IMPACT OF PROPHYLACTIC USE OF COLONY STIMULATING FACTORS ON THE PATTERN OF NEUTROPENIA AND INFECTIONS IN MODERATELY INTENSIVE CHEMOTHERAPY

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ABSTRACT

In this study, colony stimulating factors (CSF) were used to prevent neutropenia during moderately intensive chemotherapy in 26 episodes of chemotherapy (12 of acute lymphoblastic leukaemia (ALL) and 14 patients with other malignancies). CSF was administered in doses of 5 µg/kg of body weight within 24 hours of completion of chemotherapy for 7 days in 6 patients and for 10 days in others. Twenty six age and sex matched patients of ALL were included as controls. In the CSF group, incidence of severe neutropenia (grades 3 and 4) reduced significantly by 42.3 per cent though overall incidence of neutropenia did not differ much. Mean duration of neutropenia reduced by 4 days. Nadir total leucocyte count and absolute neutrophil count were significantly higher. There was no difference in the incidence of anaemia, thrombocytopenia and requirement of blood transfusions. Overall infections were less and incidence of severe infections reduced by 42.3 per cent. The duration of infection and of fever was shortened. Requirement of antibiotics was also reduced. All patients in CSF group recovered from infection, while 1 patient died in the control group. Mean duration of delay in chemotherapy was reduced from 10 days in control group to 3 days in CSF group. CSF administration resulted in an escalation of the cost by 112.24 per cent. However shortened duration of antibiotics, hospitalisation, reduced laboratory expenses compensated it by 66.94 per cent. Our study indicates that the prophylactic use of CSF is beneficial and cost effective in moderately intensive chemotherapy with a high incidence of febrile neutropenia. Administration for 10 days appears to be more beneficial than 7 days.

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KEYWORDS: Chemotherapy; Colony Stimulating Factors; Cost-Benefit Analysis; Neutropenia; Prophylaxis.

Introduction

Chemotherapy, as a part of multimodal therapy, has significantly improved the outcome in patients with malignancies. Nevertheless it is accompanied by many unpleasant and life threatening toxicities. Bone marrow suppression and resultant neutropenia is a common problem [1].

High incidence of morbidity and mortality in a potentially curable group of patients, despite adequate management with antibiotics and supportive care, is undesirable and unacceptable [1,2]. Febrile neutropenia frequently delays the subsequent chemotherapy or compromises the dose and this reduced dose intensity may lead to reduced re-

sponses and decreased survival. Toxicity due to the therapy is a demotivating factor for further continuation of therapy. Use of antibiotics, prolonged hospital stay and the additional supportive care escalate the overall cost of management.

To derive the maximal benefit of chemotherapy it is necessary to minimise or prevent its complications, particularly neutropenia. Colony stimulating factors (CSF), an important member of family of haemopoietic growth factors, have been demonstrated to be effective in treatment as well as prevention of neutropenia [1-4]. These studies have indicated that the incidence, severity, and duration of neutropenia could be reduced.

In India, though CSF are in wide use, there is

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no published data on the benefits of their use and cost effectiveness. We undertook this controlled prospective study with the aim of evaluating the efficacy and cost benefit of prophylactic use of CSF in moderately intensive chemotherapy.

Material and Methods

This study was conducted at the Malignant Diseases Treatment Centre, Command Hospital (SC), Pune during January 1995 to June 1996. The subjects were patients receiving moderately intensive chemotherapy, with a high (> 50%) incidence of febrile neutropenia. A total of 26 episodes were studied. Twelve episodes were in paediatric patients with acute lymphoblastic leukaemia (ALL) receiving high dose of cytosine arabinoside during induction. Fourteen episodes were in patients (6 paediatric and 8 adult) with other malignancies (Ewing's sarcoma (8), non Hodgkin's lymphoma (2), multiple myeloma (2) and peripheral neuroectodermal tumours (2)) on combination chemotherapy experiencing two or more events of febrile neutropenia in the past.

All patients were administered CSF commencing 24 hours after completion of chemotherapy. The original protocol was to administer CSF for a period of 7 days, but on observation of a high incidence of neutropenia in the initial 6 episodes (Group I), the duration was increased to 10 days in the remaining (Group II). CSF was administered in doses of 5 µg/kg of body weight per day subcutaneously once daily. Two available products (GM-CSF and G-CSF) were used in the study depending on availability. In 22 episodes G-CSF was used and GM-CSF in 4 episodes.

Post-chemotherapy period was studied in respect to (a) neutropenia: incidence, severity, duration, nadir total leucocyte (TLC) and absolute neutrophil count (ANC); (b) infection: incidence, severity and duration; (c) antibiotics: requirement of antibiotics and duration of use; (d) impact on dose intensity: delay and or dose compromise in next chemotherapy schedule. For assessing severity WHO and ECOG grades were used (Table 1). The results in ALL patients were compared with controls consisting of paediatric patients who received same protocol without CSF. In patients with other malignancies their previous episodes while on similar chemotherapy protocols without CSF were

taken for comparison.

TABLE 1

Grades of leucopenia, neutropenia and infection (WHO/ECOG Criteria)

Grade	Leucopenia (/cu mm)	Neutropenia (/cu mm)	Infection
0	> 4000	>2000	None
1	3000-3999	1500-1999	Minor
2	2000-2999	1000-1499	Moderate
3	1000-1999	500-999	Severe
4	< 1000	< 500	Life threatening

Statistical analysis was carried out using software 'EPI' and 'SPSS for Windows'. T test for two independent samples was used for comparison of the control and CSF groups. For comparison of group I with group II ANOVA was employed.

Results

Pre-chemotherapy haematological parameters of both groups (control and CSF group) are tabulated in Table 2 and no significant difference was observed on statistical analysis in both groups indicating their homogeneity.

Post-chemotherapy neutropenia: Post-chemotherapy neutropenia of all grades was observed in 17 episodes (65.4%) of CSF group as compared to 23 (88.5%) out of 26 episodes. This difference was not significant ($p=0.13$). However, severe neutropenia (WHO grade 3 and 4) was observed in 15 (57.7%) episodes of the control group and 4 (15.4%) of the CSF group ($p=0.005$) (Table 3).

The mean duration of neutropenia was 6 days in CSF group as against 10 days observed in control group ($p=0.032$). The day of nadir count did not differ. Nadir total leucocyte count (TLC) and absolute neutrophil count (ANC) in both groups differed significantly. Mean lowest observed TLC was 512/cumm in control group while it was 1100/cumm in CSF group ($p=0.027$); ANC was 128 and 630/cumm respectively ($p=0.018$) (Table 3).

Febrile neutropenia and antibiotics: Infection, as indicated by onset of fever, occurred in 20 (76.9%) episodes in control group as compared to 8 (30.8%) episodes in CSF group with highly significant difference ($p=0.005$) (Table 4). Severe

TABLE 2

Prechemo-therapy parameters : both groups

Parameter	Controls (N = 26)	CSF GP (N = 26)	Statistical significance
Age:			
Paediatric gp	6.4 yr	6.0 yr	(0.945) NS
Adults	49.5 yr	43.8 yr	
TLC: (/cumm)			
Median	5585	5926	(0.875) NS
Range	3400-10800	3200-11200	
Neutrophils (%)	62	58	(0.732) NS
ANC (/cumm)	3544	3472	(0.891) NS
Hb (%)	9.94	9.92	(0.910) NS
Platelet (/cumm)	176000	144666	(0.630) NS

TABLE 3

Haematological parameters - post chemotherapy

Parameter	Controls (N = 26)	Test GP (N = 26)	P Value	Remarks
Neutropenia				
Occurrence (%)	23 (88%)	17 (65%)	0.13	NS
Severity				
1 and 2	8	13	0.005	HS
3 and 4	15 (57%)	4 (15%)		
Duration: (mean)	10 days	6 days	0.032	S
Day of nadir	10th day	9th day	0.897	NS
Nadir TLC	512/cumm	1100/cumm	0.027	S
ANC (/cu mm)	128/cumm	630/ cumm	0.018	HS
Anaemia (no of pts)	12	11	0.75	NS
Thrombocytopenia (no of pts)	11	10	0.75	NS
Blood transfusions (no of pts)	7	6	0.74	NS

infection (grade 3 or 4) was observed in 12 (46.2%) of the controls and 3 (11.5%) of the CSF group ($p=0.007$). Mean duration of infection was reduced by 3 days ($p=0.023$). Antibiotics were required in 20 patients of control group and 8 of CSF group and the mean duration of antibiotic therapy reduced by 3 days ($p=0.02$). All but one patient from control group recovered from the infection, while all patients recovered in CSF group. Duration of fever differed significantly with a mean decrease in duration of 4 days ($p=0.04$).

Impact on Dose Intensity: (Table 5) Subsequent chemotherapy was delayed in 20 (76.9%) episodes

of control group with a mean delay of 10 days, as compared to 5 (19.2%) of CSF group with a mean delay of 3 days. There was dose compromise in 9 episodes (34.61%) in the controls while only 1 patient of CSF group had a reduction in dose.

Duration of CSF administration: We compared groups I and II by ANOVA method to determine any difference. Results (Table 6) revealed that the effects are more pronounced with 10 days of CSF therapy. Incidence of neutropenia remained unaltered, but severity and duration of neutropenia lessened; nadir TLC and ANC were significantly higher. Incidence, severity and duration of infections were significantly reduced in group II. Duration of fever was shorter and requirement of antibiotics was also reduced. Similarly, the impact on dose intensity was altered favourably.

In most patients the treatment was well tolerated. In one patient we observed severe chills and rigor and had to change the brand of CSF. In 2 patients, there was fever on first two days.

Cost Benefit Analysis: We calculated the cost of supportive care for febrile neutropenia with and without CSF. For the analysis, the cost of drugs at hospital supply rates at the time of study were taken. Cost of CSF was Rs 3500 per vial of 300 µg and cost of antibiotics Rs 1500 per day (for Cefotaxime and Amikacin). Laboratory expenditure of Rs 1500 per patient per episode of febrile neutropenia was incurred, which included the actual cost of the tests. Consultation cost, human cost in laboratory, nursing and other services have not been taken into account, being a service run hospital. As depicted in Table 7, the addition of CSF to the treatment escalated the total cost by 112.2 per cent; and there was a reduction in expenditure on antibiotics by 48.7 per cent; hospital stay by 14.9 per cent, and laboratory investigations by 3.4 per cent. These compensated for the cost escalation to a large extent, which finally was 45.3 per cent over the base cost.

The benefits observed with use of CSF have been reduction in morbidity and mortality. There was a reduction in incidence of serious infections in 34.6 per cent patients and the duration of fever and infection by an average of 3-4 days. In this study, one patient died due to neutropenia in control group and none in CSF group. Another

TABLE 4

Impact on febrile neutropenia

Parameter	Controls (N = 26)	Test Gp (N=26)	Difference	2-Tailed P Value	Remarks
Infection					
Occurrence	20 (76.92%)	8 (30.76%)	46.16%	0.005	HS
Severity					
1 and 2	8	6			
3 and 4	12 (46.15%)	2 (07.69%)	38.46%	.007	HS
Duration (days)	9	6	3 days	.023	S
Antibiotics	20	9			
used (no of pts)	(76.92%)	(34.61%)	42.31%	.036	S
Duration (days)	12	9	3 days	.02	S
Fever peak (°F)	104	102	2° F		
Fever duration (days)	9	5	4 days	.04	HS
Recovery from infection (no of patients)	19/20 (95%)	9/9 (100%)	5%	0.663	NS
No of patients died	1/16 (6.25%)	0	5%	0.32	NS

TABLE 5

Impact on dose intensity of chemotherapy

Parameter	Controls (N = 26)	Test Grp (N = 26)	Difference	2 tailed P Valuc	Remarks
No of patients with delay in next course (%)	20 (76.92%)	5 (19.23%)	57.69%	.0002	HS
Mean no of days	10 days	3 days	7 days	.004	HS
Range	3-18 days	2-8 days	1-10 days	—	—
Reduction in dosage	9 (34.61%)	1 (3.84%)	30.77%	.00004	HS

advantage observed was the impact on dose intensity; chemotherapy was delayed in 80 per cent patients of control group and there was reduction of dose intensity in 33.3 per cent, while in the CSF group, the delay was in 19.0 per cent patients with no appreciable reduction in dose intensity.

Discussion

Haemopoietic CSF and interleukins, endogenous substances produced in human tissues, are involved in the regulation, proliferation as well as differentiation of the haemopoietic precursor cells by both direct and indirect actions [1-4].

Amongst many recognised cytokines, G-CSF and GM-CSF have been commercially available for past few years. Though substantial clinical and

laboratory evidence has accumulated to illustrate the effects of CSF, many questions remain unanswered due to short experience with the drug and limited number of trials. Available evidence [1-10] indicates their benefit in (a) decreasing neutropenia associated with chemotherapy, (b) high dose chemotherapy and BMT, (c) peripheral cell mobilisation for PBSCT and (d) for some novel methods, such as leukaemic cell recruitment into cell-cycle (pre-therapeutic priming) for a high cell kill.

In high-dose chemotherapy, prophylactic use of haemopoietic growth factors has been reported to decrease the incidence, severity, and duration of neutropenia, thus reducing the morbidity and mortality. Also, they enable the delivery of intended

TABLE 6

Comparison of duration of CSF therapy

Parameter	Control (N = 26)	CSF gp (N = 26)	Group I (N = 6)	Group II (N = 20)	P value	Remarks
Neutropenia						
Incidence (%)	23 (88.46%)	17 (65.38%)	5 (83.33%)	12 (60%)	.22	NS
Nadir TLC (cu/mm)	512	1160	950	1370	.027	S
Nadir ANC (cu/mm)	128	530	456	604	.0133	S
Grade 3 and 4 (no of pts)	15 (57.69%)	4 (15.38%)	2 (33.33%)	2 (10%)	.021	S
Duration (days)	10	6	7.2	4.8	.000	HS
Infection						
Incidence	20 (76.92%)	8 (34.61%)	3 (50%)	5 (25%)	.002 in group II	HS
Severity (grade 3 and 4)	12 (47.61%)	1 (4.76%)	1 (16.66%)	0 (0%)	.971	NS
Duration	9	5.4	6.7	4.1	.018	S
Antibiotic duration	12	8	10	6	.012	S
Duration of fever	9	5.2	6.0	4.2	.013	S
Dose Intensity						
No of pts with delay	20 (76.92%)	5 (19.23%)	3 (50%)	2 (10%)	.002	HS
Mean delay (No of days)	10	3.1	4	1.5	.004	HS

TABLE 7

Cost-benefit analysis

Parameter	Cost per patient (Rs)	Cost Control Gp	Cost CSF Gp	Remarks
Cost of CSF (for 10 days)				
Adult: (08)	35,000	—	2,80,000	Overall cost increased by 112.2%
Child: (18)	15,000		2,70,000	
Cost of antibiotics	1500/day	3,60,000	1,21,500	Overall cost reduced by 48.67% (66.39% of antibiotics)
Lab expenses (addl inv for infected pts)	1500/ episode	30,000	13,500	Overall cost reduced by 3.36% (55% of lab expenses)
Hospital stay (during febrile neutropenia)	500/day	1,00,000	27,000	Overall cost reduced by 14.89% (73% of hosp stay exp)
Total cost		4,90,000	7,12,000	Overall cost escalation by 45.30
Human Factors				
Mortality		One	Nil	Reduction in mortality
Morbidity		76.92%	34.61%	Reduction in morbidity
Duration of illness		09 days	06 days	-- do --
Severe infections		05 pts	01 pts	-- do --
Dose compromise		16 pts (76.19%)	One	Proper Dose intensity assures best chances for responses and Survival
Stress and strain on patient		Not Measurable	Not Measurable	Reduces the strain for patient and staff.
Stress and strain on the staff		Not Measurable	Not Measurable	-- do --

dose intensity to derive maximal therapeutic benefits [1-3]. Gerhardt et al observed decreased serious infection rate, hospitalisation, fever, shortened duration of neutropenia and increased response rates in patients of NHL [7].

In our study there was a significant reduction in severe neutropenia and the duration of neutropenia. The nadir TLC was higher with an increase in ANC. Differences remained significant on statistical analysis. Amongst infections in the neutropenic patients, there was a significant reduction in incidence, severity and duration. Antibiotics were required in less number of patients and for a shorter duration. All patients recovered from infection in CSF group while one patient died amongst the controls. These results are similar to those observed by Gerhardt et al [7]. The other major benefit observed in this study was that CSF administration seemed to facilitate the administration of intended dose intensity in most patients.

The major limitation in the usage of CSF is the high cost and hence the use has to be rational and judicious, carefully identifying the clinical situations to derive the maximal cost benefit. With high dose or moderate dose chemotherapy with an increased incidence of neutropenia, cost benefit is likely to be observed [3], while it may not be so with conventional chemotherapy with less incidence of neutropenia. With the use of CSF, overall cost is expected to go high, but the duration of hospitalisation, cost of antibiotics, and the improvement of quality of life are likely to compensate for the cost escalation. Cost benefit analysis has been done in very few studies [4]. In our study, CSF administration resulted in escalation of the cost by 112.2 per cent, but here was reduction in cost of antibiotics, hospitalisation, laboratory expenditure, which brought down the cost escalation to 45.3 per cent. The benefits were reduction of mortality and morbidity, stress and strain on the patients and staff. This reiterates the first of the guide-lines of American Clinical Society of Oncology (ASCO) [1,4], which recommended the use of CSF in specific situation (a) in chemotherapy protocols with more than 40 per cent incidence of febrile neutropenia; (b) as prophylaxis in patients

with past incidence of febrile neutropenia and (c) as an adjunct in severe febrile neutropenia not responding to antibiotics and anti-fungal drugs.

There is a growing concern for consideration during administration of CSF, and that is of higher incidence of other dose-related toxicities such as thrombocytopenia, nephrotoxicity or cardiotoxicity. In future, it is likely that broad spectrum CSFs and newer chemo-protectants will be in use, which will have reduce neutropenia and thrombocytopenia. Such a combination will definitely reduce chemotherapy related morbidity and mortality, allowing the oncologist to deliver a proper dose intensity with a better overall outcome.

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