therapeutics has developed CLT-008, a clinical-grade product consisting of pooled *ex vivo* expanded myeloid progenitors from screened healthy donors [61]. CLT-008 can be cryopreserved and used as universal "off-the-shelf" allogeneic product in case of probability of radiological or nuclear incidents [61]. The CLT-008 has been evaluated in two phase-1 safety studies in a total of 75 patients with hematologic malignancies, one study in patients receiving chemotherapy and radiation conditioning for an umbilical cord blood transplant (NCT00891137), and the other in patients with leukemia receiving consolidation or induction chemotherapy (NCT01297543) [62]. Preliminary

data from these studies suggest that CLT-008 is safe and well tolerated: efficacy signals with respect to mucositis and duration of fever, observed in the absence of high-level peripheral blood CLT-008 chimerism, suggest that CLT-008-derived myeloid effector cells preferentially migrate to chemotherapy-damaged mucosal tissues where they could function to mitigate infection risk [63]. A phase-II randomized trial is currently ongoing in acute myeloid leukemia patients in induction therapy: the primary outcome is the duration of febrile episodes and the estimated completion date is March 2018 (NCT02282215).

## THE FUTURE

Despite the failure to provide definite evidence of GTs benefits, important information have emerged from previous statistically uninformative studies. For example, several retrospective studies have clearly suggested that the positive response to GTs can be anticipated only in patients with potential bone marrow recovery [19,39,47]. In addition, the absolute neutrophil count increment after transfusion may not necessarily predict the clinical response to the treatment [55]. In the meantime, however, other aspects remain unsettled. Indeed, below we have illustrated some issues that in our opinion may be worthy of reconsideration.

**Granulocyte transfusion doses.** It is not evident which GT dose predicts their efficacy nor how it should be calculated [56]. In order to provide comparable figures, in Table I and II we displayed whenever possible the median doses of neutrophils. It is evident that average doses widely differ among the studies (from 2.0 to $15.5 \times 10^8$ cells/kg). These differences reflect both the type of recipients, if adults or children, as well as the type of donors and mobilization. Basically, community donors receive G-CSF at variable doses, eventually accompanied by dexamethasone, and undergo one-day collection. In contrast, volunteers recruited among patients' relatives and friends receive only G-CSF and undergo two-consecutive-day apheresis, with the second collection containing significant lower amount of granulocytes. Based on the first studies conducted in the G-CSF era, both USA and European transfusion guidelines state that an apheresis granulocyte

collection should contain at least $1x10^{10}$ granulocytes, with a target dose of at least $1.5\text{-}3x10^{8}$ cells/kg [64,65]. Although the strategy "the more the better" might sound valuable, no tight dose-effect correlation has emerged so far. For example, pediatric patients usually receive significantly higher doses than adults, due to the lower body weight [20,24,31,34,38,40,42]. Nevertheless, also in this setting, no clear advantages for patients receiving higher doses have been demonstrated [20,24,38]. In the RING study, enrolling both adult and pediatric patients, a high target transfusion dose was planned (at least $40x10^{9}$ granulocytes per transfusion, that is more than $5.5x10^{8}$ cells/kg for an average 70-kg patient) [55]. To this purpose, donors were given 480 μg of G-CSF and 8 mg of dexamethasone prior to one-day collection. Nonetheless, the target dose ($\geq 6x10^{8}$ cells/kg) was reached in 29/48 pts (60.4%) of patients: according to the study primary outcome (day 42-survival plus infection response), these subjects did better than 13 patients in the low-dose group ($<6x10^{8}$ cells/kg; 59% versus 15%, p=0.01) but not than 42 patients in the control group (59% versus 37%, p=0.11). Unfortunately, no detailed information (age, underlying disease, bacterial or fungal infections, etc) on the low and high dose groups were provided [55]. In a recent revision of a series of 96 patients receiving granulocytes collected from relatives or friends, we found that GTs affected the mortality from bacterial infections in a dose-related manner: patients receiving average doses higher than $3x10^{8}$ cells/kg had similarly poor outcome as patients receiving insufficient doses ($<1.5x10^{8}$ cells/kg) [41]. Notably, neutrophils constitutes an important source of molecules that mediate the unbalanced inflammatory response implicated in the pathophysiology of sepsis [66,67] as well as in pulmonary transfusion reactions [68]. Therefore, the undesirable delivery of the burden of cytokines and chemokines may be a possible explanation of the detrimental effect exerted by the massive transfusion of high granulocyte amounts to septic patients [41]. Moreover, it deserves to be mentioned that GTs, like all blood products, can cause profound negative dose-dependent effects on the immune system, a condition termed transfusion-related immune modulation (TRIM) [69]. Since the detrimental effect of high granulocyte doses has not observed in patients with fungal infections, it might be conceivable that to control these infections higher amounts of granulocytes are

necessary [41]. All together, these findings suggest that identify optimal transfusion doses is relevant to assess their efficacy, with different doses required for bacterial or fungal infections could be required.

**Irradiation of granulocyte apheresis products.** The majority of retrospective and prospective studies on GT efficacy report that cell products are infused after irradiation to prevent transfusion-associated graft versus host disease (TA-GvHD) due to contaminant lymphocytes. Whereas it impairs neutrophil and monocyte function [70,71], the irradiation of granulocyte concentrates is universally and strongly recommended [64,65]. Frereich et al. have recently explored the effects of non-irradiated GTs in a randomized study in 108 leukemic patients [72]. Surprisingly, they did not observe TA-GvHD and the median survival was comparable in both arms [72]. Nevertheless, irradiated products resulted in a slight lower ANC increment, probably due to the impaired maturation of myeloid precursors following irradiation [72]. Collectively, these findings suggest that removing lymphocytes by methods alternative to irradiation, might lead to reduced toxicity and greater efficacy of GTs, likewise improving our understanding of the efficacy of granulocytes and their progenitors.

**Granulocyte transfusions and pulmonary infections.** It is currently debated the use of GTs in neutropenic patients with severe pulmonary infections, due the possible lung sequestration of infused cells. GTs often cause mild adverse reactions such as fever, chills, and transitory hypoxia, usually relieved by single hydrocortisone/corticosteroid administration. Nevertheless, in some patients with antibodies against human leukocyte antigens (HLA) or human neutrophil antigen (HNA), granulocytes sequestration in the pulmonary capillaries may occur, causing transfusion related acute lung injury (TRALI) and respiratory failure [73]. Neutrophil activation is fundamental in the pathogenesis of TRALI: in general, TRALI occurs when patients' own neutrophils are activated by the exposure to stimuli contained in transfused blood products. Inversely, in patients receiving GTs, neutrophils' activation is triggered by recipient' own alloantibodies [73]. Patients with invasive pulmonary aspergillosis may carry a particular risk for this complication [46], but this

finding has not been confirmed by several retrospective and prospective studies [17,19,20,24,27,30,32,34,36-39,41-43]. Although some authors recommend to avoid GTs in patients with pulmonary involvement [74], respiratory complications can be efficaciously prevented by the pre-transfusion match between recipient and donor [31]. In fact, positive leuko-agglutination test (carried out by assaying the serum of recipient against donor' granulocytes) can reveal the presence of HLA or HNA antibodies associated with respiratory complications [14,31]. Moreover, when the effect of leukocyte compatibility has been specifically investigated in randomized trials, the advantage for HLA-matched granulocyte components in term of ANC increments has been demonstrated [75].

**Granulocyte transfusions and hematopoietic stem cell transplantation (HSCT)**. Two studies, reported data collected in HSCT patients [27,40]; additionally, HSCT patients have been included in many of the published studies [19-26,30-31,34-36, 39,41-43,45,46,54,55]. Although it is arduous to decipher the results obtained exclusively in HSCT patients, these studies did not highlight substantial findings exclusive for HSCT patients, suggesting that GT effects in this setting might overlap those observed in the non-HSCT population. Nonetheless, an additional issue deserving consideration in patients undergoing allogeneic HSCT is the possible immunization due to previous GTs. This aspect is sparsely investigated in transfusion routine, but HLA or HNA antibody development is very frequent among patients receiving GTs [14]. Even though the positivity for HLA-antibody does not significantly affect the overall survival and the incidence of GVHD in transplanted patients [75,76], it has been recently associated with delayed neutrophil engraftment in those receiving HLA-mismatch HSCT [77].

## CONCLUSIONS

At present, despite statistical evidences are lacking, GTs are still perceived in our and other institutions as a lifesaving tool to support neutropenic patients with life threatening infections until their bone marrow recovery. Sharing procedures for donor identification and cell mobilization,

pursuing common criteria to identify which patients will benefit of GTs during febrile neutropenia and define indications and therapeutic cell doses are absolutely urgent to pinpoint the true advantage of using GTs. On the other hand, adopting equal end points and outcomes to evaluate both clinical response to treatment and biological functions of neutrophils and chemokines during sepsis, need to be clarified. These are the pre-requisite to design clinical and biological informative studies supported by likeminded institutions, gathered to achieve harmonized treatments, appropriate patient population and sufficient statistical power.

## AUTHOR'S CONTRIBUTION

C.G.V., F.F., L.P and L.T. designed the study, collected and analyzed data and wrote the manuscript. All authors approved the final version of the manuscript.

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**Table I.** Results of retrospective trials on granulocyte transfusions in the G-CSF era in adult and pediatric populations (only studies with more than 10 patients have been included)

| Reference and study type | Study population and indication for GTx | N. of patients (type of infections) | Age*(year) | Mobilization | PMN /kg per GT*<br>PMN per GT* | Number of GTx* | Outcome and clinical remarks |
|---|---|---|---|---|---|---|---|
| Illerhaus et al. (2002)<br>Ref. 17<br>Pilot study | Hematological pts.<br>Treatment (18 IE) or prophylaxis (24 IE) of severe infections in neutropenia | 42<br>(FI and BI) | n.r. (adults) | G-CSF 5 µg/kg | n.r.<br>Therapy: 2.6 x $10^{10}$ (0.3-8.6)<br>Prophylaxis: 3.20 x $10^{10}$ (0.73-8.51) | 3 (1-25)<br>3 (1-4) | Resolution of infection in 12/18 pts (67%);<br>prophylaxis not useful |
| Cesaro et al. (2003)<br>Ref. 18 | Hematological pts; severe infections in neutropenia | 13<br>(15 IE: 4 G-BI,1 G+BI, 1 FI, 2 MI, 7 FUO) | 7 (3-14) | G-CSF 300 µg | n.r.<br>3.2 x $10^{10}$ (0.3 - 6.4) | 4 (2-11) | Complete recovery in 6/15 IE (40%) and partial recovery in 3/15 IE (20%) |
| Rutella et al. (2003)<br>Ref. 19 | Hematological pts; febrile persistent severe neutropenia | 18<br>(11 BI, 7 FI) | 43 (18-52) | G-CSF 5 µg /kg | 4.3 x $10^{8}$/kg (0.6-18.5)<br>1.7 x $10^{10}$ (0.2-5.2) | 2 (1-8) | Favorable response in 10/18 pts (55%): 6/11 (54%) with BI, 4/7 (57%) with FI |
| Sadfar et al. (2004)<br>Ref. 45<br>Controlled | Cancer patients with *Candida* species bloodstream infections | 25<br>(FI) | 49 ± 18 | G-CSF 5 µg/kg + Dex 8 mg | n.r.<br>5.6 x $10^{10}$ (4-10) | n.r. | Overall IMR 48% (12/25) |
| Grigull et al. (2006)<br>Ref. 34 | Hematological pts; sepsis and neutropenia | 32<br>(10 FUO, 10 BI, 8 FI, 4 VI) | 7.4 (0.2-16) | Single dose of glycosylated G-CSF+ Dex 8 mg | n.r.<br>6.3 x $10^{10}$ (1.9-13.9) | 5 (1-19) | OS 59% (19/32 pts): 82% (9/11 pts) in bacterial sepsis |
| Kikuta et al. (2006)<br>Ref. 20<br>Pilot study | Cancer pts with febrile neutropenia | 13<br>(10 BI, 2 FI, 1 MI) | 3 (0.3-17) | Single dose of G-CSF | 6 x $10^{8}$/kg (1-15)<br>0,6 x $10^{10}$ (0,2-1.5) | 2 (1-4) | Resolution of infection in 9/13 pts (69%) |
| Ofran et al. (2007)<br>Ref.35 | Neutropenic pts with life-threatening infections | 47<br>(28 FI, 15 BI, 4 FUO) | 37 (16–68) | Single dose of G-CSF 300 µg + 2 doses of PDN 20 mg | n.r.<br>3.6 x $10^{10}$ (0.2-14.7) | 6 (2–29) | IRM 38% |

**Table I.** (continues) Results of retrospective trials on granulocyte transfusions in the G-CSF era in adult and pediatric populations (only studies with more than 10 patients have been included)

| Reference and study type | Study population and indication for GTx | N. of patients (type of infections) | Age*(year) | Mobilization | PMN /kg per GT* / PMN per GT* | Number of GTx* | Outcome and clinical remarks |
|---|---|---|---|---|---|---|---|
| Drewniak et al. (2008) Ref. 21 | Hematological pts. Therapy (16 pts) or prophylaxis (4 pts) of severe infections in chemotherapy-induced neutropenia | 13 pts (20 IE: 16 FI, 4 BI) | 6 (1-21) | G-CSF 5 µg/kg + Dex 8 mg | $2.0 \times 10^8$/kg (3-5)<br>n.r. | Therapy 3 (1-10)<br>Prophylaxix 6 (4-9) | Control of infection in 11/16 pts (68%; no infection in the prophylaxis group |
| Quillen et al. (2009) Ref. 36 | SAA pts; neutropenia -related bacterial or fungal infections | 33 (16 FI, 15 BI, 2 MI) | 38 (7-67) | G-CSF 5 µg/kg or G-CSF 480 µg | n.r.<br>$6.8 \times 10^{10} \pm 2.3$ | | OS at discharge: 58% (19/33 pts), including 8/18 pts with invasive FI (44%) |
| Al-Tanbal et al. (2010) Ref. 22 | Hematological pts (AL, SAA, CGD) Resistant bacterial or fungal infections in severe neutropenia | 22 (16 FI, 15 BI, 8 VI, with MI) | 28.8 (15-52) | G-CSF 5 µg/kg or G-CSF 5 µg/kg + Dex 20 mg | n.r.<br>$2.8 \times 10^{10}$ (1.1-5.4) | 5 (3-18) | Clinical improvement in 15/22 pts (68.2%) |
| Ang et al. (2011) Ref. 37 | Hematological pts (AL, SAA, CGD) Severe neutropenic sepsis | 15 (10 MI, 3 FI, 1 BI, 1 VI) | 42 (19-63) | G-CSF 300 µg + Dex 8 mg | $8.5 \times 10^8$/kg (4.9-16.7)<br>$6.5 \times 10^{10}$ (3.1-13.2) | 3 (2-9) | IRM 67% (10/15 pts) |
| Atay et al (2011) Ref. 38 | Severe life-threatening infections in pediatric patients with FN or defective granulocyte functions | 35 (18 FI, 8 FUO, 7 G-BI, 2 G+BI) | 108.5 months (17-211) | G-CSF 480 µg + Dex 8 mg | $3.5 \times 10^8$/kg (0.3-12.3)<br>$2.7 \times 10^{10}$ (0.4-6.8) | 3 (1-18) | Day +30 OS 77.1% Day +60 OS 65.7% IRS 82.4% (29/35 pts). |
| Kim et al (2011) Ref. 39 | Hematological pts (AL, SAA) with febrile neutropenia | 128 (138 IE: 60 FUO, 10 FI, 68 BI: 33 G+, 20 G-, MI 15) | 45 (18-90) | G-CSF 300 µg + Dex 8 mg | $9.6 \times 10^8$/kg (4.7-18.0)<br>$5.9 \times 10^{10}$ (2.9-11.8) | 5 (3-38) | Day 28 IRS 64.7% |
| Cherif et al. (2013) Ref. 23 | Hematological pts with neutropenia and severe infections | 30 (37 IE: 19 BI, 11 FI, 7 VI, with MI) | 46 (3-82) | G-CSF 300 µg + hydrocortisone 100 mg | n.r.<br>$3.5 \pm 1.3 \times 10^{10}$ | 3 (1-14) | In 11 pts resolution of infections could be related to GTxs |

**Table I.** (continues) Results of retrospective trials on granulocyte transfusions in the G-CSF era in adult and pediatric populations (only studies with more than 10 patients have been included)

| Reference and study type | Study population and indication for GTx | N. of patients (type of infections) | Age*(year) | Mobilization | PMN/kg per GT* / PMN per GT* | Number of GTx* | Outcome and clinical remarks |
|---|---|---|---|---|---|---|---|
| Raad et al. (2013) Ref. 46 | Hematological patients with invasive aspergillosis | 53 (compared to 75 non-transfused pts with invasive aspergillosis) | 44 (9–75) | G-CSF Dex | n.r. / n.r. | 7 (1–44) | IRM 60% (in comparison with 40% in pts not receiving GTx) |
| Diaz et al. (2014) Ref. 24 | Granulocyte dysfunction or severe neutropenia and acute life-threatening infections | 13 (5 BI, 5 FI, 3 FUO) | 9.5 (1-20) | G-CSF 600 µg + Dex 8 mg | 11.8 x $10^9$/kg / 6.7 x $10^{10}$ | 8.5 (2-39) | Complete or partial clinical response in 12/13 pts (92%); IRM 15% and OS 42% |
| Sadfar et al. (2014) Ref. 25 | Cancer patients with neutropenia related severe infections | 74 (42 BI, 33 FI, 10 VI, with MI) | 56 (12-81) | G-CSF 5 µg/kg + Dex 8 mg | n.r. / 5.6 x $10^{10}$ (4-10) | 4 (1-50) | In 34/74 pts (46%) GTxs were discontinued due to clinical response and neutrophil count recovery |
| Kadri et al. (2015) Ref. 47 | Invasive *Fusarium* infection | 11 (FI) | 46 (17-58) | G-CSF 5 µg/kg or G-CSF 480 µg | n.r. / 6.84 ± 2.34 x $10^{10}$ | 7 (2-39) | Response rate 91% (10/11 pts); OS 45% |
| Nikolajeva et al. (2015) Ref. 40 | Prophylaxis (3/28) or treatment (25/28) of severe infections after allogeneic HSCT | 28 (14 FI, 6 BI, 5 FUO) | 6.5 (3.5–9) | G-CSF 5 µg/kg | 15.5 x $10^8$/kg (3-80) / 3.56 x $10^{10}$ (0.58-8.36) | 6 (1-14) | OS 64% (18/28) Day 28 mortality 3.8% Day 100 mortality 19 % 2 deaths for infections |
| Teofili et al. (2016) Ref. 41 | Hematological patients (AL and lymphomas) Febrile persistent severe neutropenia | 96 114 IE (57 BI, 24 FI, 10 FUO, with MI) | 46 (20-74) | G-CSF 300 µg | 2.1 x $10^8$/kg (0.46-7.34) / 1.5 x $10^{10}$ (0.1-7,5) | 4 (1-14) | IRM dependent on the median dose 44.4% in the low-dose (<1.5 x $10^8$/kg) 18.4% in standard-dose (1.5-3.0 x $10^8$/kg) and 48.4% in high-dose (>3.0 x $10^8$/kg) |

* Age, granulocyte doses and number of transfusions are given as Median (range) or Mean ± SD values, unless otherwise specified. §control group did not receive GTxs. §§ Most pts received on average ≥ 0.6x$10^9$ PMN/kg (the equivalent of 42 x $10^9$ granulocytes for a 70-kg subject) whereas a minority (~30%) of pts received a lower dose, as low as 0.09 x $10^9$ PMN/kg (the equivalent of 6 x$10^9$ cells for a 70-kg subject)
OS: overall survival; IRM: infection-related mortality; IE: infectious episode; IRS: infection-related survival; IRM: infection-related mortality rate; GTx: granulocyte transfusions; HSCT: hematopoietic stem cell transplantation; FUO: fever of unknown origin; pts: patients; BI: bacterial infections; FI: fungal infections; VI: viral infections; MI: mixed bacterial + fungal infections; G+: Gram-positive; G-: gram-negative; FN: febrile neutropenia; PMN: polymorphonucleated cells; Dex: Dexamethasone; PDN: prednisone ; SAA: severe aplastic anemia

**Table II.** Results of prospective trials on granulocyte transfusions in the G-CSF era in adult and pediatric populations.

| Reference and study type | Study population and indication for GTx | N. of patients (type of infections) | Age* (year) | Mobilization | PMN/kg per GT*<br>PMN per GT* | Number of GTx* | Outcome and clinical remarks |
|---|---|---|---|---|---|---|---|
| Dignani et al. (1997)<br>Ref. 26<br>Pilot study | Hematological pts with neutropenia-related FI | 15<br>(all FI) | 30 (18-73) | G-CSF 5 µg/kg | n.r.<br>Mean: 4.1 x $10^{10}$ (10-116) | 8 (3-16) | Favorable response in 8/15 pts (53%) |
| Peters et al. (1999)<br>Ref. 42 | Hematological pts with neutropenia related bacterial and fungal infections | 30<br>(17 BI, 13 FI) | 7 (3-65) | G-CSF 5 µg/kg | 2.6 x $10^{8}$/kg (1.2 - 10.3)<br>4.53 x $10^{10}$ (0.86-14.38) | 7 (3-65) | 21/30 pts (70%) alive without infection at d. 100:<br>- 14 out of 17 BI (82%)<br>- 7 out of 13 FI (54%) |
| | | | | PDN 50/75/100 mg according to donor body surface | 2.5 x $10^{8}$/kg (0.2-18.8)<br>1,34 x $10^{10}$ (0.15-4.94) | | |
| Price et al. (2000)<br>Ref. 27<br>phase I/II | Treatment of infections in HSCT recipients | 19<br>(13 FI, 4 BI, 2 MI) | 34 (7-58) | G-CSF 600 µg + Dex 8 mg | n.r.<br>Mean: 8.1 ± 0.2x$10^{10}$ (2.3-14.4) | 8 (1-25) | Resolution of infections in 8/19 pts (42%);<br>- 0/5 pts with invasive aspergillosis cleared the infection;<br>- 4/19 pts (21%) alive on day 30 post HSCT |
| Lee et al. (2001)<br>Ref. 28 | Neutropenia-related resistant infections | 25<br>(14 MI, 8 BI, 3 FI) | 38 (7-62) | G-CSF 5 µg/kg | n.r.<br>Mean: 5.5 x $10^{10}$ (0.2-19.6) | 2.1 (1-7) | Favorable response in 10/25 pts (40%):<br>- FI (72.7%)<br>- G-BI (60%) |
| | | | | Dex 3mg/$m^2$ | n.r.<br>Mean: 5.1 x $10^{10}$ (1.8-11.1) | | |
| | | | | G-CSF +Dex | n.r.<br>Mean:10.6 x $10^{10}$ (4.7-17.9) | | |
| | | | | Overall | n.r.<br>Mean: 6.6 x $10^{10}$ (0.2–19.6) | | |
| Lee et al. (2004)<br>Ref. 29 | Neutropenia-related resistant infections | 32<br>(FI and BI)) | 37 (15-62) | G-CSF 5 µg/kg + Dex 3 mg/$m^2$ | n.r.<br>8.2 x $10^{10}$ (2.1-17.9) | 4 (1-11) | Favorable response in 19/32 pts (59.4%): 80% with FI, 66.7% G-BI, 50% G+BI |
| Mousset et al. (2005)<br>Ref. 30 | Hematological patients; therapy (44 IE) or prevention (23 IE) of neutropenia-related infections | 52,<br>(67 IE: 51 FI, 8 BI, 6 FUO, most MI) | Prophylaxis 56 (27-64)<br>Intervention52 (21-68) | G-CSF 5 µg/kg ± Dex 8 mg | n.r.<br>4.3 x $10^{10}$ (0.3-20.3) | Prophylactic 4 (1-12)<br>Intervention4 (1-32) | No infections in prophylactic GTx (0/23)<br><br>Infection control in 36/44 pts (82%)<br>( 92% in BI and 78% in FI) |

**Table II.** (continues) Results of prospective trials on granulocyte transfusions in the G-CSF era in adult and pediatric populations

| Reference and study type | Study population and indication for GTx | N. of patients (type of infections) | Age* (year) | Mobilization | PMN/kg per GT*<br>PMN per GT* | Number of GTx* | Outcome and clinical remarks |
|---|---|---|---|---|---|---|---|
| Sachs et al.(2006)<br>Ref. 31<br>Phase II | Hematological pts with neutropenia-related infections | 27<br>(15 FUO, 7 FI, 5 BI) | 8 (0-18) | G-CSF<br>7.5 µg/kg | 8 x $10^9$/kg (1-26)<br>1.9 ± 0.7 x $10^{10}$ | 2 (1-10) | Resolution of infection in 25/27 pts (92.6%) |
| Seidel et.al (2008)<br>Ref. 54<br>Randomized controlled phase III | Solid or hematologic cancer pts; febrile neutropenia with pulmonary or soft tissue infiltration | 72 adults (79 IEs) randomized to receive GTx (40) or as controls (39) | 47 (13–75) controls<br>45 (19–59) GTx | G-CSF<br>5 µg/kg | 6.6 x$10^8$/kg/ (1.2-16)<br>n.r. | 3 ( 1–13) | Day 28 survival after randomization; resolution of the infection, adverse effects : no difference between arms |
| Seidel et al. (2009)<br>Ref. 43 | Hematological pts; neutropenia-related invasive bacterial or fungal infections | 49 children, 10 adults (92 IE: 55 BI, 31 FI, 6 VI 16 MI) | 6.2 (0.1-17)<br>21 (18-28) | G-CSF 5 µg/kg + PDN 50 mg | 11 x $10^8$/kg (1-91)<br>n.r. | 8 (1-65) | OS day +28: 72%<br>OS day +100: 52% |
| Heim et al. (2011)<br>Ref. 32 | Chronic granulomatous disease with severe infections | 10<br>(5 G+BI,3 FI, 2 G-BI) | 12 (4-23) | G-CSF 5 µg/kg and/or<br>Dex 8 mg | n.r.<br>5.2 ± 2.8 x $10^{10}$ (1.3- 11.3) | 26 (2-64) | Resolution of infection in 9/10 pts, despite 8 were alloimmunized and had poor increase of neutrophil count after transfusion. |
| Massey et al. (2012)<br>Ref. 44 | Hematological pts with febrile neutropenia | 13 children, 17 adults<br>(FI and BI) | 8 (5-15)<br>52 (38-56) | GTx from whole blood buffy coats<br>PMN per pack: 1×$10^{10}$ (0.3-1.6) | n.r.<br>Children<br>1.2 x $10^{10}$ (0.9-2.5)<br>Adults<br>1.9 x $10^{10}$ (1.2-2.5) | Adults: two packs and children 10-20 mL/ kg | Recovery of neutrophils and survival in all except 2 adult patients |
| Ozturkmen et al. (2013)<br>Ref. 33<br>Phase I/II | Hematological pts with neutropenia-related infections | 13<br>(5 BI, 3 FI, 1 MI, 4 FUO) | 129 months (36-202) | G-CSF 5 µg /kg + Dex 8 mg | 6 ± 3 x $10^8$/kg (0.1–1.2)<br>2.9 ± 1.2 x $10^{10}$ (0.4–5.5) | 3.7 (1-11) | Clinical response: 69.2%<br>Hematologic response: 53.8%<br>IRM 30.8%,<br>Day 28- IRS: 60% |
| Price et al. (2015)<br>Ref. 55<br>Randomized controlled phase III | Hematological pts with neutropenia-related infections | 49 pz in the control arm§(26 FI, 23 BI)<br>48 in the GTx arm (27 FI, 21 BI) | 46.9 ±20.2 controls<br>54.9 ± 17.2 GTx arm | G-CSF 480 µg + Dex 8 mg | ≥ 6x$10^8$/kg or 0.09 x$10^9$ /kg[§§]<br>5.5 x $10^{10}$ (26.1-72.5) | 5 (1-20) | Day +42 post randomization, survival + infection response: 42% in treated and 43% in controls groups; trend for better outcome in pts who received ≥ 0.6x$10^9$ PMN/kg |

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OS, overall survival; IRM, infection-related mortality; IE, infectious episode; IRM, infection-related mortality rate; GTx, granulocyte transfusions; HSCT, hematopoietic stem cell transplantation; FUO, fever of unknown origin; pts, patients; BI, bacterial infections; FI, fungal infections; VI, viral infections; MI, mixed bacterial + fungal infections; G+, Gram-positive; G- , gram-negative; PMN: polymorphonucleated cells; Dex: Dexamethasone; PDN: prednisone