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GRANULOCYTE COLONY-STIMULATING FACTOR-PRIMED LEUKOCYTE TRANSFUSIONS IN CANDIDA TROPICALIS FUNGEMIA IN NEUTROPENIC PATIENTS

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ABSTRACT

Optimal management of fungemia in neutropenic patients is still controversial. Several reports have already stressed the poor prognosis in invasive candidiasis (80% mortality in several reports). Therefore granulocyte transfusions would appear to be useful in the management of these infections. We report the use of rhG-CSF-primed granulocyte transfusions plus amphotericin B in two neutropenic patients who developed life-threatening systemic fungal infections. This approach was successful and both patients fully recovered from the infection.

Key words: granulocyte transfusions, G-CSF, fungal sepsis

Fungemia remains an important cause of morbidity and mortality during severe and prolonged neutropenia in hematological neoplasias, with Candida species accounting for 98% of this infection (i.e. *Candida tropicalis* and *Candida kruzei*).[1] Risk factors that have been identified include the use of central venous catheters (CVC), steroids, combination antibiotics, parenteral nutrition and a previous history of fungal infections.[2,3] Often the prognosis is also severe when combined therapy has been administered.[1]

Recently, the use of granulocyte transfusions has been revisited,[4] particularly after the introduction of rhG-CSF in healthy donors.[5] Overwhelming fungemia in neutropenic patients appears to be one of the elective indications for this treatment.

We describe two cases of *Candida tropicalis* sepsis in patients who developed prolonged neutropenia after chemotherapy and who received amphotericin B and transfusions of irradiated sibling-derived leukocytes after G-CSF stimulus.

Patients and Methods

Case #1

A 39-year-old AML patient was administered consolidation therapy (cytosine arabinoside and mitoxantrone) through a CVC inserted in the subclavian vein. Six days after the end of chemotherapy the patient became febrile (38°C) and empiric antimicrobial therapy was started (ceftazidime, amikacin and vancomycin); ANC was $< 0.1\times10^9$/L. The fever persisted and empiric amphotericin B was started. Violaceous erythematous pustules appeared on the patient's neck and face and rapidly spread over the whole body surface. Due to poor compliance the patient was shifted to a liposomal amphotericin B formulation. In view of persisting neutropenia and the patient's rapidly deteriorating clinical condition, rhG-CSF 5 µg/kg/day was started. Blood cultures from peripheral blood and the CVC documented *Candida tropicalis* fungemia (8 specimens from two consecutive days). *Candida tropicalis* was also isolated from skin lesion, stool and CVC cultures. The patient received transfusions of irradiated (15 Gy) leukocytes obtained from an HLA-identical brother who was submitted to rhG-CSF 16 µg/kg/day for 5 days and leukapheretic procedures after giving informed consent. A mean daily dose of 12.4×10^9 PMN was transfused ten days after the introduction of antifungal treatment (amphotericin B delivered at that time: 670 mg, 350 mg of liposomal formulation). The general status of the patient started to improve and fever disappeared four days after the last leukocyte transfusion. The total dose of amphotericin B administered was 2870 mg. A stable ANC $> 0.5\times10^9$ was reached 28 days after the end of chemotherapy. The patient is currently alive in CR 12 months after the infection.

Case #2

A 43-year-old patient affected by Waldenström's macroglobulinemia received cyclophosphamide 7 g/sm followed by rhG-CSF 5 µg/kg/day for hematopoietic progenitor collection. During the aplastic phase (PMN $< 0.1\times10^9$/L) he developed fever and received broad-spectrum antibiotics (ceftazidime and amikacin). Three days later, due to persisting fever, amphotericin B was empirically started. Violaceous erythematosus skin lesions developed. *Candida tropicalis* was isolated from peripheral blood cultures for two consecutive days. No other specimens were found to be positive for fungi. Liposomal amphotericin B (100 mg/daily) was added to the antifungal treatment, but the clinical condition of the patient deteriorated. After giving informed consent, two haploidentical brothers received rhG-CSF 10 µg/kg/day and were submitted to a total of five leukapheretic procedures to collect granulocytes (a total of 51.2×10^9 neutrophils). The irradiated (15 Gy) buffy-coats were transfused to the patient seven days after amphotericin B was started. Fever persisted three days after the last transfusion but *Candida tropicalis* was no longer isolated from peripheral blood cultures. The total amphotericin B dose delivered was 2750 mg. The patient recovered PMNs $> 0.5\times10^9$/L 37 days after the end of chemotherapy (Figure 1) and is currently alive and well without signs of chronic candidiasis, despite persistent immunosuppression, 10 months after the infectious episode.

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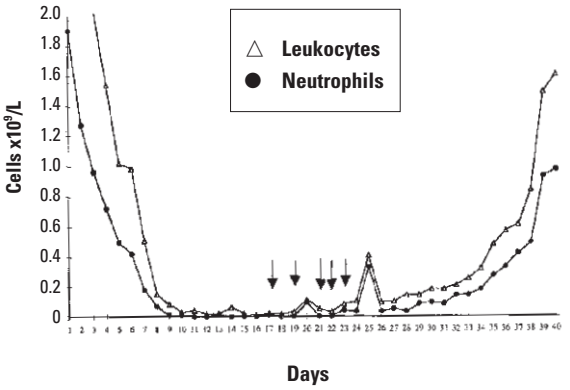

Figure 1. Hemopoietic recovery in case #2. Arrows indicate granulocyte transfusions.

Discussion

The employment of granulocyte transfusions in neutropenic patients receiving chemotherapy has been a controversial issue.

Strauss in 1993[6] analyzed thirty papers reporting the use of granulocyte transfusions plus antibiotics in severely neutropenic patients. He pointed out that the studies were highly variable with regard to diagnoses, types of infection, antimicrobial agents used, quantity of PMN and number of transfusions given. Combining data demonstrated that the efficacy of this approach was mainly limited to bacterial septicemia.

Because one of the major factors that diminishes the efficacy of granulocyte transfusions in treating infections in neutropenic patients has been the low number of PMNs available in granulocyte concentrates, the safe administration of rhG-CSF to normal blood donors[7] justifies a reassessment of the utility of this approach.

In 1994 and 1995, two reports evaluated the efficacy of granulocyte transfusions in neutropenic patients.[4,5] The use of rhG-CSF-primed leukocyte transfusions was undertaken at M.D. Anderson Cancer Center[5] in fifteen patients with prolonged neutropenia and established fungal infections (8 systemic) that showed inadequate improvement with antifungal therapy. After a median of six transfusions, nine patients demonstrated an objective response to transfusions and a shortening of neutropenia compared to nonresponding patients.

Grigg *et al*.[9] reported 4 cases of G-CSF-stimulated granulocyte collections in neutropenic patients with sepsis. The transfusions produced an increase in circulating granulocyte numbers in 3 of the 4 patients treated and an improvement in the infection in 1 case.

Our patients, both severely neutropenic ($< 0.1\times10^9$/L) and not expected to achieve bone marrow recovery within a week from documented fungal sepsis, showed signs and symptoms of life-threatening infection despite antimicrobial and correct antifungal therapy. Strict microbiological surveillance of the patients permitted rapid identification of the infective agent and the use of rhG-CSF and G-CSF-primed leukocytes improved host defenses, contributing to the resolution of sepsis and to the favorable outcome despite the persistence of severe neutropenia.

Furthermore, there is historical and current evidence in animal models and in humans that PMNs play a vital role in the control of fungal infections and that this role can be enhanced with G-CSF and/or interferons (IFN). Recently, Roilides *et al*.[10] showed *in vitro* evidence that incubation of PMNs from healthy volunteers with G-CSF and/or IFN enhanced antifungal activity in damaging *Candida* pseudohyphae, probably by modulating cellular membrane receptors. No hyphal damage has been documented by incubating G-CSF and/or IFN alone with hyphae. *Candida tropicalis* appeared to be the most susceptible species.

Our experience and historical data confirm and justify renewed interest in granulocyte transfusions as a therapeutic approach, in association with conventional antifungal drugs, for fungemia in severely neutropenic patients. Furthermore, the employment of rhG-CSF permits collection of adequate amounts of neutrophils that produce a significant post-trasfusional increment, thus enhacing their role in severely neutropenic patients with overwhelming fungal sepsis.

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