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Review

Granulocyte transfusions in the management of neutropenic fever: A pediatric perspective

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ABSTRACT

Severe neutropenia-associated invasive bacterial or fungal infections are still the major cause of mortality and morbidity in children receiving cancer chemotherapy. Granulocyte transfusion therapy has been used for many years in the management of neutropenic patients with severe infections in whom the clinical condition deteriorated despite appropriate antimicrobial treatment. Transfused granulocytes can increase the recipient's blood neutrophil count and accumulation of them into the site of infection. There are some data obtained from retrospective or prospective observational studies in pediatric granulocyte transfusion therapy, but results are not conclusive. This review appraises the potential benefits and risks of the use of granulocyte transfusion in children with neutropenic fever.

Contents

1. Introduction

Despite improvement in treatment modalities, neutropenic fever is still the most common cause of mortality and morbidity in pediatric cancer patients. Febrile reactions occur in approximately one-third of neutropenic episodes in children with chemotherapy-induced neutropenia or shortly after hematopoietic stem cell transplantation (HSCT) [1]. When the absolute neutrophil count decreases below 500 cells/μL, the risk of severe bacterial or fungal infection increases [2]. Prompt evaluation of the patient and treatment with broad-spectrum antibacterial or antifungal therapy with adequate supportive care are mainstays of therapy [3]. However, these treatment modalities cannot control infections in all patients, and additional therapies are needed for patients in whom the clinical condition deteriorates. In such situations, granulocyte transfusions from healthy donors are used to increase the neutrophil accumulation in the sites of infection [4].

Granulocyte transfusion therapy (GTT) has been used for many years in the management of neutropenic patients with severe infections [5]. The studies conducted in the 1970s and 1980s have contradictory results showing positive or no beneficial effects [6,7]. In studies reporting the negative effects of GTT, transfusing an insufficient granulocyte dose was associated with failure of therapy [8]. Thus, difficulties in the separation of granulocytes from other blood cells, the risk of adverse events, and development of more effective antimicrobial or antifungal drugs contributed to a decrease in the use of GTT. In the 1990s, the improvement of the leukapheresis techniques and the availability of granulocyte colony-stimulating factor (G-CSF) increased the practice of GTT [9]. In children, prospective studies related to GTT are limited in the literature. In this article, we review the use of GTT in children with neutropenic fever.

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2. Neutropenic fever

Fever in neutropenic children (absolute neutrophil count (ANC) <500 cells/μL or expected to decrease below 500/μL in 48 h) is defined as a single oral temperature >38.3 °C or oral temperature >38 °C over at least one hour [10]. Chemotherapy-induced neutropenia is frequently associated with fever in 10%–50% of patients with solid tumors and 80% of those with hematologic malignancies will develop fever after a chemotherapy course. Documented infection rates in children with neutropenic fever range from 10% to 40%, and the most common severe infection is bacteremia in profoundly neutropenic patients (ANC <100 cells/μL) in reported studies [11–13]. The International Pediatric Fever and Neutropenia Guideline recommends monotherapy with an antipseudomonal penicillin or a fourth-generation cephalosporin or a carbapenem as empirical therapy in pediatric patients presenting with high-risk neutropenic fever. Risk stratification of patients should be based on primary diagnosis, clinical condition, duration of neutropenia and presence of documented infection. Prolonged neutropenic fever (≥96 h), primary diagnosis of AML, high-risk acute lymphoblastic leukemia (ALL) or relapsed acute leukemia, use of high-dose corticosteroids, and allogeneic HSCT are conditions associated with a high risk of invasive fungal disease. The guideline recommends initiation of caspofungin or liposomal Amfotericin-B as an empirical treatment and continuing until neutropenia is resolved [14]. In neutropenic patients who do not respond to medical treatments, GTT is a potentially effective choice to overcome infections. Reported indications for GTT use in neutropenic children are proven gram-negative or fungal infections in more than 80% of the cases [15].

3. Neutrophil mobilization and granulocyte collection from healthy donors

Normally, 5% of the total body's neutrophils circulate in the peripheral blood, and 60% are in the marginated pool. Thus, pharmacologic agents have been used to increase the number of neutrophils collected from donors by mobilization from the bone marrow into the circulation [16]. The neutrophil count increase begins within 2 h after granulocyte-colony stimulating factor (G-CSF) administration (5–10 μg/kg), and peaks 12 to 18 h later reaching 7- to 10 fold [17]. The combination of G-CSF and 8 mg dexamethasone results the greatest neutrophil yields, significant reduction of G-CSF dose and decreased side effects like muscle and bone pain, headache, fatigue and nausea [18]. When these two agents are used together, the transfused neutrophils have been shown to function normally and have prolonged survival in the recipient [19]. The side effects are usually mild and occurred in more than 90% of granulocyte donors. They resolve when white the cell count returns to normal limits. However, uncommon severe side effects like splenic rupture, retinal hemorrhage, acute iritis, and thrombosis have been reported in the literature [20]. Headache, flushing, hypertension, hyperglycemia and increased gastric acidity are common side effects which are associated with steroid use. Long term use of systemic steroid therapy has been associated with posterior subcapsular cataracts, but in granulocyte donors, no significant risk of cataracts was reported compared to platelet donors [21]. Theoretically, using G-CSF in donors with a prior history of hematopoietic malignancy or family predisposition may transform normal hematopoietic stem cells to a malignant clone. However, Shaw et al. investigated the long term effects of exposure to more than one dose G-CSF in healthy donors, and reported no increased incidence of hematological malignancies [22]. Consequently, informed consent, family history, medical assessment and microbiological screening are recommended for each granulocyte donor [23]. Because Cytomegalovirus (CMV) transmission can occur, CMV seronegative patients should be transfused with cells from CMV seronegative donors [16].

Previously, granulocytes were obtained from the buffy coat component preparation of whole blood but a large number of units with a high volume were required [24]. Continuous flow centrifugation leukapheresis is now the standard technique to collect granulocytes based on density differences between the cells. Hydroxyethyl starch (HES) is used to decrease contamination of erythrocytes and platelets in the granulocyte suspension [25]. Because the final hematocrit of granulocyte suspensions may be as high as 2% to 7%, the patient and donor's ABO and RhD blood group should be compatible, and cross-matching must be performed [16]. The acute effects of leukapheresis are mostly related to the citrate used for anticoagulation of the blood during this procedure. Symptoms of hypocalcemia, nausea, vomiting, hypotension, allergic reactions, and rarely air embolism were reported. Also, using HES may cause transient hypertension with flushing and headache [26].

The use of G-CSF plus dexamethasone 12 h before leukapheresis to collect granulocyte suspension has become a standard procedure. Drewniak et al. reported that the function of neutrophils from granulocyte suspensions were intact at 24 h, but the release of proinflammatory cytokines and a pH decrease following 36–48 h storage were observed [27]. Another study showed that granulocyte suspensions stored at 10 °C preserved respiratory burst, killing and migrating activity *in vivo* [28]. Ideally, granulocyte suspensions should be transfused as soon as possible after apheresis collection, otherwise, stored at room temperature (20–24 °C) without agitation for infusion in a maximum of 24 h. Granulocyte suspensions should be irradiated to prevent transfusion-associated graft-versus-host disease (TA-GVHD) before administration to the neutropenic patient [29].

4. Granulocyte transfusion in neutropenic children

Mortality rate is still high in neutropenic children with severe bacterial or fungal infection despite timely initiation of antimicrobial or antifungal agents. Using pre-stimulation with G-CSF and steroids in donors and recent advances in apheresis techniques resulted in an increase of GTT practices for children. Most of the data in pediatric GTT are obtained from observational studies.

A prospective study reported that GTT was effective in 30 neutropenic children, and 2% of bacterial, 56% of aspergillus and 50% of candida infections were resolved on day 100 [30]. Sachs et al. prospectively evaluated 27 patients with severe bacterial and fungal infections, and reported GTT resulted in a high improvement rate (25 of 27). They concluded that the high response rate might be related to early initiation of GTT (a median of 6 days of infection period) compared with other studies [31]. Uppuluri et al. also showed early use of GTT resulted in an improved survival rate from 41 to 54% in 72 children receiving 230 granulocyte infusions [32]. A retrospective study evaluated 111 GTT in 35 neutropenic children or defective granulocyte functions, and they reported infection-related and overall survival rates of 82% and 77%, respectively, on day 30 [33]. Ozturkmen et al. reported 69.2% clinical, and 53.8% hematologic response rate in their study [34]. Another study showed 92% clinical response, and 15% infection-related mortality in 18 children who received GTT. They reported that 46% of children developed respiratory adverse events but all of them improved [35].

Several studies showed that higher granulocyte counts in the apheresis product results in greater control of infection [36,37]. Siedel et al. assessed 778 GTT in 49 children and 10 young adults, and reported that median ANC increment on day 5 was associated with administered number of granulocytes. They suggested that daily transfusions of at least 1.4×10^8 granulocytes/kg proba-

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