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Donor Granulocyte Transfusions in Patients with Hematologic Malignancies and in Recipients of Hematopoietic Stem Cell Transplantation

Al-Jasser AM[1] and Al-Anazi KA[2*]

1 Riyadh Regional Laboratory, Ministry of Health, Saudi Arabia
2 Department of Adult Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia

***Corresponding author:** Khalid A. Al-Anazi

kaa_alanazi@yahoo.com

Department of Adult Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia.

Tel: 966-03-8431111
Fax: 966-03-8427420

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Abstract

Despite the progress achieved in antimicrobial therapies and supportive care, infections remain a major cause of morbidity and mortality in patients with hematologic malignancies and in recipients of hematopoietic stem cell transplantation. In the 1990s, there was renewed interest in donor granulocyte transfusions due to the availability of granulocyte-colony stimulating factor and advanced apheresis technology. The results of several clinical trials did not show clear advantage of adding granolucyte concentrates to antimicrobial therapies due to significant defects that affected the final results of these trials.

With the recent increase in incidence of multidrug resistant bacteria and invasive fungal infections in neutropenic patients and the reduced efficacy of the recently introduced antimicrobial agents, the need for transfusing donor granulocytes to these patients is renewed again. However, well designed, multicenter randomized controlled trials that include large numbers of patients are needed to determine the effectiveness of donor granulocyte transfusions in these severely immunocompromised patients.

Keywords: Donor granulocyte transfusion; Neutropenia; Hematologic malignancy; Hematopoietic stem cell transplantation; Multidrug resistance; Invasive fungal infections

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Introduction

Neutrophils are phagocytic granulocytes derived from pluripotent stem progenitor cells in the bone marrow (BM) and they constitute the key effectors of the innate immune system [1-3]. Granulocytes or polymorphonuclear leukocytes (PMNLs) play an integral part in host defense and are critical for controlling bacterial and fungal infections as risks of infections increase when PMNLs ≤ 500/µL [4-8]. Neutrophils are the major pathogen-fighting cells and they represent the first line of defense against a wide range of infectious pathogens such as bacteria, mycobacteria, protozoa and fungi [3,9]. They are able to: (1) be recruited at the site of infection, (2) recognize and phagocytose microbes, and (3) kill pathogens through a combination of cytotoxic mechanisms [9]. PMNLs are the most common leukocytes found in the peripheral blood of healthy individuals as they account for 50%-70% of all circulating leukocytes [3,6,9]. A healthy person weighing 70 kilograms (Kg) produces approximately 10^{11} PMNLs per day [6]. PMNLs spend their total life span of 9-10 days in 3 main areas: BM, peripheral blood and body tissues [6]. However, the half-life of a circulating neutrophil is about 7 hours [10].

Neutrophil disorders can be divided into: (1) disorders of neutrophil number causing neutropenia that can be identified by complete blood count, and (2) disorders of neutrophil function causing dysfunctional neutrophils that can be diagnosed by phagocytic tests, functional assays and the recently introduced genetic testing [1,11,12]. Neutropenia can be transient or chronic, congenital or acquired, and idiopathic or antibody mediated [1,11]. Examples of congenital neutropenia include: benign familial neutropenia, cyclic neutropenia, severe congenital neutropenia and inherited BM failure syndromes

[1,11]. Acquired neutropenia can be related to: infection, diet, drugs or malignancy [1,11]. In patients with overwhelming sepsis, neutrophils become dysfunctional due to the development of neutrophil paralysis or failure of neutrophils to migrate to the sites of infection [2,13-16].

In patients with hematologic malignancies (HMs), fever is often the first and may be the sole sign of infection as these patients have suppressed inflammatory responses [17,18]. Febrile neutropenia (FN) is defined as a single oral temperature of > 38.3°C (101°F) in a neutropenic patient [19]. FN is a serious complication in patients with HMs receiving cytotoxic chemotherapy [18,19]. It is considered a medical emergency as infections in neutropenic patients can progress rapidly and lead to life-threatening complications [17-20]. Therefore, prompt identification of FN and early initiation of empirical antimicrobial therapy can: prevent progression into sepsis, prolong survival and improve quality of life of patients with HMs [17-19]. In patients with neutropenia, the strongest predictor of recovery from infections is the recovery of neutrophil production by the BM or having adequate numbers of neutrophils in the peripheral blood or body tissues [21].

Infections in HMs and in HSCT

Patients with HMs especially acute leukemia (AL) and recipients of hematopoietic stem cell transplantation (HSCT) are the most severely immunocompromised patients particularly during the prolonged episodes of treatment-related granulocytopenia. Hence, infectious complications remain a major cause of morbidity and mortality in these patients [22-24]. The recent evolution of drug-resistant bacterial and fungal infections in this group of patients is alarming [22-24]. The main risk factors for infections in patients with HM and in recipients of HSCT are: HM itself; cytotoxic chemotherapy given to control their AL; chemotherapy and radiotherapy given in the conditioning therapy prior to HSCT; prolonged neutropenia; mucositis; central venous catheters (CVCs); environmental factors; gut colonization by bacteria; acute graft versus host disease (GVHD) and its immunosuppressive therapy; and presence of comorbid medical conditions such as diabetes mellitus [22,24-29]. The main interventions to control infections in patients with HMs and in recipients of HSCT are: (1) strict infection control measures such as hand hygiene, use of gloves and masks, provision of low bacterial diet, and isolation in single rooms; (2) use of prophylactic and pre-emptive antimicrobials; (3) adoption of antimicrobial stewardship programs; and (4) in case of multidrug resistant (MDR) microorganisms, the use of drug combinations containing new and more potent old antimicrobials such as lenozolid, daptomycin, tigecycline, colistin, voriconazole and amphotericin-B [22,23].

Bloodstream infections (BSIs)

Patients with HMs and recipients of HSCT are highly vulnerable to BSIs due to prolonged neutropenia and chemotherapy-induced mucositis [30]. BSIs cause significant morbidity and mortality in these patients [31-33]. In neutropenic patients having BSIs, there are two recent developments: (1) a shift in dominance from Gram-positive to Gram-negative bacteria (GNB), and (2) emergence of MDR organisms. Hence, the case-fatality rate remains high [30,32-37]. Strategies that may help in reducing the incidence of MDR bacterial infections include: (1) de-escalation strategy and adoption of antibiotic stewardship, (2) application of strict infection control measures, (3) limitation of the use of certain prophylactic antibiotics such as fluroquinolones during prolonged neutropenia, and (4) the use of recently introduced antibiotics such as ceftolozane/ tazobactam and ceftazidime/ avibactam [30-33,37]. Also, breakthrough yeast BSIs particularly those caused by *non-albicans Candida species* are increasingly reported in patients with HMs receiving antifungal prophylaxis [38]. Management of these breakthrough yeast BSIs includes: switching to a different antifungal agent and prompt removal of CVCs [38].

Invasive fungal infections (IFIs)

IFIs remain an important cause of morbidity and mortality in immunocompromised patients with HMs and in recipients of HSCT having FN [39-44]. The diagnosis of IFIs remains a challenge due to the low sensitivity and specificity of not only the clinical manifestations but also the microbiological cultures and the radiological tools [39]. In such patients, the following strategies have been shown to improve survival: (1) initiation of preemptive antifungal therapy at the first sign of IFI, and (2) administration of antifungal prophylaxis in high-risk (HR) patients [40]. Prompt initiation of appropriate antifungal treatment early in the course of IFIs reduces mortality related to these infections [39]. However, the rapid development of MDR in the management of IFIs in immunocompromised individuals is a real challenge [41]. Selection of the individual antifungal agent to be used should take the following considerations into account: (1) patient factors, (2) the specific pathogen causing the IFI, (3) the site of infection, and (4) drug-related factors such as: cost, convenience, drug resistance, drug-food interaction, drug-drug interaction and adverse effects of individual drugs [42,43]. Hence, management of IFIs in patients with HMs requires an individualized treatment plan [40]. Recently, the frequency of yeast infections has decreased, but the incidence of non-Aspergillus mold infections caused by: *Mucor*, *Fusarium*, *Rhizopus* and *Scedosporium species* has increased [44-46]. The recent increase in the incidence of non-Aspegillus mold infections can be explained by: the increasing use of immunosuppressive agents, selection of these molds due to antifungal prophylaxis, better recognition of these infections, construction work and natural disasters [45].

Donor Granulocyte Transfusions (DGTs)

History of DGTs

The initial events in the history of DGTs are: (1) in the year 1883, Metchinikoff described the phagocytic function of white blood cells or neutrophils; (2) in 1934, Struma injected neutrophils or leukocyte cream intramuscularly into neutropenic patients hoping that breakdown products would stimulate endogenous neutrophil function; (3) in the year 1953, Brecher et al. found that: (1) in lethally-irradiated dogs, harvested neutrophils could circulate and migrate to sites of inflammation, and (2) rat leukocytes retained some physiological activity when injected into neutropenic mice; and (4) in the 1960s, 3 groups of

scientists (Levin et al., Freidreich et al. using untreated chronic myeloid leukemia patients as donors for PMNLs, and Bodey et al.) established the following: (1) the quantitative relationship between circulating leukocytes and infection in patients with AL, and (2) the potential of leukocyte transfusion in the management of neutropenic patients [6,10].

DGTs were first introduced in the 1970s by using (1) continuous flow centrifugation apheresis, (2) donor stimulation by corticosteroids, and (3) hydroxyethylstarch, used as red blood cell sedimenting agent, which facilitated efficient cell separation [5,6,10]. Using this technique, approximately 2-3 × 10^{10} PMNLs per procedure were attainable. Later on, controlled clinical trials and observational studies showed conflicting outcomes and due to transfusing limited doses of donor granulocytes and encountering side effects such as fever, pulmonary toxicity and transmission of cytomegalovirus infection, DGTs were almost entirely abandoned due to the availability of new potent antimicrobial agents and the progress in supportive care measures [5,6].

In the 1990s, there was renewed interest in the use of DGTs to enhance host defenses and to treat infections due to the following reasons: (1) the evolution of MDR bacteria, (2) the increase in the incidence of IFIs despite the presence of new antimicrobials, (3) the availability of granulocyte-colony stimulating factors (G-CSF) to mobilize granulocytes from the BM to the peripheral blood, and (4) the availability of recent apheresis machines with advanced technology that allowed large volume procedures to be performed in order to obtain at least 6-8 × 10^{10} PMNLs per session of apheresis [5,6,21,47].

So, the need to administer donor granulocytes in neutropenic patients existed since the 1970s although interest has changed over the years due to technical issues, availability of certain antimicrobials and the recent changes in the spectrum of infections as well as the increase in the number of immunocompromised patients who are in need of DGTs [48,49].

Leukapheresis machines

The old filtration leukapheresis used nylon fibers to yield large amounts of PMNLs. Unfortunately, filters were traumatizing and activating cells, thus promoting release of granules and activating complements and the cells obtained had short life-spans and impaired tissue response [6]. However, the new continuous flow centrifugation leukapheresis that was initially developed in the 1960s has undergone several modifications and is now considered the standard methodology for collection of PMNLs [6]. With the current leukapheresis technology, collection of large numbers of granulocytes can be obtained from healthy donors in order to transfuse them to neutropenic patients with HMs and recipients of HSCT who have infectious complications [50]. The modern apheresis machines can process 7-10 liters of blood over 3 hours [51]. In October 2012, a new pooled granulocyte component derived from irradiated whole blood/buffy coat in platelet additive solution and plasma became available and it was expected to replace the old pooled leukocyte buffy coat component [49,52,53]. DGTs are expensive and are not always conveniently available as this technology and experienced medical and technical personnel are available in certain institutions [50].

DGTs remain an important modality in patients with difficult-to-treat opportunistic infections as they bridge till spontaneous recovery of neutrophils in patients with neutropenia caused by cytotoxic chemotherapy or HSCT [47,52]. However, the use of DGTs should be limited to patients with neutropenia caused by BM failure or in patients with neutrophil dysfunction in whom the possible benefits outweigh the expected hazards [49,53].

Old and New Clinical Trials on the Use of DGTs

Early clinical trials

The main old clinical trials on the use of DGTs include: (1) between 1972 and 1982, several clinical trials were performed and they yielded mixed results but 6 reports showed favorable responses to DGTs; (2) in 1982, a randomized controlled trial of therapeutic DGT was conducted in patients with sepsis due to GNB and it showed no significant difference in benefit between the group who received and the group who did not receive DGTs; and (3) between 1985 and 1995, there was gradual disappearance of the use of DGTs except in few medical centers [54]. The following reasons attributed to disappearance of DGTs: improvements in supportive care, development of new antimicrobials and difficulties encountered in collecting and transfusing donor granulocytes. However, as early as the year 1975 it had been reported that good responses were encountered in patients receiving higher doses (HDs) of DGTs [54]. Additionally, 2 meta-analyses of clinical trials using DGTs showed clinical efficacy of trials using HDs of donor granulocytes [6,55].

More recent studies and trials

DGTs have been used to prevent infections (primary prophylaxis) or reactivation of infections (secondary prophylaxis) during periods of prolonged neutropenia such as neutropenia associated with cytotoxic chemotherapy and conditioning therapies prior to HSCT as well as neutropenia associated with diseases such as chronic granulomatous disease (CGD) [21,56,57]. Some studies have shown the efficacy of HD-DGTs in controlling severe infections in neutropenic cancer patients [58]. However, prophylactic use of DGTs is not generally recommended due to absence of evidence of effectiveness, but unfortunately most of the studies on the prophylactic role of DGTs had been performed before the era of G-CSF and new apheresis technology [5,21,50].

As early clinical trials showed no clear benefit of DGTs, the therapeutic use of DGTs in neutropenic patients having infections remained a controversial issue [7,59-62]. The yields of leukapheresis have increased significantly following the introduction of G-CSF to mobilize granulocytes and the use of modern apheresis machines [60]. Additionally, multiple studies that avoided defects in the design of early clinical trials have shown that use of DGTs in patients with prolonged neutropenia having serious bacterial or fungal infections is beneficial and may be life-saving [59,61-65]. The more recent clinical studies and meta-analyses on the use of DGTs in neutropenic patients having severe bacterial infections or IFIs highlighted that the following points should be taken into consideration in order to avoid the disappointments experienced in the past: (1) administration of

HDs of granulocytes, (2) provision of leukocytes that are cross-match compatible with the recipient, and (3) proper timing or early transfusion of granulocyte concentrates [55,65-68]. However, the prophylactic use of DGTs to prevent infectious complications in neutropenic patients has remained more controversial than the therapeutic use of DGTs [52,58,66,67].

The RING trial

The Resolving Infection in Neutropenia and Granulocyte (RING) trial was a randomized controlled clinical trial that evaluated effect of antimicrobial therapy versus antimicrobial therapy combined with DGTs in patients with neutropenia following cytotoxic chemotherapy or HSCT [4,5,54,69-71]. The trial showed no apparent overall survival (OS) benefit from DGTs but the trial was compromised by inadequate study enrollment. However, a post-hoc secondary analysis suggested that HDs of granulocyte transfusions were effective [4,5,54,71].

Criticism of Published Studies

The cochrane meta-analyses

The Cochrane systematic review and meta-analysis published in 2015 included 11 clinical trials involving 653 patients having neutropenia following chemotherapy or HSCT [72]. There was no difference in: (1) 30 day all-cause mortality, and (2) overall infection rate between the group of patients who had received DGTs and those who had not received DGTs. However, there was reduced risk of bacteremia and fungemia in patients who received prophylactic DGTs and there was correlation between the doses of granulocytes and the risk of infection, that is, doses of granulocytes ≥ 10×10^{10} neutrophils/day were more effective in controlling infections [54,72,73]. Additionally, the authors suggested including larger number of patients e.g. approximately 2748 patients in future randomized clinical trials in order to obtain statistically significant results [54,72,73].

Defects in published trials and challenges facing DGTs

The following problems were encountered in the early as well as the more recent clinical trials on the use of DGTs in neutropenic patients: (1) selection of patients, that is, lack of consistency in selecting not only appropriate patients but also controls, (2) small numbers of patients were included, but large numbers are needed to obtain statistical power to indicate benefit, and (3) early trials focused on short-term survival while patients were dying because of either disease or infection [10,54,74].

Despite the lack of solid evidence of efficacy, DGTs have been used as adjunctive therapy for severe and progressive infections in neutropenic patients [8,10,21]. The efficacy and feasibility of DGTs have changed considerably over the past 5 decades [8,58]. Response rates to DGTs in patients with neutropenia having severe and uncontrolled bacterial or fungal infections have ranged between 30% and 83% and although DGTs have improved survival in certain studies, the main determinants of OS in these patients are: (1) the underlying disease process, and (2) the time taken to have endogenous neutrophil recovery [8,10,21,58,71]. Therefore, the remaining challenges facing the use of DGTs are: optimal selection of patients, optimal timing of use, use of optimal technique, and administration of optimal dose, that is, HD-DGTs [52,58,75,76].

Current Use of DGTs

Rationale for using of DGTs

Patients with HMs and recipients of HSCT develop prolonged neutropenia which is a risk factor for various infectious complications. In these patients: (1) infections remain an important cause of morbidity and mortality and they account for 40% of deaths, (2) the incidence of infection is directly related to the degree and duration of immunosuppression, and (3) the risk of infection increases rapidly when neutrophil count falls below 500 cells/μL [6,10,47,54]. Recovery of neutrophils is essential to counteract bacterial and fungal infections [10]. DGTs have been broadly used to prevent or treat life-threatening infections in patients with prolonged neutropenia or neutrophil dysfunction [47,75].

The following are justifications for the use of DGTs: (1) the recent shift in the spectrum of infections in neutropenic patients with the increase in the incidence of MDR bacteria in patients with neutropenia related to: HMs, HSCT or BM failure; (2) the recent increase in the incidence of IFIs in neutropenic patients due to *Aspergillus*, *Fusarium* and *Zygomyces species* despite the availability of broad spectrum antifungal drugs, new generations of antifungal agents and G-CSF; (3) the recent increase in the number of patients with AL requiring cytotoxic chemotherapy and in the number of recipients of various forms of HSCT as both groups of patients develop severe and prolonged neutropenia; and (4) the availability of G-CSF and modern apheresis technology [6,10,47,54,76].

Current indications for DGTs

The indications for DGTs are: (1) patients with HMs having prolonged neutropenia following cytotoxic chemotherapy, (2) recipients of HSCT having prolonged neutropenia, (3) patients with severe aplastic anemia (SAA) having infectious complications, (4) neutropenia in septic neonates, and (5) neutropenia in patients with CGD [5,6,54,56,76-82]. The following are minimal criteria to initiate DGTS: (a) absolute neutrophil count (ANC)<500 cells/μL except in CGD; (b) evidence of bacterial or fungal infection: clinical (symptoms and signs), microbiological (positive cultures), pathological (tissue biopsy), and radiological (chest X-ray, computerized axial tomography scans); and (c) unresponsiveness to antimicrobial therapy for at least 48 hours except in extreme circumstances with life-threatening infection [54]. However, the following are not indications for DGTs: fever in the absence of documented infection and the prophylactic use of DGTs [51].

Donor selection and stimulation

The following are the criteria used for selection of granulocyte donors: (1) ABO/RhD compatibility with recipient, (2) age: <60 years in males and <50 years in females, (3) cytomegalovirus (CMV) negative donors for CMV negative recipients, (4) negativity

for blood transfusion-associated infections within 30 days of granulocyte donation, (5) no history of allergies to steroids or starch, and (6) good vascular access [5,54,70]. However, the following are contraindications for donating granulocytes: (1) pregnancy, (2) history of tuberculosis or fungal infection, (3) diabetes mellitus, (4) hypertension, (5) glaucoma, and (6) peptic ulcer disease [5,54,56].

In preparation for donation, the selected donor will receive G-CSF 300 µ gram subcutaneously on the day prior to apheresis. Corticosteroids in the form prednisolone 60 mg or dexamethasone 8 mg can also be given orally one day prior to apheresis [5,6,51,54].

Storage and transfusion of donor granulocytes

Donor granulocyte concentrates should be: (1) stored at 20-25°C; (2) irradiated using 15-30 Gy of gamma or X-ray irradiation to prevent GVHD; and (3) transfused within 24 hours, preferably within 6 hours of finishing collection. However, leukofiltration is not needed [5,6,49,51,54,70,76]. It may be possible to store granulocyte concentrates for 24-48 hours with adequate preservation of neutrophil function as suggested by several recent studies [69]. Before administration of granulocytes, the following pre-medications can be given to the recipient: acetaminophen 500 mg and diphenhydramine 25 mg [54].

Adverse effects and complications of DGTs

The medications used in mobilization of granulocytes (G-CSF and corticosteroids) have the following adverse effects: fever, headache, bone pains, arthralgia, fatigue and insomnia, while during granulocyte collection: pain, tingling, fatigue and mild changes in vital signs may occur [54]. Although the use of G-CSF in patients with SAA and congenital neutropenia has been reported to predispose to myelodysplastic syndrome [83-87], several studies have shown that the use of G-CSF in patients with chronic neutropenia, recipients of HSCT, and heathy donors of granulocytes or stem cells is safe and does not promote detectable monosomy 7 or trisomy 8 [87-91].

In the recipient, DGTs are associated with the following complications: (1) fever, chills, hypotension and allergic reactions, (2) in about 5% of patients, respiratory complications such as transfusion-related acute lung injury (TRALI) causing cough, dyspnea, progressive respiratory distress and pulmonary radiological changes can be encountered, (3) alloimunization to HLA and HNA antigens, (4) transfusion transmitted infections such as CMV, (5) transfusion-associated GVHD, and (6) polycythemia rubra vera evolving in a recipient of DGTs has been reported [5,6,8,49,54,70,92-95].

Discontinuation of DGTs

The following represent justifications to discontinue the administration of donor granulocytes: (1) resolution of the target infection, (2) BM recovery manifested by return of the recipient's endogenous ANC to ≥ 500 cells/µL for 3 consecutive days, (3) lack of granulocyte donors, and (4) worsening of the clinical condition of the patient with poor response to DGTs requiring change in the management of the patient [5,51,54].

DGTs in Specific Populations of Patients

DGTs in patients with HMS

Bacterial and fungal infections remain a significant cause of morbidity and mortality in patients with HMs and in recipients of HSCT [74,94]. In patients with neutropenia, transfused granulocytes can increase the neutrophil count of the recipient and can accumulate at the site of infection as shown by specific granulocyte scintigraphy [7,96]. In neutropenic patients having infection, DGTs seem to be a useful adjunctive therapy, that is, once used in conjunction with G-CSF and antimicrobial therapy [96]. The following groups of patients are less likely to benefit from DGTS: (1) patients in whom neutropenia persists without myeloid recovery, (2) patients in whom corticosteroids cannot be discontinued, and (3) patients with serious comorbidities such as significant liver dysfunction or renal failure [75]. A large randomized clinical study that included 128 patients with various HMs having evidence of IFIs did not show any improvement in the outcome of IFIs in patients who had received DGTs in addition to antifungal therapy. On the contrary, it showed worse outcome in patients having fungal lung infections [97].

In pediatric oncology patients with neutropenia, DGTs have been shown to improve the short-term outcome [98]. DGTs are particularly effective in the treatment of patients with HMs and in recipients of HSCT who develop severe bacterial infections caused by MDR organisms such as *Acinetobacter baumanni* and *Pseudomonas aeruginosa* [8,99]. In certain studies, DGTs have increased the ANCs of recipients and complete clearance of infections has been reported [94]. In patients with FN, DGTs constitute a valuable tool to improve the outcome of infections in neutropenic patients provided adequate doses of granulocytes are administered [100]. So, despite the conflicting data, DGTs appear to be beneficial in the management of adult oncology patients with neutropenia [101].

DGTs in SAA

In patients with SAA, several studies have shown that DGTs may have an adjunctive role in treating severe bacterial infections or IFIs in addition to G-CSF and antimicrobial therapy [79,102-104]. However, HLA alloimmunization can be encountered but it is not an absolute contraindication to granulocyte therapy [79,104]. Several studies have shown beneficial effect of DGTs when combined with G-CSF and antimicrobial therapy in patients with SAA experiencing severe bacterial infections or IFIs [8,79,103,105,106].

DGTs in neonatal sepsis and CGD

Several studies and case series/reports have shown efficacy of DGTs in treating severe infections including IFIs in patients with CGD and in neonates with sepsis [56,77,81,82,107-109].

DGTs in recipients of HSCT

In recipients of HSCT, neutropenia is the single most important risk factor for the development of IFIs [8,110]. Recipients of allogeneic HSCT have defects involving different components of their immune systems which subsequently increase the risk of

having IFI [8,110]. Experimentally, granulocyte transfusions have been shown to be effective in the treatment of neutropenic hosts with pulmonary aspergillosis [111]. Donor granulocytes have donor-derived antifungal T-cells, hence administration of donor granulocytes is one of the approaches that aid in restoration of immunity and fighting fungal infections [8,110,112].

Donor granulocyte concentrates have a role in preventing progression of existing fungal infections in recipients of HSCT having neutropenia [113]. In a single center case-series that included 11 patients and in a systematic review of literature that included 23 patients with disseminated infections caused by *Fusarium species*, DGTs contributed to high response rates by bridging the periods of BM suppression and neutropenia [113]. Also, in a single center experience, that included 28 recipients of HSCT over 10 years, single donor granulocytes have been shown to reduce the incidence of infections and possibly reduce the overall incidence of GVHD [114]. Although the prophylactic use of granulocyte concentrates is not generally recommended, DGTs were administered preemptively in 3 pediatric recipients of allogeneic HSCT with chronic infections and their use was associated with positive outcome [115].

Conclusions and Future Directions

DGTs were first introduced in 1970s as adjunctive therapy in neutropenic patients having serious bacterial or fungal infections. As the initial results were equivocal, the procedure almost disappeared from clinical practice for 2 decades. In the 1990s, interest in DGTs was renewed after the availability of more advanced apheresis machines and the granulocyte mobilizing agent G-CSF. The more recently published studies have indicated advantage of DGTs in properly designed clinical trials.

Future studies and clinical trials should take the following points into consideration in order to avoid the drawbacks of the previous studies: (1) including large numbers of patients, (2) administration of HDs of granulocyte concentrates, (3) provision of leukocytes that are cross-match compatible with the recipient, and (4) proper timing or early administration of DGTs. Properly designed multicenter randomized clinical trials are needed to clearly define the role of DGTs in neutropenic patients with HMs and in recipients of HSCT.

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