Infectious Disorders

Clinical efficacy and prediction of response to granulocyte transfusion therapy for patients with neutropenia-related infections

We investigated the efficacy of transfusing granulocytes into 32 patients with severe neutropenia-related infections and the factors that predict response to this therapy. Our findings suggest that granulocyte transfusion therapy is useful for treating neutropenic patients with fungal infections and that ^{99m}Tc-HMPAO-granulocyte scintigraphy can be used to predict response to granulocyte transfusion therapy.

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Neutropenia-related infection is the main causes of morbidity and mortality in patients with hematologic malignancy.[1,2] Granulocyte transfusion therapy is used to treat neutropenic patients with severe infections which do not respond to appropriate antimicrobial agents.[3-5] However, it is necessary to establish the optimal doses and administration schedule of the mobilizing agent.[6-8] There are currently no clinical parameters known to predict the response to granulocyte transfusion.[9]

This prospective study was designed to investigate the safety and efficacy of granulocyte transfusion therapy in 32 patients with severe neutropenia-related infections and the factors that predict response to the therapy. ABO-compatible healthy donors were injected subcutaneously with 5 μg/kg of granulocyte colony-stimulating factor (G-CSF) 12-14 h before the leukapheresis procedure, and then injected intravenously with 3 mg/m^2 dexamethasone 15 min before leukapheresis.

Granulocyte transfusions were given at least daily until: (i) the infection improved; (ii) the blood neutrophil level in the recipient increased to > 500/μL; (iii) the donor became unavailable; (iv) the infection worsened after the administration of appropriate quantities of granulocytes; or (v) severe complications arose due to the transfusion. Responses to therapy were defined as follows: (i) *improvement*, when the clinical signs and symptoms of infection, including pyrogenic changes and radiation findings, improved, or when the bacterial culture tests were negative; (ii) *no change*, when the severity of infection was unchanged after the therapy; and (iii) *aggravation*, when the patient's symptoms and signs worsened as a result of the therapy. Patients who showed *improvement* were assigned to the *responsive group*, and those who showed *no change* or *aggravation* were assigned to the *non-responsive group*.

Four patients underwent ^{99m}Tc-HMPAO planar imaging, with 500,000 counts acquired at 1 h (early image) and 4 h (delayed image) after intravenous injection with 740 MBq (20 mCi) of ^{99m}Tc-HMPAO-labeled granulocytes just before transfusion into the patients. For the semi-quantitative assessment, the lesion-to-normal lung ratios (L/N) were calculated from the geometric mean counts of the anterior and posterior images, obtained 1 h and 4 h after infusion of the ^{99m}Tc-HMPAO-labeled granulocytes.

Leukapheresis was performed 120 times in 100 healthy normal donors, giving a mean yield of 8.2×10^{10} (range: 2.1-17.9×10^{10}) granulocytes. Some donors showed mild adverse effects, such as myalgia and bone pain (15%), headache (12%), and rash (1%), after receiving G-CSF. Most studies involve oral administration of dexamethasone, in conjunction with subcutaneous injection of G-CSF, approximately 12 h before leukapheresis, and 30% of the donors develop insomnia linked to the dexamethasone.[10] Although we gave dexamethasone intravenously, 15 min prior to granulocyte collection, we did not observe any cases of insomnia.

Table 1. Influence of different variables on the response to granulocyte transfusion therapy (GTX).

Variable	*Patients with response (n=19)*	*Patients with no response (n=13)*	*p value*
Mean age (range)	38 (15-62)	36 (16-57)	0.923
Median duration before GTX			
Neutropenia, days (range)	22 (9-50)	13 (7-44)	0.233
Antimicrobial agent, days (range)	16 (6-30)	15 (7-36)	0.744
G-CSF/GM-CSF, days (range)	10 (1-32)	12 (7-22)	0.631
N. of organisms isolated (%)			
Fungi	12 (80.0)	3 (20.0)	0.026
Gram-negative bacilli	12 (66.7)	6 (33.3)	0.341
Gram-positive cocci	6 (50.0)	6 (50.0)	0.403
GTX			
Mean n./patient (range)	3.8 (1-8)	3.8 (1-11)	0.571
Mean dose, ×10^{10} (range)	7.6 (2.1-15.5)	9.2 (3.5-17.9)	0.043
Mean ANC/μL (range)			
Before GTX	267 (0-2,190)	211 (0-700)	0.537
1 h after GTX	714 (0-3,920)	305 (0-1,148)	0.053
24 h after GTX	633 (0-4,550)	349 (0-1,400)	0.680

Nineteen patients (59.4%) responded to the granulocyte transfusion therapy, while 13 (40.6%) did not. The 13 non-responders included 12 patients (37.5%) with *no change* and 1 patient (3.1%) with *aggravation*. There were no significant differences between *responsive* and *non-responsive* groups in terms of age, neutropenic period before granulocyte transfusion therapy, period of administration of growth factors and antimicrobial agents, frequency of granulocyte transfusion therapy or dosage of granulocytes, or neutrophil counts at 1 h and 24 h after therapy. Favorable responses were seen in 80.0%, 66.7%, and 50.0% of the patients who were infected with fungi, Gram-negative and Gram-positive bacteria, respectively (p = 0.03; p= 0.34, p = 0.40) (Table 1). Adverse reactions due to the granulocyte transfusion therapy were two cases (6.2%) of arrhythmia and one case (3.1%) of pulmonary edema. There were no cases of mortality directly associated with the granulocyte transfusion therapy itself.

Granulocyte scintigraphy of the two patients with favorable responses showed abnormal granulocyte uptake in early imaging, as assessed by high L/N ratios (2.37 and 2.25), and persistent retention in delayed imaging (L/N ratios of 1.65 and 1.51, respectively). Granulocyte scintiscans of two patients who were non-responders did not show any granulocyte

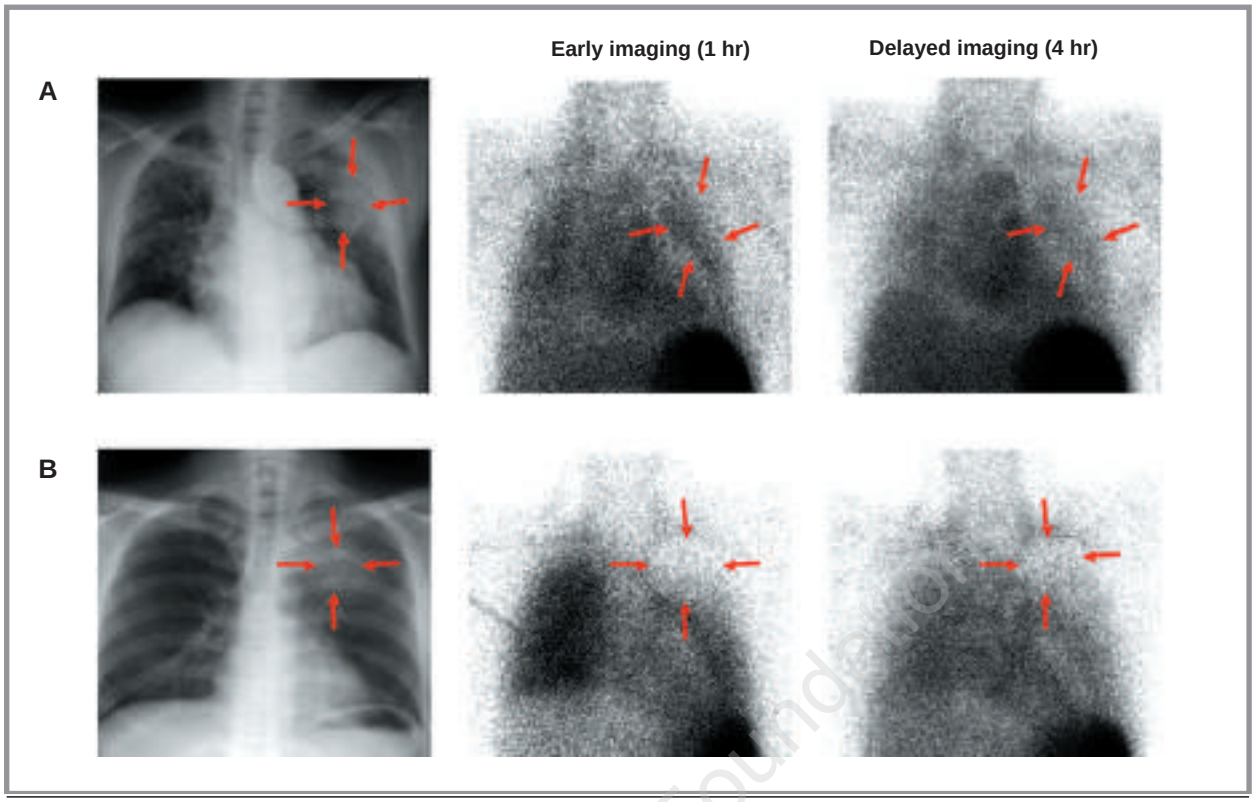

Figure 1. Granulocyte scintigraphy using ^{99m}Tc-HMPAO in patients with neutropenia-related pneumonia. (A) Patient with a favorable response to transfusing granulocytes: increased uptake in the early image which persisted in the delayed image. (B) Patient with no response: no uptake in either the early or delayed image of the lesion.

uptake into the infiltrative lung lesions, either in early (L/N ratios of 0.64 and 0.70) or delayed imaging (L/N ratios of 0.82 and 0.52) (Figure 1).

In conclusion, this study shows that the combination of G-CSF and dexamethasone is effective in mobilizing the granulocytes of normal healthy donors for use in granulocyte transfusion therapy, and that, although furher data are needed from controlled trials, granulocyte transfusions seem to be a useful adjuvant therapy for neutropenic patients with refractory fungal infections. In addition, ^{99m}Tc-HMPAO-granulocyte scintigraphy, which is used to measure granulocyte uptake at the focus of an infection, may be useful in predicting response to granulocyte transfusion therapy.

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Key words: granulocyte transfusion, neutropenia, infection, ^{99m}Tc-HMPAO-granulocyte scintigraphy.

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