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 kruzie).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 (cefazidime, amikacin and vancomycin); ANC was < 0.1 x 10^9/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.

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 x 10^9/L) he developed fever and received broad-spectrum antibiotics (cefazidime and amikacin). Three days later, due to persisting fever, amphotericin B was empirically started. Violaceous erythematous 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 16 µg/kg/day and were submitted to a total of five leukapheresis procedures to collect granulocytes (a total of 51.2 x 10^9). 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 2870 mg. A stable ANC > 0.5 x 10^9/L was reached 28 days after the end of chemotherapy. The patient is currently alive in CR 12 months after the infection.

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Received November 29, 1996, accepted March 10, 1997.
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number of PMNs available in granulocyte concen-
trates, the safe administration of rhG-CSF to nor-
mal blood donors justifies a reassessment of the
utility of this approach.
In 1994 and 1995, two reports evaluated the
efficacy of granulocyte transfusions in neutropenic
patients. The use of rhG-CSF-primed leukocyte
transfusions was undertaken at M.D. Anderson Cancer Center in fifteen patients with prolonged
neutropenia and established fungal infections (8 systemic) that showed inadequate improvement
with antifungal therapy. After a median of six trans-
fusions, nine patients demonstrated an objective response to transfusions and a shortening of
neutropenia compared to nonresponding patients.
Grigg et al 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
(< 0.1x10^9/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 cor-
correct antifungal therapy. Strict microbiological sur-
veillance of the patients permitted rapid identifica-
tion 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 persis-
tence of severe neutropenia.
Furthermore, there is historical and current evi-
dence 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 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 con-
ventional antifungal drugs, for fungemia in severely
neutropenic patients. Furthermore, the employ-
ment of rhG-CSF permits collection of adequate
amounts of neutrophils that produce a significant
post-transfusional increment, thus enhancing their
role in severely neutropenic patients with over-
whelming fungal sepsis.

Discussion
The employment of granulocyte transfusions in
neutropenic patients receiving chemotherapy has
been a controversial issue.
Strauss in 1993 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 effi-
cacy of this approach was mainly limited to bacteri-
al septicemia.
Because one of the major factors that diminishes
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References
1. Meunier F, Aoun M, Bitar N. Candidemia in immunocompromised
2. Annaloro C, Onana A, Tagliaferri E, et al. Efficacy of differ-
ent fungal infections in neutropenic patients follow-
fusion of granulocyte concentrates from donors primed with granulocyte
stimulating factor and response of myelosuppressed patients with
efficacy in treating fungal infections in neutropenic patients follow-
5. Roilides E, Holmes A, Blake C, et al. Effects of granulocyte colony-
stimulating factor and interferon-y on antifungal activity of human
polymorphonuclear neutrophils against pseudohyphae of different