DOI: 10.4149/BLL_2012_041

Bratisl Lek Listy 2012; 113 (3)
175 – 181

REVIEW

Granulocyte transfusions

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Abstract: Neutrophils play an essencial role in the defense of the body against bacterial and fungal infections. Disorders of their number or function significantly increase the risk of life-threatening infection. In spite of the development of growth factors, new broad spectrum antibiotics and antifungal drugs against nearly all known pathogens, severe neutropenia associated with bacterial or invasive fungal infections remains a major cause of morbidity and mortality in patients undergoing aggressive cancer chemotherapy or hematopoietic stem cell transplantation. Lately, an interest about granulocyte transfusions was renewed, what is a logical approach in the management of patients with prolonged 'reversible' severe neutropenia and severe infection, which is not controlled with appropriate antimicrobial and supportive treatment, including recombinant hematopoietic growth factors. It was a consequence of advances in the field of apheresis science, use of sedimenting agents and expecially advances in mobilization of granulocytes to the peripheral blood. It became now possible to collect large numbers of neutrophils. Therefore, the clinical use of granulocyte trasfusions, as a potential life saving treatment option in patients with severe neutropenia and uncontrolled infection in spite of appropriate antimicrobial therapy should be considered, with regard to possible benefits and risks *(Ref. 74)*. Full Text in PDF *www.elis.sk*.
Key words: transfusion, granulocytes, neutropenia.

List of abbreviations: ANC – absolute neutrophil count, DXM – dexamethason, G-CSF – granulocyte-colony stimulating factor, GT – granulocyte transfusion, GTX – granulocyte transfusions, HES – hydroxyethylstarch, IVIG – intravenous immunoglobulines, PMN – polymorphonuclears.

Neutrophils (PMN) play an essential role in the body's first line defense against bacterial and fungal infections. Their primary function is to destroy the invading pathogens in sites of infection through the process of phagocytosis (1). Disorders in quantity or function of neutrophils result in a weak body´s immune system. Severe neutropenia**,** defined as an absolute neutrophil count of less than $0.5x10^9$/l, occurs frequenty in oncology and hematology patients, mostly following the administration of chemotherapy and immunosuppressive therapy, transplantation of hematopoietic stem cells or other cancer treatments. It is a well-recognized risk factor predisposing patients to life-threatening infections (2) with a direct correlation between a risk of infection and the depth and duration of neutropenia (3). The same consequences as neutropenia have functional neutrophil disorders, for example chronic granulomatous disease, due to failure to locate, phagocytose and kill invading patogenic microorganisms.

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Granulocyte transfusions

In spite of the advances in medicine, severe neutropenia associated with infection, remains a major cause of morbidity and mortality in patients undergoing aggressive cancer chemotherapy or hematopoietic stem cell transplantation (4, 5, 6). Granulocyte transfusion (GT) therapy is a logical approach in the management of patients with prolonged 'reversible' severe neutropenia and severe infection, which is not controlled with an appropriate antimicrobial and supportive treatment, including recombinant hematopoietic growth factors. Neutrophils from healthy donors are supposed to temporary raise the patient´s granulocyte count and to help to fight the infection. The minimum cell dose required for a measurable neutrophil increment is $2–3x10^{10}$ cells, not less that $1x10^{10}$ cells (7). With a sufficient dose of neutrophils, normal or near normal blood neutrophil count can often be reached and sustained for up to 24 h (8, 9).

The thrilling story of granulocyte transfusions: enthusiastic scene entry, fall and ressurrection

Although the idea of replacing missing or dysfunctional granulocytes by their transfusion originated already in the previous century, it´s efficacy has still not been completely proven due to varying and maybe not convincing available data. The first attempt to intramuscularly inject a "leukocyte cream" to neutropenic patients was documented in 1934 (10). Twenty years later leukocytes were transfused to lethally irradiated dogs, they migrated to the areas of infection (11). In the 1960s, granulocytes for trasfusion were obtained from patients with chronic myelogenous leuke-

mia. Although first reports were quite promising, due to lack of donors, possible engraftment and risk of pathogens transmission, then healthy donors became favoured (12). In the 1970s, when granulocytes from healthy donors were already employed, the results of the studies became more contradictive, showing positive results, but partial or no beneficial effect as well. Seven studies of therapeutic GT reported on the response of infected neutropenic patients to treatment with GT plus antibiotics versus patients given antibiotics alone (13–19). In five of the seven studies, a certain degree of success following the GT treatment was documented. In 3, there was a significant overall benefit (16–18) and in two in certain groups of patients only (13, 15). By contrast, two studies reported the overall negative results for GT (14, 19). Successful trials used relatively high doses of PMNs from erythrocyte and leukocyte compatible donors. In studies showing negative results, low doses of PMN were transfused, donors were selected solely on the basis of AB0 blood group, and the nontransfused control subjects responded particularly well to antimicrobials alone (13, 14, 19). The failure of GT in five studies might be explained, as least in part, by an inadequate quantity and varying quality of neutrophils in GT what was confirmed also by a meta-analysis performed in 1996 by Vamvakas (20). Doses of less than 10^{10} granulocytes per m^2 of body surface area disn´t elevate the neutrophil count, which consequently might affect the clinical response. Administration of low doses of granulocytes was done due to low levels of circulating granulocytes in the peripheral blood of healthy donors and due to difficulties in separation granulocytes from other blood cells even if this has been facilitated by addition of sedimenting agents. Besides the lack of randomized trials demonstrating efficacy, also other practical problems in storing, logistics and processing of granulocytes, together with potential adverse events and the development of more potent antimicrobial agents and alternative agents such as recombinant hematopoietic growth factors and intravenous immunoglobulines (IVIG), contributed to a dramatic decline in the use of GT (7, 21–24).

New era

A modern GT is defined as a transfusion, in which PMNs are obtained from donors stimulated with granulocyte-colony stimulating factor, with or without corticosteroids, and which are collected by means of centrifugation leukapheresis with an erythrocyte-sedimenting agent, during the processing of relatively large volumes of donor blood.

In the early 1990s, it was discovered that G-CSF is a powerful mobilizer of granulocytes from the bone marrow into the peripheral blood and that these neutrophils can be harvested from normal donors treated with a single dose of G-CSF (25). G-CSF is a glycoprotein, a haematopoietic growth factor specific for the granulocytic cell lineage. It is responsible for proliferation and differentiation of neutrophil precursors and for stimulation of various functions of mature neutrophils. G-CSF causes also mobilization of CD34+ hematopoietic progenitor cells to circulating blood. A recombinant G-CSF is therefore widely used in a chemotherapy-induced myelosuppression and peripheral blood stem cell collection for autologous and allogeneic hematopoietic stem cell transplantation.

Subsequent studies established that an addition of dexamethasone (DXM) to G-CSF enhances the harvest and that this combination allows collection of the highest granulocyte yields (8, 24, 26–29). Several studies showed that neutrophils obtained from healthy donors who have been treated with G-CSF, with or without additional corticosteroids, appear to have normal or near normal functional characteristics and can migrate in vivo to the sites of inflammation (30–33). Moreover, it was found out that these G-CSF primed neutrophils have a different transcriptional profile and, as a consequence of various prosurvival proteins, a prolonged life-span (34).

With G-CSF mobilization and improvement in apheresis practice "high-dose GT" became available and the enthusiasm of scientists was renewed, inspiring them to reevaluate the clinical efficacy in patients receiving adequate larger doses of granulocytes (9, 25, 35–38). Recent studies have promising but still overall inconclusive results. At this time, no randomized clinical trials of modern therapeutic GT have been reported. However, many case reports suggest a success, but it is impossible to firmly ascribe the good outcome to the GT (39–43). The benefits of GT in studies with larger numbers of patients are unclear because of the lack of concurrent control patients treated with antibiotics alone (8, 44–48). Based on these preliminary findings, bacterial infections appeared to respond quite well to modern GT, and relatively mild fungus and yeast infections responded modestly well. However, serious fungus infections with tissue invasion often resisted (44–49).

Therapeutic, prophylactic GT and pediatric GT

Before the use of G-CSF, prophylactic GT had a marginal value (50–56). Although modern prophylactic GT appears to be promising, their efficacy, potential adverse effects, and economic analysis, similarly to therapeutic GT, await a definition by randomized clinical trials of sufficient numbers of patients.

In pediatric practice, therapeutic GT are prescribed for children with marrow failure and severe neutropenic infections using the same criteria as in adults. Because of the possibility of alloimmunization to leukocyte and red cell antigens, particularly to the Kell blood group, plus the risk of transfusion-transmitted infections, therapeutic GT are recommended only for progressive infections that cannot be controlled with antimicrobial drugs (57). Neutropenia must be viewed differently in neonates than in older children. Because normal neonates exhibit a physiologic neutrophilia, absolute blood PMN counts as high as $3x0^9$/l (ie, relative neutropenia due to age) might prompt consideration of GT. Four of the six trials (58) found a significant benefit for GT, but the studies were insufficiently homogeneous to permit clear recommendations regarding the efficacy of GT.

Current practice

The possibility to collect greater numbers of granulocytes contributed largely to the renewal of interest in the use of GT (49,

59–60). As granulocyte donors can be employed family members or friends, compatible with the patient in AB0- and Rh (D)-antigen system. In some trials, healthy volunteers from the community of apheresis donors were employed (49). Every potential donor has to be interviewed and examined properly, fulfilling similar criteria as standard apheresis donor. In the case of alloimmunized patients, donors should preferably be also leukocyte compatible, HLA-matched or selected by leukoagglutination crossmatching. However, the best method to accurately assess the compatibility has yet to be determined (61). Except for life-threatening situations, donors should be CMV- seronegative. Mobilizing agents used to enhance the circulating pool of neutrophils in peripheral blood include recombinant human G-CSF with or without corticosteroid administration. Currently, PMN donors are optimally stimulated using 300 to 480 μg G-CSF given subcutaneously, plus 8 mg dexamethasone taken orally, approximately 12 hours before beginning leukapheresis. Granulocyte collections are performed on continuous flow apheresis devices. To improve the separation of granulocytes and erythrocytes, which have similar specific gravity, erythrocytes-sedimenting agent, traditionally hydroxyethyl starch (HES), has to be continuously added to the donor's blood during the apheresis procedure. Although the donation of granulocytes is generally considered safe for healthy individuals, donors have to be observed during the mobilization period, during and after apheresis procedure and, if possible, also later.

Before administration to the patient, GT should be irradiated to prevent transfusion-associated graft-versus-host disease (62). The irradiation of neutrophils does not affect their in vitro functions, including respiratory burst activity and phagocytosis. There is a general agreement that GTs should be administered as soon as possible after collection, ideally within 6 hours (63). The administration continues daily (every other day is most probably appropriate for children only) until the complete recovery from infection or until the neutrophil count of more than $0{,}5x10^9$/l is reached.

According to the "Clinical Guidelines for the use of Granulocyte Transfusions" prepared by the Granulocyte Working Group led by Elebute, GT can be used as supportive therapy in patients, who fulfil all of the following criteria:

1) severe neutropenia (ANC <0.5x10/^{9}l) due to congenital or acquired bone marrow failure syndromes,
2) administration of active treatment in an attempt to achieve disease remission,
3) proven or highly probable fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy as demonstrated by visible spreading lesions on skin, mucosa or radiological examination,
4) neutrophil recovery is expected (ANC>$0.5x10^9$/l) in the near future and/or definitive therapy of curative potential is planned (64).

Another indication presents a known congenital disorder of neutrophil function regardless of the neutrophil count, if there is a proven or highly probable fungal or bacterial infection unresponsive to an appropriate antimicrobial therapy. GT should not be administred if spontaneous neutrophil recovery is not anticipated, no further active treatment is planned and in patients with fever of unknown origin. Sepsis in the absence of either neutropenia or known neutrophil dysfunction can´t be considered as indication for GT as well.

Because the right timing of GT is of high importance for the clinical outcome, the organisation of the whole process should be perfect: including donors management, collection and processing of GT, logistics and administration, with regard to the safety of both donors and patients. However, it´s obvious that further clinical and laboratory studies are needed. Randomized controlled trials should help to clarify the efficacy of GT therapy and identify which subgroup of patients benefits the most. The main problem of randomized controlled trials remains the ethical issue of not providing possible curative treatment in life-threatening situation. Currently, there is an ongoing study called The RING Study (Resolving Infection in Neutropenia With Granulocytes), with the official title: High Dose Granulocyte Transfusions for the Treatment of Infection in Neutropenia. This study will compare the safety and effectiveness of GT with standard antimicrobial therapy versus the safety and effectiveness of standard antimicrobial therapy alone in increasing granulocyte numbers and in improving survival rates in people with bacterial or fungal infection during neutropenia.

Donor´s associated side effects
G-CSF and corticosteroid administration

The short-term administration of G-CSF to normal donors is generally well tolerated. Common side effects include bone pain, myalgias, arthralgias, headache, fever, nausea, gastrointestinal discomfort, paresthesias, chest pain, chills and fatigue. Symptoms are present in more than 90 % of donors, they are usually mild and readily relieved with acetaminophen or ibuprofen. They resolve within a few days after the drug is discontinued and the donor's leukocyte count returns to normal within 7–10 days. Less than 10 % of donors experience symptoms so severe that the drug has to be discontinued or the dose modified. They are mostly caused by exacerbation of the underlying donor´s illness. From more severe side effects, splenic rupture, retinal hemorrhage, acute iritis, gouty arthritis and thrombotic events have been reported (65–66).

The long-term effects of exposure to G-CSF are unknown. The data regarding long-term follow-up of normal donors who received G-CSF for granulocyte collection are limited. Theoretically, donors with a prior history of malignancy or a strong family predisposition to acute myeloid leukemia or myelodysplasia can be at a higher risk of developing hematologic malignancies (67). The Research on Adverse Drug Events and Reports (RADAR) project reviewed clinical literature on adverse events that occur when G-CSF is administered to healthy individuals for peripheral blood stem cells collection (68). There were three donors who developed acute myeloid leukemia. To date, anyway, it remains unclear whether there is any association between G-CSF administration and hematologic malignancies developement, yet no evidence has been reported (69–70).

Common side effects associated with corticosteroids include headache, flushing, insomnia, euphoria, palpitations, epigastric acidity and hyperglycemia. The use of corticosteroids remains

controversial, especially because in the past some cases on development of posterior subcapsular cataract were reported. But a proper prove is still missing (71–72). In general, the stimulation of donors with G-CSF and DXM is considered as a safe procedure, without any association with long-term adverse vascular, hematologic or malignant outcomes.

The use of central venous catheter

Sometimes, to ensure vascular access before the apheresis procedure, an insertion of central venous catheter is necessary. Ideal are double- or triple-lumen dialysis catheters.

Naturally, also the use of central venous catheters is associated with a number of complications. The most common mechanical complications during the insertion of central venous catheters are arterial puncture, hematoma, and pneumothorax. Other possible complications are development of catheter-related thrombosis and catheter-related infections. Infections can arise by several different mechanisms: infection of the exit site, followed by migration of the pathogen along the external catheter surface; contamination of the catheter hub, leading to intraluminal catheter colonization; and hematogenous seeding of the catheter.

Other rarely described adverse events were cardiac tamponade, arrythmias caused by irritation from the guidewire or losing the guidewire into the vein, and major venous air embolism through the catheter itself.

Apheresis procedure

The acute effects of apheresis donation are mainly relatively mild and easily treatable. The most common are ion imbalancies; other reactions are uncommon or rare (hypotension, allergic reactions, etc). To prevent coagulation and clumping of the blood during apheresis procedure, an anticoagulant, usually citrate, is needed. Despite compensatory mechanisms of the body, citrate infusion can decrease ionized calcium levels also in blood vessels, not only in the apheresis set. Consequently, symptoms of hypocalcemia can develop (e.g. perioral paresthesias and acral paresthesias, shivering, light-headedness, twitching, tremors). Some patients experience nausea and vomiting. As the ionized calcium levels fall further, these symptoms may progress to carpopedal spasm, tetany, and seizure. Other reported complications asociated with citrate administration are hypotension, prolongation of the QT interval on electrocardiogram and fatal arrhythmia. Magnesium, as a divalent cation, is also bound by citrat. Its levels fall more rapidly with a more prolonged recovery. Symptoms of hypomagnesemia are similar to those of hypocalcemia. The citrate consumes also hydrogen ions and can result in a higher donors´ blood pH. However, significant metabolic alkalosis does not occur as donors should have normal renal function and do not recieve large amounts of citrate. Furthermore, the rise in blood pH results in a shift of hydrogen ions from intracellular locations and a concurrent flux of potassium into these cells, causing hypokaliemia.

The mechanism of hypotension development during apheresis procedure may be combined and multifactorial, resulting from the intravascular volume depletion, vasovagal reactions, citrate reactions, severe allergic reactions and air embolism. Regarding allergic reactions in granulocyte donors, there are two possible patterns of their generation. Rarely, reactions to ethylene oxide, which is used to sterilize the disposable sets, can develop in donors who have donated by apheresis numerous times. Another possible mechanism is activation of the alternative complement cascade by HES resulting in mild urticarial reactions, but also possible severe reactions with respiratory and cardiac arrest. Therefore, people with a history of any allergies should be excluded from granulocyte donations.

The risk of bleeding during and after granulocyte donation is due to various factors. Typically, after each granulocyte donation, there is a drop in hematocrit of 7 % and a fall in platelet count of 22 % due to the loss of platelets and red blood cells to the product, and secondly, due to the dilution and volume expansion caused by the HES. The use of HES is also associated with a risk of coagulopathy, especially when high molecular weight HES is used and when multiple collections are necessary over consecutive days.

Except of allergic reactions and coagulopathy as mentioned before, HES as a plasma expander, can cause also transient hypertension with flushing and headache.

A very rare complication of apheresis procedure can be air embolism, when more than 3 to 8 mL/kg of air enters the venous system through either a leak in the hemapheresis instrument or the venous access. Thanks to sensors for air detection in all modern hemapheresis instruments, the procedure is stopped before this could happen.

About long-term effects of apheresis donation, there are not enough data and further research is needed. Recent evidence suggests, however, that it may cause bone demineralization and cataract formation.

Recipient-associated side effects

In general, G-CSF-primed GT are tolerated relatively well. Adverse reactions are seen in 6~13 % of transfusions. The most frequent reactions as fevers and chills are preventable by antipyretics or corticosteroids, but routine prophylaxis with these agents is controversial. More severe reactions, including hypotension, pulmonary infiltrates and respiratory distress, may occur in approximately 1–5 % of transfusions (73). Although an association between pulmonary infiltration and Amphotericin B administration has not been confirmed, it is preferred to separate the administration times. From other complications, CMV infection, graft-versus-host disease, alloimmunization and platelet refractoriness can develop. After irradiation of the granulocyte products, the risk of graft-versus-host disease has become insignificant. The incidence of leukocyte alloimmunization has been reported to be 24 % (74).

Conclusion

It became possible to collect large numbers of neutrophils by modern leukapheresis techniques from G-CSF and glucocorticoids stimulated donors. GT deserve to be considered a potential life

saving treatment for patients with neutropenic infections, which do not respond quickly and completely to antibiotics alone, balancing possible benefits, risks and expenses. Prophylactic GT are likely to be useful in the setting of hematopoietic stem cell transplantation.

Because the right timing of GT is of high importance for the clinical outcome, once the decision has been made to provide either therapeutic or prophylactic GT, organisation of the whole process should be perfect, with regard to the safety of both donors and patients.

It is important to avoid problems in communication and logistics, to harmonize the recruitment of donors, their examining, beginning of donors stimulation, collection of PMNs, processing of GT, etc. Therefore, institutional guidelines should be elaborated and a register of granulocyte donors should be established to obtain long-term follow up and to reveal potential long-term adverse effects of the donation.

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Received March 16, 2011.
Accepted January 9, 2012.