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Lack of benefit of Granulocyte Macrophage or Granulocyte Colony Stimulating Factor in Patients with Febrile Neutropenia

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Abstract

Objectives: To compare the clinical benefits of granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) plus standard supportive care to supportive care alone among cancer patients with febrile neutropenia.
Methods: Clinical data were collected retrospectively from 148 consecutive cancer patients with neutropenia and fever. Patients had hematologic (i.e., acute leukemias or lymphoproliferative disorders) or non-hematologic malignancies (i.e., solid tumors including carcinoma of breast, lung, or colon). Clinical variables analyzed included: age and sex; underlying malignancies; chemotherapy regimens; symptoms at time of presentation; duration of fever prior to study enrollment; days from chemotherapy until administration of GM-CSF or G-CSF; number of previous neutropenic episodes; duration of fever and day of defervescence; absolute neutrophil count on day of defervescence; duration of neutropenia; number and types of antibiotics used; day amphotericin B begun; number of culture-documented infective episodes involving bloodstream, lung, pleura, urinary tract, gastrointestinal tract, intravenous cannulae, or skin; types of antimicrobial isolates; cost of cytokine therapy; length of hospital stay and clinical outcome.
Results: The use of myeloid growth factors increased the number of circulating peripheral white blood cells, but no significant effect was noted in terms of duration of neutropenia or fever, number of culture-proven infections (except pneumonia; $p < 0.04$), length of hospital stay, or survival.
Conclusion: In areas with limited health care resources, expensive treatment with GM-CSF or G-CSF should be reserved for patients with complicated febrile neutropenia where the expected risk of infection is high and the documented infections that are refractory to antibiotic duration of neutropenia is prolonged, or those with treatment (JPMA 52: 206, 2002).

Introduction

The precise role of hematopoietic growth factors in the management of patients with neutropenia and fever remains uncertain. Granulocyte-colony stimulating factor (G-CSF or filgrastin) and granulocyte macrophage-colony stimulating factor (GM-CSF or sargramostim) have become popular modalities used in the management of patients with cancer chemotherapy-induced neutropenia. A number of clinical studies have demonstrated

the potential ability of these factors to decrease the duration of cytotoxic-induced neutropenia, number of febrile days and reduce hospital stay[1-5]. However, not all investigators have demonstrated substantial benefit from the use of myeloid colony stimulating factors[6-8] and their relatively high cost must be seriously considered when contemplating the use of G-CSF and GM-CSF in countries like Pakistan with limited health care resources. In order to determine the appropriateness and cost-effectiveness of these cytokines in local setting, we conducted a comparative study of GM-CSF or G-CSF plus standard supportive care versus supportive care alone in chemotherapy-induced neutropenic fever and evaluated several targeted outcome measures.

Patients and Methods

During the period January 1997 through March 1998, clinical data were collected retrospectively from consecutive patients seen on the oncology service with neutropenia (defined as an absolute neutrophil count < 500/cu mm or between 500-1,000/cu mm but rapidly dropping) and fever (defined as a temperature elevation above 38.3°C. Patients had hematologic (i.e., acute leukemias or lymphoproliferative disorders) or nonhematologic malignancies (i.e., solid tumors including carcinoma of breast, lung, colon). Various chemotherapy regimens are shown in Table 1.

Table 1. Cancer chemotherapy regimens used in growth factor-treated patients and control subjects.

Chemotherapy regimen/dose+	No. of patients Receiving GM-G/CSF*	Control subjects
AD	12	10
ADE	3	2
AM	1	2
Hi-D Ara-C	3	4
AC	8	12
FAC	4	8
CMF	3	10
AN	4	6
Paclitaxel	5	2
AT	4	1
NVB + CDDP	3	7
CHOP	7	11
ABVD	3	7
COPP	2	6
Cyclo + Carbo Platin	2	4
Taxol + Carboplatin	4	-
BEP	3	1
CDDP + SFU	5	2
1 fos + DOX	3	1
1 CE	5	2
1 fos + Etoposide	2	1

Conventional supportive care involved initiation of empiric two-drug antibacterial therapy with the development of fever (generally, piperacillin/tazobactam plus amikacin; vancomycin was added if patients had evidence of catheter-related infection such as signs of inflammation around a central or peripheral catheter, or tenderness overlying a subcutaneous catheter port). Empiric antifungal treatment with iv amphotericin B was begun if patients remained febrile for more than five days. Due to economic considerations, growth factors were begun at the time of development of fever rather than at the onset of neutropenia. Growth factors were administered in the following doses: G-CSF ugfkg] (n = 27) or GM-CSF ug/m2} (n = 40). Therapy with growth factors was continued for a mean of

3.93 days (range 1-9 days).
Clinical variables analyzed included age and sex; AD = cytosine arabinoside 100 mg/rn^2 x 7d plus daunorubicin 45 mg/rn^2 x 3d; ADE = cytosine arabinoside 100 mg/rn^2 x 7d plus daunorubicin 45mg/rn^2 x 3d plus etoposide 100 mg/rn^2 x 4d; AM = cytosine arabinoside 100 mg/rn^2 x 7d plus mitoxantrone 12 mg/rn^2 x 3d; HiD Ara-C = 1.5 gm/rn^2 q12h x 3d; AC = adriarnycin 60mg/rn^2 plus cyclophosphamide 600 mg/rn2; FAC = 5-FU 500 mg/rn2 plus adriamycin 50 mg/rn2 plus cyclophosphamide 500 mg/rn2; CMF = cyclophosphamide 600 mg/rn2 plus methotrexate 40 mg/rn2 plus 5-FU 600 mg/ m^2; AN = adriamycin 50mg/rn^2 plus nanelbine 30 mg/rn^2, AT = adriamycin 50 mg/rn^2 plus docetaxel 75mg/rn^2; Paclitaxel 175 mg/rn^2; NVB + CDDP = nanelbine 25 mg/rn^2 day I & day 8 plus cisplatin 100 mg/rn^2; CHOP = cyclophospharnide 750 mg/rn^2 plus adriamycin 50mg/rn^2 plus vincristine 1.4 mg plus prednisolone 60 mg; ABUD = adriamycin 25 mg/rn^2 plus bleomycin 10 mg/rn^2 plus vinblastine 6 mg/rn^2 plus DTIC 375 mg/rn^2; COPP cyclophosphamide 650 mg/rn^2 plus vincristine 1.4 rng plus procarbazine 100 mg/rn^2 x l4d plus prednisolone 40 mg ; Cyclo + Carbo Platin = cyclophosphamide 750 mg/rn^2 plus carboplatinum AUC5; Taxol + Carbo = taxol 135 mg plus carboplatinum AUC 5; BEP = bleomycin 30 rng days 1, 8, and 15 plus etoposide 100 mg/rn^2 x 5d plus cisplatin 20 mg/rn^2 x 5d; CDDP + 5FU cisplatin 100 mg/rn^2 plus 5-FU 1 gm/m^2 x 4 days; 1 fos + DOX = 1 fosfomide 3 gm/rn^2 x 3d plus doxorubicin 20 mg/rn^2 x 3 days; I fos + Etoposide = I fosfdmide 2 gm/rn^2 x 3d plus etoposide 100 mg/rn^2 x 3d; ICE 1 fosfomide 1.2 gm/rn^2 x 5d plus carboplatinum 400 mg/rn^2 plus etoposide 100 mg/rn^2 x 5d.
symptoms at time of presentation; duration of fever prior to study enrollment; days from chemotherapy until admission; number of previous neutropenic episodes; duration of fever and day of defervescence; absolute neutrophil count on day of defervescence; duration of neutropenia; number and types of antibiotics used; day amphotericin B begun; number of culture-documented infective episodes involving bloodstream, lung, pleura, urinary tract, gastrointestinal tract, intravenous cannulae, or skin; types of antimicrobial isolates; cost of cytokine therapy; length of hospital stay and clinical outcome.

Statistical Methods

Data were summarized as means with standard deviation, or medians with ranges (for continuous variables) and as frequencies and percentages (for categorical variables). Univariate analysis was performed using a two independent sample t-test, Pearson's chi-square and Fisher's exact test wherever appropriate. A p value < 0.05 was considered statistically significant. Analyses were carried out using the statistics software program SPSS (release 8.0.0, standard version, copyrightO SPSS Inc.).

Results

Demographic and clinical variables for the two study groups are shown in Table 2.

Table 2. Baseline demographic and clinical features in 148 patients with febrile neutropenia treated with GM/G-CSF or standard supportive care.

Variable	GM/G-CSF (n = 67)	Without GM/G-CSF (n = 81)	p value
Age (years)	44.85 ± 20.29	49.50 ± 14.80	0.121
Sex M:F	26:41	39:42	0.254
Diagnosis			
Hematologic	19 (28%)	18 (22%)	
Non-hematologic	48 (72%)	63 (78%)	0.391
Days from chemotherapy	11.09 ± 4.70	13.09 ± 9.32	0.118
No of prior neutropenic episodes	0.72 ± 0.88	0.42 ± 0.72	0.029
Presenting symptoms			
Mucositis	5 (9%)	7 (7%)	0.79
Diarrhoea	25 (37%)	30 (44%)	0.97
Vomiting	14 (21%)	17 (21%)	0.98
Abdominal pain	12 (18%)	10 (12%)	0.34
Cough	19 (28%)	19 (20%)	0.22
Bleeding	2 (3%)	6 (7%)	0.29
ANC* day of admission	338.7 ± 402	332.1 ± 273.2	0.92

* Absolute neutrophil count.

The groups were comparable in terms of numbers and percentages of hematologic and non-hematologic malignancies, days until fever, presenting symptoms, and absolute neutrophil count at the time of fever. A significantly higher proportion of patients in the group receiving growth factors had experienced previous episodes of febrile neutropenia.

Clinical outcomes

The absolute neutrophil count on the day of defervescence was higher in the growth factor-treated group although the difference was not statistically significant (Table 3).

Table 3. Outcome measures for 148 patients with febrile neutropenia treated with GM/G-CSF or standard supportive care.

Variable	GM/G-CSF (n = 67)	Without GM/G-CSF (n = 81)	p value
ANC* day afebrile			
Mean	2,571.39 ± 2980	1,433.47 ± 1947	0.079
Days to defervescence	4.80 ± 2.76	3.55 ± 2.0	0.008
Number of pathogens from clinically relevant infections			
Blood	17 (51%)	19 (54%)	0.29
Urine	10 (31%)	4 (11%)	0.05
Stool	0	2 (6%)	-
Other	6 (18%)	10 (29%)	0.31
Total	33	35	
Pneumoni	3	11	< 0.04
Bilateral pneumonia	1	0	NS
Pleural effusion	7	8	NS
Other	16	24	NS
Length of hospital stay (days)	6.21 ± 2.57	5.17 ± 268	0.018
Death	6 (9%)	13 (16%)	0.199

* ANC = absolute neutrophil count.

\+ Three and six bacteremias associated with indwelling Infusaport^{R} catheters in the GM/G-CSF and standard care groups, respectively.

Requirements for antimicrobial agents were not significantly different (data not shown), Patients treated with growth factors took more than one day longer to achieve defervescence and also remained in the hospital one day longer ($p < 0.008$ and $p < 0.018$,

respectively). Six patients (9%) in the cytokine treatment group and 13 (16%) in the control group died during febrile neutropenia (not statistically significant).

Sites of infection and recovery of pathogens

The numbers and types of clinically relevant infections and the recovery of pathogens from blood, stool and several other body sites were comparable between the two groups. However, more subjects in the cytokine-treated group had urinary tract infections (10 versus 4; $p < 0.05$), while a significantly higher number of patients in the control group were found to have pneumonia; overall, 15 patients developed radiographic evidence of pulmonary infiltrates, 11 of cytokine therapy ($p = 0.026$). The incidences of pleural effusions on chest x-ray were similar.

A total of 68 microbiologic isolates were cultured during 148 episodes of febrile neutropenia (46% yield) (Table 4).

Table 4. Microorganisms isolated from febrile neutropenic patients with documented infections treated with GM/G-CSF or standard supportive care.

Organism	GM/G-CSF	Without GM/G-CSF	Total No. of isolates
Gram-Negative Bacteria	22	17	39
Acinetobacter spp.	1	2	3
Escherichia coli	13	5	18
Klebsiella pneumoniae	-	5	5
Other Klebsiella spp.	1	1	2
Pseudomonas aeroginosa	2	1	3
Other Pseudomonas spp.	-	1	1
Proteus mirabilis	1	-	1
Enterobacter aerogenes	1	-	1
Vibrio cholerae	-	2	2
Haemophilus influenzae	2	-	2
Moraxella catarrhalis	1	-	1
Gram-Positive Bacteria	7	13	20
Staphylococcus aureus	1	2	3
Coagulase-negative staphylococci	1	4	5
Streptococcus pneumoniae	-	1	1
Other Streptococcus spp	2	4	6
Bacillus spp.	3	1	4
Corynebacterium spp.	-	1	1
Fungal	4	5	9
Candida spp.	3	4	7
Other yeasts	1	-	1
Aspergiillus spp.	-	1	1
Total	33	35	68

Overall the numbers of bacterial and fungal pathogens isolated from the two study groups were comparable (Table 4). Aerobic Gram-negative bacteria were most commonly isolated from both the treatment and control groups (22 versus 17 isolates, respectively); fewer gram-positive bacteria were isolated from patients treated with growth factors (not significant).

Discussion

Despite their widespread popularity in oncologic practice, there is a lack of published data demonstrating clear survival benefits. Therfore the routine use of costly hematopoietic colony stimulating factors as adjuvant therapy for neutropenic patients with unexplained

fever is not currently recommended[9]. The administration of G-CSF and GM-CSF in many of the studies has demonstrated a reduction in the days to neutrophilic recoveiy and a reduction of morbidity[10-13]. Rowe and associates used GM-CSF in older patients with acute myeloid leukemia; the remission rate was 60% and 44% in the placebo group. Beneficial effects including survival were also demonstrated in the GM-CSF arm. All these patients had a day ten bone marrow performed and only if there were no leukemic cells in the marrow was randomization done[12].

In the present study of febrile patients recently undergoing induction chemotherapy, neither GM-CSF nor G-CSF significantly reduced the duration of neutropenia or fever, decreased the incidence of culture-proven infective episodes (except pneumonia), reduced the duration of hospitalization, or improved overall clinical outcomes.

In an attempt to maximize patient benefits and minimize adverse effects on health care systems and society, the American Society of Clinical Oncology (ASCO) and the Infectious Diseases Society of America have published consensus guidelines for the rational use of these agents with cancer chemotherapy and febrile neutropenia[9,13]. It should be emphasized, however, that for many of these recommendations data from randomized clinical trials are not available. The use of myeloid stimulating factors in cancer chemotherapy induction is not routinely recommended but instead is based on risk stratification of patients, itself being dependent on a number of clinical variables. For certain conditions where worsening of the clinical course is predicted and there is an expected long delay in recovery of the marrow, one of these agents may be indicated. Such conditions include pneumonia, hypotensive episodes, severe cellulitis or sinusitis, systemic fungal infections and multiorgan dysfunction secondary to sepsis. Therapy with colony-stimulating factors may also be considered in patients who remain severely neutropenic and have documented infections that fail to respond to appropriate antimicrobial treatment[9,13].

There are several limitations of this study; firstly, data were collected retrospectively and hence randomization was not possible. However, since the data were collected from consecutive patients presenting over a short study period of 14 months, it minimized the effects of several potential confounding variables. The short study period meant that variations in certain variables (e.g., types of underlying cancers, chemotherapy dose-intensities, patterns of microbial pathogen isolation and antibiotic resistance, use of antifungal prophylaxis, and choices of empiric antimicrobial therapy) were notably limited. Furthermore, the decision to use or not use growth factors (before and during the study) was based purely on the basis of financial affordability by the patient, and thus may have reduced potential bias in patient selectiOn. Another limitation of the study is that data for G-CSF and GM-CSF were combined, although cytokine selection was made randomly. Nevertheless, although some reports have suggested that G-CSF may result in a faster neutrophil recovery compared to GM-CSF, this has not been a consistent finding and no significant differences between the two agents have been reported for clinically-relevant end points such as the infectious complications, length of hospitalization, use of antibiotics, hospital costs and mortality.

Thirdly, treatment with growth factors was begun a mean of 11 and 13 days post-chemotherapy in respective study groups and patients generally had experienced neutropenia several days before the development of fever. This delayed initiation of cytokine therapy was not because study subjects had low-risk (delayed-onset) neutropenia but was due to the financial limitations of our patients. This practice is in line with ASCO

guidelines[9].
In poorer countries like Pakistan very expensive therapeutics may adversely affect the economics of the patient, family and society. In our setting the use of GMCSF and G-CSF must be governed by proven efficacy, specific indications and cost-effectiveness. The results of our study indicate that these cytokines may not confer significant benefits to patients with uncomplicated febrile neutropenia and according to current guidelines should be reserved for complicated cases where the expected risk of infection is high and the duration of neutropenia is prolonged, or for patients with documented infections that are refractory to antibiotic treatment.

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