A acute onset of idiopathic very severe aplastic anemia (vSAA, neutrophils <0.2×10^9/L) in a young patient may require urgent transplantation. Invasive aspergillosis is a life-threatening complication in aplastic patients, because antifungal treatment is ineffective in the absence of neutrophils and the presence of the infection is a serious obstacle to transplant procedures. We were able to perform a successful transplant in a young man suffering from vSAA who presented with disseminated pulmonary aspergillosis by treating the mycotic infection with amphotericin B and transfusions of granulocytes that had been harvested from G-CSF-stimulated donors.

**Case Report**

R. V., a 19-year-old male, was in excellent clinical condition in February 1995 when he was called up for military service. About two weeks later, without any apparent cause, he became pale and asthenic and developed high grade fever. Admitted to a local hospital, he was found to be suffering from severe pancytopenia and bilateral pneumonia and he was transferred to our unit on February 24, 1995. A diagnosis of idiopathic vSAA (neutrophils <0.2×10^9/L, platelets 3×10^9/L, desert bone marrow) was made, with documentation by CT scan and microbiology of rhinosinusitis and bilateral pneumonia due to Aspergillus fumigatus (Figure 1a).

Since the patient had an HLA-identical brother, an urgent bone marrow transplant was planned. In the meantime we treated his life-threatening invasive mycosis by combining amphotericin B (Fungizone, Squibb, 1.5 mg/kg/d from March 7, total dose 3.5 g) with granulocyte transfusions given every other day before and after transplant. Conditioning (cyclophosphamide 50 mg/kg/d for 4 days) was started on day 20 from the onset of symptoms (day 14 from diagnosis). Bone marrow cells given: 3.63×10^8/kg. GvHD prophylaxis consisted of cyclosporin A 3 mg/kg/d from days -1 to +20 iv, then 10 mg/kg/d orally for one year. The patient also received GM-CSF (Molgramostim, Schering-Plough, 300 mg/d from days +1 to +30) and G-CSF (Filgrastim, Amgen, 300 mg/d from days +9 to +30), itraconazole (400 mg/d from day +27), acyclovir (from days -7 to +30), polyspecific (30 g twice weekly) and anti-CMV (100 mL, twice weekly) IgG. Time to neutrophil (>0.5×10^9/L) and Platelet (>25×10^9/L) was verified at +16 and +40 days, respectively. The patient is currently in complete hematological and microbiological remission 14 months after transplantation. Granulocyte apheresis from G-CSF stimulated donors provides a high number of activated neutrophils. At the dose given (300 µg/day) donor tolerance to G-CSF was excellent. This new approach is indicated when life-threatening infections develop in patients exposed to prolonged severe neutropenia.

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platelet (>25 x 10^9/L) recovery was +16 and +40 days, respectively. Microbiology became negative within two weeks. At day +46 a repeat amphotericin B course (100 mg every other day, total 3 g) was required because of a recurrence of fever and the presence of aspergillus in the sputum. No signs of acute or chronic graft versus host disease appeared during the post-transplant period. In October 1996, 19 months after transplantation, the patient is in complete hematological and microbiological remission (Figure 1b).

Granulocyte apheresis from G-CSF-stimulated donors

Nine granulocyte concentrates obtained from three donors were infused over two weeks. Aphereses were performed with relatives of the patient (including the bone marrow donor) who shared the same blood group; the patient and the donors were all positive for anti-CMV IgG. In order to avoid presensitization against donor antigens, the bone marrow donor was utilized as a granulocyte donor only after transplantation. After giving informed consent, each donor received 300 µg of r-metHuG-CSF (Filgrastim, Amgen) once a day for 5 days. Their circulating neutrophils immediately peaked between 30 and 40 x 10^9/L; moderate bone pain was the only complaint. Apheresis procedures were performed every other day and were well tolerated. Mean bag content was 18.7 x 10^9 neutrophils. Each bag was irradiated before infusion.

Comment

Aspergillosis is usually a late complication of AA, often triggered by immunosuppressive treatments; in our patient invasive aspergillosis was diagnosed simultaneously with vSAA before any treatment was given. An aplastic patient with invasive aspergillosis is the worst possible candidate for a bone marrow transplant. A recent review reports that only 10% of aplastic patients with invasive aspergillosis respond to standard anti-fungal treatment. Transfusion of granulocytes to prevent or treat infection in neutropenic patients was studied in the 70's. Reduction of bacterial infections and mortality were described, but harvest yield was low and concern was raised about the possibility of pulmonary damage. Nowadays, the availability of colony-stimulating factors has increased the neutrophil yield up to six times, without significant side-effects in the donor; neutrophil function in the harvest is fully retained or even increased. This has triggered new interest in granulocyte transfusion.

The favorable outcome in our patient suggests that granulocyte transfusion should be included in the treatment strategy for such patients. Lung sequestration is a well-known phenomenon after granulocyte infusion, which in this case may have favored the resolution of the pneumonia. Also, it is possible that neutrophil activation by growth factors played some role in the antymycotic defense.

References