Outcomes of Granulocyte Colony-Stimulating Factor or Granulocyte-Macrophage Colony-Stimulating Factor Use in Neutropenic Patients Infected with Human Immunodeficiency Virus

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ABSTRACT

Objective: To characterize the effects of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) on clinical outcomes in neutropenic HIV-infected patients, by means of a retrospective cohort study at an urban teaching hospital.

Method: Data were reviewed from all patients discharged between January 1, 1996, and August 31, 1997, with human immunodeficiency virus and neutropenia (absolute neutrophil count (ANC) <1000 cells/μL), with outcome measures of length of stay, infectious complications, and survival to discharge.

Results: Of the 228 discharged patients who met selection criteria, 71 had received G-CSF or GM-CSF; 157 controls had not. Cases had lower CD4+ cell counts (30 vs. 54 cells/μL; $P = 0.017$) and lower nadir ANCs (372 vs. 579 cells/μL; $P < 0.001$). Granulocyte-CSF or GM-CSF usage was not associated with the frequency of site-related infections, fever, or sepsis (all $P > 0.20$). No difference was found in duration of hospitalization (23 vs. 21 days; $P > 0.20$). In a logistic regression model for survival to discharge, higher nadir ANC and CSF use were independently associated with improved survival ($P = 0.034$ and $P = 0.026$, respectively).

Conclusion: Use of G-CSF or GM-CSF was associated with improved survival to discharge among hospitalized HIV-infected patients with neutropenia.

Key Words: *granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor, HIV, neutropenia*

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Neutropenia frequently complicates human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), with up to a 40% prevalence of low absolute neutrophil counts (ANCs) reported.[1] Causes of HIV-related neutropenia include myelophthisic processes, HIV-induced autoimmune abnormalities, chemotherapy against HIV-related malignancies, and use of antimicrobials against HIV and opportunistic infections. Whereas neutropenia is a risk factor for bacterial infection in cancer patients,[2,3] the risk contribution of neutropenia for infectious complications in HIV has been unclear.[4–9]

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used to lessen the severity and duration of neutropenia due to chemotherapy.[10] These agents have not been shown to reduce mortality or hospital stay in patients with febrile neutropenia,[11–15] and are not routinely recommended in chemotherapy-related febrile neutropenia, according to the guidelines of American Society of Clinical Oncology.[16,17] Their use in HIV disease is less well-studied. Granulocyte-CSF and GM-CSF (CSFs) have been shown to be safe and effective as adjuncts, allowing full-dose administration of ganciclovir.[18–20] Recently, reports have found G-CSF, when used in an oupatient setting to keep the ANC over 500 cells/μL, reduces the frequency of bacteremia in HIV-infected individuals and improves survival.[21,22]

To determine whether CSF use affects clinical outcomes among hospitalized, neutropenic HIV-infected patients, the authors conducted a retrospective review of inpatients with HIV and neutropenia at an urban teaching hospital in New York. The primary aims were to quantify the effects of CSFs on survival to discharge, length of stay, and frequency of infectious episodes.

MATERIAL AND METHODS

Study Characteristics and Patients

This was a retrospective cohort study of HIV-seropositive inpatients at the Beth Israel Medical Center in New York, an 800-bed urban university teaching hospital and

tertiary care center. Selection criteria included a diagnosis of HIV and an ANC of less than 1000 cells/μL during hospital course. Patient confidentiality was preserved by assigning study-specific identifiers and using only these identifiers in the study's database. Eligible patients were identified from the hospital database of all discharge diagnoses. International Classification of Diseases (ICD, 9th Revision, Department of Health and Human Services, US Government Printing Office, Washington, DC, 1997) codes used were those for agranulocytosis, neutropenia, and pancytopenia (288.0 and 284.8) and any AIDS-related diagnosis code (including 042 and V08 for AIDS and HIV, as well as codes for any AIDS-defining opportunistic infections), for the period from January 1, 1996, to August 31, 1997. The occurrence of an ANC less than 1000 cells/μL was confirmed by review of laboratory data.

The records of all patients who met selection criteria were reviewed by one of the authors (BKA). Data on patient demographics, clinical history, and hospital course were collected on a standardized data collection instrument. Patient demographics recorded included date of birth, race or ethnicity, gender, age, history of injection drug use (IDU), admission and discharge dates, and date of neutropenia onset.

Clinical history abstracted included the most recent CD4+ cell count, myelosuppressive chemotherapy use within 1 month of neutropenia onset, presence of central venous catheter, use of myelosuppressive antimicrobial agents (trimethoprim-sulfamethoxazole, ganciclovir, zidovudine, amphotericin, pyrimethamine, sulfadiazine, and pentamidine) within 1 week of neutropenia onset, and documented *Mycobacterium avium* complex (MAC) or biopsy-documented bone marrow infiltration by tuberculosis, lymphoma, or histoplasmosis.

Records were reviewed to obtain information on nadir ANC, duration of neutropenia (at 3 strata of <1000 cells/μL, <500 cells/μL, and <200 cells/μL), the number of neutropenic episodes, and the development of infectious complications during neutropenia. In all cases, complete blood counts (CBCs) were performed at least every other day while patients were neutropenic. A neutropenic episode was considered distinct if there were at least 7 non-neutropenic days between days of neutropenia.[23] Infectious complications included fever (defined as an oral or rectal temperature of >38°C), sepsis (defined as systolic blood pressure <90 mmHg, organ dysfunction, lactic acidosis, oliguria, or altered mental status in the setting of presumed infection), development of bacteremia or fungemia (defined as a recognized pathogen on blood cultures), and of site-related infections (e.g., endocarditis, pneumonia, meningitis, enterocolitis, cellulitis, intra-abdominal infections, catheter-related infections, and urinary tract infections). Infectious complications were required to meet the National Institute of Allergy and Infectious Diseases' clinical endpoint definitions.[24] Outcomes were survival to discharge and length of stay.

Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor Use

Standard doses of G-CSF and GM-CSF were 300 μg and 250 μg, respectively, given via subcutaneous injection. Colony-stimulating factor dosing was analyzed with respect to frequency (daily vs. 3 times/wk), duration of use, and days of neutropenia within each stratum prior to initiation of therapy. Delay in administration of G-CSF or GM-CSF was defined as 1 or more days of neutropenia prior to CSF initiation.

Statistical Analyses

Statistical analysis was performed with the Statistics Package for Social Sciences (SPSS for Windows™6.0.1, SPSS Inc., New York). Infectious complications and duration of neutropenia were analyzed by neutropenic episodes, and length of stay and survival to discharge were analyzed by admissions. Independent sample t-tests were used to compare continuous variables, and chi-square tests were used to compare noncontinuous variables. Logistic regression was used when two or more variables were associated with each other and a dichotomous variable. Pearson's and partial correlations were used to determine associations among continuous variables.

RESULTS

Population Derivation

Between January 1, 1996, and August 31, 1997, 640 admissions from 478 patients with discharge diagnoses of neutropenia and an AIDS-related disorder were identified. For 398 discharges, there was no documented ANC less than 1000 cells/μL. Among 168 patients, 242 admissions were found to meet study criteria. Fourteen admissions were excluded owing to incomplete records, leaving 228 evaluable admissions (among 163 patients). Of these, 71 admissions (cases) among 51 patients received CSFs (51 G-CSF; 20 GM-CSF) and 157 admissions (controls) among 112 patients did not.

Of the 228 admissions, 13 (representing 11 patients) involved more than one neutropenic episode per admission (33 episodes in these admissions). Six of these patients (total of 17 episodes) received CSFs in one or more episodes and did not in other episodes during the same admission. These six (of whom 3 died) were excluded from analyses of CSF effects on length of stay and survival analyses.

Baseline Characteristics

Cases had significantly more admissions than controls (1.7 vs. 1.3, P = 0.02). Baseline characteristics are shown in Table 1. Cases more frequently had a history of injection drug use (IDU), had received myelosuppressive

Table 1. Case Characteristics

	Cases Receiving CSF (n = 71)	*Controls (n = 157)*	*P**
Age (y) (mean ± SD)	39 ± 11	40 ± 9	
Sex (%)			
Male	50 (71)	114 (73)	
Female	21 (29)	43 (27)	
Race (%)			
White	19 (27)	27 (17)	
Black	24 (34)	64 (41)	
Hispanic	24 (34)	63 (40)	
Asian	3 (5)	3 (2)	
IDU history (%)	21 (31)	77 (51)	0.006
CD4+ (mean ± SD)	30 ± 58	54 ± 85	0.017
Nadir ANC (mean ± SD)	372 ± 227	579 ± 242	<0.001
Recent chemotherapy (%)	14 (20)	2 (1)	<0.001
Marrow infiltrative disorder (%)	35 (49)	58 (37)	
MAC	35	53	0.034
Histoplasmosis	0	2	
Tuberculosis	0	3	
Lymphoma	0	1	
Antimicrobial therapy (%)	59 (83)	129 (82)	
Cotrimaxozole	44	107	
Ganciclovir	27	22	<0.001
Zidovudine	19	47	
Pyrimethamine	7	6	
Sulfadiazine	5	6	
Intravenous pentamidine	4	6	
Intravenous amphotericin	5	14	
Other	3	8	
Central venous catheter (%)	30 (43)	35 (22)	0.002

*Only significant P-values (by chi-square analysis) are shown. IDU = injection drug use; ANC = absolute neutrophil count, MAC = *M. avium* complex.

chemotherapy within the previous month, had received ganciclovir within 1 week of neutropenia onset, had a central venous catheter, and had MAC infection. Patients undergoing chemotherapy had a lower nadir ANC (234 vs. 538 cells/μL; P < 0.001). No other significant relation among baseline characteristic was found (all P > 0.10).

Colony-Stimulating Factor Use

In 16 cases, CSFs were administered three times per week instead of daily. In 37 cases, CSF administration was delayed, with a median delay of 3 days. Patients who had a lower nadir ANC had longer delays in administration (P = 0.03). These differences in dosing regimens were not associated with any differences in baseline characteristics or outcomes. Colony-stimulating factors were continued until recovery from neutropenia, death, or discharge.

Factors Affecting Duration of Neutropenia

The severity of neutropenia (i.e., lower nadir ANC) was associated with the duration of neutropenia at each stratum (days below ANC of 1000 cells/μL, 500 cells/μL, 200 cells/μL; all P < 0.001). No other baseline characteristics were associated with duration of neutropenia at any stratum (all P > 0.1). Although there was a trend toward cases having a longer duration of neutropenia than controls (8 d vs. 6 d; P = 0.06), this did not persist when neutropenic episodes with delayed CSF administration were excluded (all P > 0.1).

Factors Affecting Infectious Complications

Table 2 shows the infectious complications in cases and controls. Cases more frequently developed fever, bacteremia, and sepsis. Cases had a higher rate of site-related infections due to more frequent catheter infections. After excluding those with delayed CSF administration (to exclude cases where infectious complications may have prompted CSF use) or catheter infections, there was no significant difference in rates of site-related infections (30% vs. 21%; P > 0.2), fever (49% vs. 48%; P > 0.9), or sepsis (30% vs. 19%; P = 0.13). However, cases still had a higher likelihood of bacteremia [odds ratio (OR) = 7.7; 95% confidence interval (CI) = 1.8-33.9; P = 0.002].

Mycobacterium avium complex infection was significantly associated with the development of bacteremia (OR = 4.0; 95% CI = 1.5-10.2; P = 0.002). The presence of a central venous catheter was significantly associated with the rate of bacteremia (OR = 5.9; 95% CI = 2.3-14.6; P < 0.001) and site-related infections (OR = 2.8; 95% CI =1.5-5.3; P = 0.001). The duration of neutropenia at any stratum, CD4+ cell count, and nadir ANC were not associated with the development of bacteremia or site-related infections (all P > 0.10).

Patients developing sepsis had longer neutropenic periods below an ANC of 500 cells/μL (3 vs. 2 d; P = 0.04), and a lower nadir ANC (398 vs. 550 cells/μL; P < 0.001). Patients undergoing chemotherapy more frequently developed sepsis [8/16 (50%) vs. 45/212 (21%);

Table 2. Infectious Complications

	Cases Receiving CSF (n = 71)	*Controls (n = 157)*	*P*
Fever (%)	46 (66)	76 (48)	0.016
Sepsis (%)	24 (34)	29 (19)	0.009
Blood-borne (%)	14 (20)	8 (5)	<0.001
Staphylococcus aureus	6	4	
Pseudomonas	3	1	
Enterobacter	0	1	
Enterococcus	2	4	
Klebsiella	2	2	
Staphylococcus epidermidis	2	0	
Fungus	1	1	
Site-Related Infections	24 (34)	33 (21)	0.033
Endocarditis	1	1	
Pneumonia	6	11	
Meningitis	1	3	
Enterocolitis	0	3	
Intra-abdominal infection	2	3	
Urinary tract infection	2	5	
Catheter-related infection	11	6	0.002
Skin/wound infection	3	3	
Pericarditis	0	1	
Pelvic inflammatory disease	0	1	

P = 0.004]. No other baseline characteristic was associated with any infectious complication (all P > 0.10).

Factors Affecting Length of Stay

For the study population, the median length of stay was 22 days. No significant difference existed between cases and controls (23 vs. 21 d; P = 0.38). Patients developing infectious complications had longer lengths of stay (25 vs. 20 d; P = 0.04). No baseline characteristics were associated with length of stay (all P > 0.10).

Factors Affecting Survival

There was no difference in overall survival to discharge between cases and controls [55/65 (85%) vs. 130/157 (83%); P > 0.7]. Among those with a nadir ANC of 251 to 500 cells/μL, cases had a higher rate of survival than controls [22/23 (96%) vs. 31/40 (78%); P = 0.03]. There was a trend toward improved survival among septic patients receiving CSFs [15/24 (63%) vs. 11/29 (38%); P = 0.075], whereas nonseptic patients had similar survival rates [cases: 42/45 (93%); controls: 121/128 (95%); P > 0.8]. Survival of septic patients with a nadir ANC of 251 to 500 cells/μL was significantly associated with CSF use [6/6 (100%) vs. 2/8 (25%); P = 0.005].

Patients surviving to discharge had lower rates of bacteremia [13/189 (7%) vs. 10/39 (26%); P < 0.001], site-related infection [39/189 (21%) vs. 18/39 (46%); P < 0.001], fever [94/189 (50%) vs. 28/39 (72%); P = 0.004], and sepsis [26/189 (14%) vs. 27/39 (69%); P < 0.001]. They had shorter lengths of stay (19 ± 13 vs. 35 ± 32, P = 0.002) and a higher nadir ANC (540 ± 251 vs. 403 ± 246; P = 0.003). Patients who survived had no significant differences from those who did not in duration of neutropenia at any stratum (all P > 0.10). No other baseline characteristic was associated with survival (all P > 0.10).

Multivariate Analyses

All variables having a univariate P-value of <0.10 with bacteremia, sepsis, and survival were tested for interactions in logistic regression models.

Independent predictors of bacteremia included CSF administration (adjusted OR = 3.2; 95% CI = 1.2–8.5; P = 0.02), MAC infection (adjusted OR = 2.7; 95% CI = 1.0–7.4; P = 0.05), and the presence of a central venous catheter (adjusted OR = 4.6; 95% CI = 1.7–12.3; P = 0.003). After excluding patients with catheter infections, CSF use was significantly associated with the development of bacteremia (adjusted OR = 6.1; 95% CI = 1.5–25.0; P = 0.01), but MAC infection and the presence of a central venous catheter were not (P = 0.17 and P = 0.99, respectively).

Patients with less severe neutropenia had decreased risk (for each increase in nadir ANC by 100 cells/μL, adjusted OR = 0.8; 95% CI = 0.7–0.9). Prior chemotherapy was not associated with the development of sepsis (P = 0.96).

Variables significantly associated with survival are shown in Table 3. Significant predictors of improved survival included less severe neutropenia (for each increase in nadir ANC by 100 cells/μL, adjusted OR = 1.3; 95% CI = 1.1–1.7; P = 0.03) and CSF use (adjusted OR = 4.2; 95% CI = 1.2–14.6; P = 0.02). Length of stay (for every increase in length of stay by 5 d, adjusted OR = 0.8; 95% CI = 0.6–0.9; P = 0.001) and sepsis (adjusted OR = 0.1; 95% CI = 0.02–0.2; P < 0.001) were associated with poorer survival to discharge. There was a trend toward CD4+ cell counts being associated with improved survival (for every increase in CD4+ cell count by 50, adjusted OR = 1.6; 95% CI = 0.9–2.8; P = 0.07).

DISCUSSION

The rationale for the use of CSFs lies in their potential to reduce the duration and severity of neutropenia, both of which have been related to the frequency and severity of infectious complications in cancer patients. Whereas the use of G-CSF or GM-CSF has been studied in chemotherapy-induced neutropenia,[10–15] their use in HIV disease is less well characterized.

The authors found CSF use, along with less severe neutropenia (i.e., higher nadir ANC), to be independently associated with improved survival to discharge in this patient population. To the authors' knowledge, this is the first evidence that CSF use improves survival in hospitalized, neutropenic HIV-infected patients. This effect was not clearly related to reduced duration of neutropenia, length of stay, or infectious complications, although the power to detect such effects may be limited, owing to the available sample size. The survival benefit was greater in those with nadir ANCs between 251 and 500 cells/μL, in whom prolonged periods with ANC below 500 cells/μL was associated with greater rates of sepsis. Survival to discharge was also higher among septic patients who received CSFs (63% vs. 38%), although this did not reach statistical significance (P = 0.075). Together, these findings suggest that CSF use may reduce the clinical severity of infectious complications in these situations.

Table 3. Logistic Regression Model for Survival to Discharge

Factor	*Adjusted OR*	*95% CI*	*Significance (P)*
CSF use	4.2	1.20 –14.60	0.0260
Nadir ANC*	1.3	1.10 – 1.70	0.0340
Duration of hospitalization†	0.8	0.60 – 0.90	<0.0010
CD4+ count‡	1.6	0.90 – 2.80	0.0741
Sepsis	0.1	0.02 – 0.20	<0.0010

*Each increase in nadir ANC by 100 cells/μL; †each increase in length of stay by 5 days; ‡each increase in CD4+ cell count by 50 cells/μL.

Patients receiving CSFs had significantly more site-related infections and prolonged durations of neutropenia, but these differences did not persist when patients in whom CSF administration was delayed by 1 or more neutropenic days were excluded, suggesting that CSF administration may have been prompted by suspicion of infection. However, CSF use also was associated independently with an increased rate of development of bacteremia, even after exclusion of patients with catheter-related infections or delayed CSF administration. The reason for this association is uncertain. Neither the duration of neutropenia nor nadir ANC were associated with bacteremia. Previous reports have suggested that CSFs administered prior to the onset of severe neutropenia may reduce the development of bacteremia.[22,25] This suggests that the timing of CSF administration may influence the risk of bacteremia. The present study is not directly comparable because CSF use was driven by clinical events. In this retrospective study, the authors could not rigorously ascertain the extent to which CSF administration was prompted by the degree of neutropenia, clinical symptoms (such as fever, sepsis, or bacteremia), or both. To the extent that CSF use was driven by clinical events, it may have reduced the sequelae of such infections rather than the rate per se. Although patients with bacteremia might be expected to have poorer outcomes, bacteremia was not associated independently with lower survival rates in this study; likewise, Keiser et al found no relation between survival and prevention of bacteremia in neutropenic HIV-infected patients treated with G-CSF.[22] This may account for the improved survival in CSF treated-patients despite their higher rate of bacteremia.

There are several limitations to these data. One potential limitation is that some patients with HIV-related neutropenia might not have been identified by the process of surveying discharge diagnostic codes. However, this would seem unlikely, because neutropenia appears to have been overcoded rather than undercoded on discharge (of 640 admissions, 242 had an ANC <1000 cells/μL). There was variability in the CSF dosing regimens prescribed. However, this likely would lessen any observed effect. Further, variability in CSF dosing had no significant effects on any outcomes. In this retrospective study, the authors could not rigorously ascertain reasons for delayed initiation of CSF therapy. Delays in CSF administration could affect comparisons of duration of neutropenia and lengths of stay, but there were no differences even when such patients were excluded. Finally, patients who received CSFs seemed to have more advanced HIV disease, as evidenced by their lower CD4+ cell counts and nadir ANCs, and greater frequency of admission. This also likely would lessen any observed benefit in survival.

In conclusion, G-CSF or GM-CSF use appears to improve survival in hospitalized HIV-infected patients with neutropenia. This effect was most marked in patients with sepsis or with ANCs below 500 cells/μL. Future study should focus on discerning the optimal timing of CSF administration, appropriate patient selection, and the effects of CSFs on long-term survival.

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REFERENCES

1. Murphy MF, Metcalfe P, Waters AH, et al. Incidence and mechanism of neutropenia and thrombocytopenia in patients with human immunodeficiency virus infection. Br J Haematol 1987; 66:337-340.
2. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever: a statement by the Infectious Diseases Society of America. J Infect Dis 1991; 162:381-396.
3. Chanock S. Evolving risk factors for infectious complications of cancer therapy. Hematol Oncol Clin North Am 1993; 7:771-793.
4. Farber BF, Lesser M, Kaplan MH, et al. Clinical significance of neutropenia in patients with human immunodeficiency virus infection. Infect Control Hosp Epidemiol 1991; 12: 429-434.
5. Whimbey E, Gold JWM, Polsky B, et al. Bacteremia and fungemia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986; 104:511-514.
6. Hambleton J, Aragon T, Modin G, et al. Outcome for hospitalized patients with fever and neutropenia who are infected with the human immunodeficiency virus. Clin Infect Dis 1995; 20:363-371.
7. Moore RD, Keruly JC, Chaisson RE. Neutropenia and bacterial infection in acquired immunodeficiency syndrome. Arch Intern Med 1995; 155:1965-1970.
8. Shaunak S, Bartlett JA. Zidovudine-induced neutropenia: Are we too cautious? Lancet 1989; 2:91-92.
9. Tumbarello M, Tacconelli E, Caponera S, et al. Impact of bacteremia on HIV infection: nine years' experience in a large Italian university hospital. J Infect 1995; 31:123-131.
10. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. N Engl J Med 1992; 327:99-106.
11. Hartmann LC, Tschetter LK, Habermann TM, et al. G-CSF in severe chemotherapy induced afebrile neutropenia. N Engl J Med 1997; 336:1776-1780.
12. Maher DW, Lieschke GJ, Green M, et al. Filgrastim in patients with chemotherapy-induced febrile neutropenia: a double-blind, placebo-controlled trial. Ann Intern Med 1994; 121:492-501.
13. Anaissie E, Vartivarian S, Bodey GP, et al. Randomized comparison between antibiotics alone and antibiotics plus GM-CSF (*Escherichia coli*-derived) in cancer patients with fever and neutropenia. Am J Med 1996; 100:17-23.
14. Dombret H, Chastang C, Fenaus P, et al. A controlled study of recombinant human-granulocyte colony-stimulating fac-

tor in elderly patients after treatment for acute myelogenous leukemia. N Engl J Med 1995; 332:1678–1683.
15. Ottmann OG, Hoelzer D, Gracien E, et al. Concomitant granulocyte colony-stimulating factor and induction chemoradiotherapy in adult acute lymphoblastic leukemia: a randomized phase III trial. Blood 1995; 86:444–450.
16. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. J Clin Oncol 1994; 12: 2471–2508.
17. American Society of Clinical Oncology. Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based clinical practice guidelines. J Clin Oncol 1996; 14:1957–1960.
18. Hermans P. Clinical use of haematological growth factors in patients with human immunodeficiency virus (HIV-1) infection. Biomed Pharmacother 1994; 48:69–72.
19. Miles SA. The use of haematopoietic growth factors in HIV infection and AIDS-related malignancies. Cancer Invest 1991; 9:229–238.
20. Kimura S, Matsuda J, Ikematsu S, et al. Efficacy of recombinant G-CSF on neutropenia in patients with AIDS. AIDS 1990; 4:1251–1255.
21. Kuritzkes D, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. AIDS 1998; 12:65–74.
22. Keiser P, Rademacher S, Smith J, et al. G-CSF use is associated with decreased bacteremia and increased survival in neutropenic HIV-infected patients. Am J Med 1998; 104:48–55.
23. De Pauw BE, Deresinski SC, Feld R, et al. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. Ann Intern Med 1994; 120:834–944.
24. Report of the Task Force of Microbiology and Infectious Diseases. NIH Publication No. 92-3220. Bethesda, MD: National Institute of Allergy and Infectious Diseases, April 1992.
25. Meynard JL, Guiguet M, Arsac S, et al. Frequency and risk factors of infectious complications in neutropenic patients infected with HIV. AIDS 1997; 11:995–998.