Effect of Recombinant Human Granulocyte Colony-Stimulating Factor (G-CSF) in the Treatment of Pseudomonas aeruginosa Bacteremia Complicating Hematologic Malignancy
—A Preliminary Study—

Hisashi FUNADA, Toshihiko MACHI, Shigeki OHTAKE, Takashi YOSHIDA and Tamotsu MATSUDA
The Protected Environment Unit and Third Department of Medicine, Kanazawa University
School of Medicine, Kanazawa 920, Japan
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Abstract

The efficacy of recombinant human granulocyte colony-stimulating factor (G-CSF) in the treatment of Pseudomonas aeruginosa bacteremia in cancer patients receiving intensive chemotherapy was studied retrospectively. In 14 of the 24 episodes of P. aeruginosa bacteremia, which occurred in 23 severely neutropenic patients with hematologic malignancies during a three-year period, G-CSF was given subcutaneously or intravenously at daily doses of 75 μg/body to 200 μg/m² of body surface. Overall, survival at one week after onset was observed in 13 patients (54%). Treatment with G-CSF, however, had no statistically significant association with one-week survival, although a favorable outcome was well correlated with an increase in the neutrophil count during therapy. On the other hand, septic shock and appropriate antibiotic therapy were the major prognostic factors. The frequency of shock was reduced by appropriate therapy, but not by G-CSF treatment. These preliminary findings thus suggested that G-CSF should not be effective in the treatment of neutropenic cancer patients with P. aeruginosa bacteremia. No adverse effects of G-CSF were observed.

Introduction

Patients with leukemia and lymphoma are at especially increased risk of developing Pseudomonas aeruginosa bacteremia during intensive induction chemotherapy. The outcome of serious infection in patients with neutropenia is usually ominous in the absence of both early diagnosis and increase in the neutrophil count during therapy. Recombinant human granulocyte colony-stimulating factor (G-CSF) has been shown to accelerate neutrophil recovery after myelosuppressive therapy, with the presence of functional cells. We report herein our preliminary experience with recombinant human G-CSF treatment in neutropenic cancer patients with P. aeruginosa bacteremia. This is a retrospective study.
Patients and Methods

Patients
During a three-year period ending in 1990, 24 episodes of *P. aeruginosa* bacteremia occurred in 23 patients with hematologic disorders (14 with lymphocytic malignancies and nine with myelogenous leukemias). Fourteen patients were male and nine female, with an age distribution of 16 to 72 years (median, 60 years). For ease of presentation, the terms episodes and patients will be used interchangeably.

Treatment with G-CSF

The recombinant human G-CSF (KRN 8601, provided by Kirin Brewery Co., Tokyo) was administered subcutaneously or intravenously at a daily dose of 75 μg/body in order to shorten the period of chemotherapy-induced neutropenia. The intravenous G-CSF in 100 ml of 5% dextrose in water or physiological saline solution was infused over a period of 30 minutes once daily. In patients with lymphocytic malignancies, the first course of intensive chemotherapy without G-CSF was followed by subsequent ones with G-CSF. The G-CSF was stopped when the neutrophil count exceeded 5000–10000/μl. Higher daily doses up to 200 μg/m² of body surface were given to some patients with highly refractory disease or those undergoing bone marrow transplantation. The use of G-CSF in bacteremic patients with myelogenous leukemias was left largely to the physicians’ discretion, because of the known in vitro stimulation of leukemic clones. Informed consent was obtained from the patients or family members.

Antipseudomonal antibiotic therapy

Therapy was considered appropriate when an aminoglycoside and at least one β-lactam antibiotic in combination, to which the *P. aeruginosa* isolate was sensitive by standardized in vitro disk susceptibility testing, were given intravenously at adequate doses, as defined by the criteria described elsewhere, and were started within 36 hours after the onset of bacteremia. The antibiotics used were essentially unchanged throughout the study period.

Bacteremia

The diagnosis of bacteremia was based on at least one positive blood culture and on clinical manifestations that could be produced by the circulating organisms. Blood cultures were carried out as described elsewhere. The onset of bacteremia was defined as the time the first blood cultures were obtained.

Septic shock

In accordance with Weinstein et al., septic shock was defined as the presence of hypotension in association with a decrease of systolic blood pressure, low urine output and/or requirement for vasopressors.

Statistics

Frequency comparisons were analyzed statistically by Fisher’s exact test.

Results

Neutrophil count at onset

The neutrophil count at onset ranged from 0 to 740/μl (median, 0/μl). Only three patients had an initial neutrophil count of more than 100/μl. All the patients, including one who underwent bone marrow transplantation, received intensive chemotherapy within two weeks prior to the onset.

Overall outcome

Duration of survival is shown in Fig. 1. Thirteen episodes (54%) with survival at one week were clearly distinguishable from the remaining 11 episodes (46%) with early death.

Thirteen of the 14 patients whose neutrophil counts increased by more than 100/μl during therapy...
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Fig. 1 Outcome of *P. aeruginosa* bacteremia in patients with hematologic malignancy in terms of duration of survival.


survived at one week. Among the group with one-week survival, all but two patients had an initial neutrophil count of less than 100/µl.

Prognostic factors

Septic shock occurred in nine patients (38%), all of whom died within one week of the onset (none of the 13 with one-week survival versus nine of the 11 with early death; \( p < 0.001 \)). On the other hand, 15 patients (63%) received appropriate antibiotic therapy, with early death in three (12 of those with one-week survival versus three of those with early death; \( p < 0.01 \)). When the relation between the two prognostic factors was considered, only one of the nine with shock received appropriate therapy, compared with 14 of the 15 without shock (\( p < 0.001 \)).

Effect of G-CSF treatment

Fourteen patients (58%) received G-CSF treatment. In six of them, the G-CSF was begun prior to the onset. The duration of G-CSF administration ranged from two to 26 days (median, nine days). The groups receiving and not receiving G-CSF were similar with respect to age, sex and underlying disorder. Duration of survival, however, had no significant correlation with G-CSF treatment (nine of the 13 with one-week survival versus five of the 11 with early death; 0.40 < \( p < 0.50 \)). Moreover, one-week survival did not seem to depend on the timing of G-CSF initiation.

The frequency of septic shock was not significantly reduced by G-CSF treatment (four of the 14 with G-CSF versus five of the 10 without G-CSF; 0.40 < \( p < 0.50 \)). Shock was not associated with the timing of G-CSF treatment.

Among the group receiving G-CSF treatment, shock occurred in only one of the 11 patients who received appropriate therapy and in all of the three who did not, with a statistically significant difference found (\( p < 0.05 \)).

Adverse effects of G-CSF

In the group receiving G-CSF treatment, there was no evidence that the growth factor stimulated the proliferation of leukemic blast cells. No other findings ascribable to G-CSF administration were observed.
Discussion

Neutropenic patients with *P. aeruginosa* bacteremia continue to have a poor prognosis. The introduction of G-CSF did not prolong survival in this series. Septic shock and appropriate antibiotic therapy were the major prognostic factors which conflicted with each other. The frequency of shock was significantly reduced by the early institution of appropriate therapy, as confirmed by Kreger et al., but not by the administration of G-CSF.

Most cases of shock occur within the first four to 10 hours after the onset of gram-negative bacteremia. On the other hand, G-CSF usually requires at least several days to restore adequate neutrophils from the chemotherapy-induced nadir, although its use has been shown to significantly shorten the period of neutropenia. In this regard, G-CSF is in most cases considered unreliable for prevention and treatment of septic shock. Indeed, as reported by Bodey et al., the present as well as previous series revealed that those patients with neutropenia, irrespective of their initial neutrophil counts, whose bone marrow function eventually recovered from the myelosuppressive effects of chemotherapy benefited from appropriate antipseudomonal therapy. The therapeutic effect of G-CSF is therefore considered to be produced while receiving appropriate antibiotics. This is also suggested by a recent case report of “breakthrough” bacteremia due to *P. aeruginosa* during the treatment of a patient with acute leukemia, which was successfully treated with the short-term addition of G-CSF to appropriate antibiotics.

The administration of G-CSF has recently been reported to significantly reduce the incidence of infectious complications by accelerating recovery from chemotherapy-induced neutropenia. Considering the difficulty in treating *P. aeruginosa* bacteremia, therefore, the prophylactic use of G-CSF seems to be of greater significance than its therapeutic application.

At any rate, this preliminary study indicates the need for a prospective, controlled study to investigate the usefulness of G-CSF in the treatment of *P. aeruginosa* bacteremia.

Side effects of G-CSF were not observed in this series. There is, however, some concern that treatment with G-CSF may result in an increase in leukemic blast cells in the bone marrow of patients with myelodysplastic syndrome or acute myelogenous leukemia, although no obvious evidence for this has yet been reported.

References