

# A Retrospective Evaluation of Low-Dose rhG-CSF in Chemotherapy-Induced Neutropenia

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## ABSTRACT

Recombinant human granulocyte colony stimulating factor (rhG-CSF) 5 µg/kg/day has been useful in reducing neutropenic sequelae of chemotherapy. In this study, the effect of a low dose regimen of rhG-CSF (1.5 to 3.0 µg/kg/day) is evaluated.

Charts of all patients who received low-dose rhG-CSF at the Saskatoon Cancer Centre and Allan Blair Cancer Centre between April 1992 and April 1993 were reviewed retrospectively. Patients must have had completed at least two consecutive cycles of chemotherapy. Patients were used as their own controls.

Ten patients received rhG-CSF during the study period, six were evaluable. Endpoints which showed significant improvement with rhG-CSF included the duration of neutropenia, use of oral antibiotics required for prophylaxis, and chemotherapy treatment delays (two-tailed, paired *t*-test,  $p \leq 0.05$ ). Significant differences were not found for the other endpoints, degree of neutropenia, hospital stay for neutropenia, IV antibiotic use, and occurrence of chemotherapy dosage reductions or increases.

RhG-CSF utilized at this low dose may prevent sequelae of chemotherapy-induced neutropenia at a manageable cost.

**Key Words:** cost, dose, neutropenia, recombinant human Granulocyte-Colony Stimulating Factor, sequelae

## RÉSUMÉ

L'administration de la forme recombinante de stimulateurs des facteurs de croissance granulocytomonocytaires (rhG-CSF), à raison de 5 µg/kg/j, s'est avérée utile pour atténuer les séquelles liées à la neutropénie d'origine chimiothérapeutique. Cette étude évalue l'effet du rhG-CSF administré à faible dose (1,5 à 3,0 µg/kg/j).

On a analysé rétrospectivement les fiches de tous les patients qui ont reçu du rhG-CSF à faible dose au Saskatoon Cancer Centre et au Allan Blair Cancer Centre entre avril 1992 et avril 1993. Les patients devaient avoir terminé au moins deux cycles consécutifs de chimiothérapie. Les patients étaient leurs propres témoins.

Dix patients ont reçu le rhG-CSF au cours de la période d'étude et six étaient évaluable. Les paramètres étudiés qui montrent des améliorations notables avec l'administration du rhG-CSF comprennent la durée de la neutropénie, l'utilisation d'antibiotiques oraux nécessaires en prophylaxie, et les reports de traitement chimiothérapeutique (test de *t* apparié bilatéral,  $p \leq 0,05$ ). Aucune différence significative n'a été

observée pour les autres paramètres; intensité de la neutropénie, durée de l'hospitalisation pour traiter la neutropénie, utilisation des antibiotiques i.v., et occasions de réductions ou d'augmentations des doses d'agents chimiothérapeutiques.

Le rhG-CSF utilisé à faible dose pourrait prévenir les séquelles liées à la neutropénie d'origine chimiothérapeutique à des coûts raisonnables.

**Mots clés:** coût, dose, forme recombinante des facteurs de croissance granulocyto-monocytaires (rhG-CSF), neutropénie, séquelles

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## INTRODUCTION

In order to achieve optimum responses in many tumours, maintaining recommended dose intensity of chemotherapy is important.<sup>1-5</sup> Myelosuppression from chemotherapy may or may not require treatment, depending on the severity. Infectious sequelae, including hospitalization and treatment with antibiotics, are undesirable effects of neutropenia. In addition, other sequelae, such as dose reductions or treatment delays may adversely affect response to treatment.<sup>6</sup> In the past decade, use of colony stimulating factors (CSFs) has hastened recovery from hematological toxicities associated with chemotherapy.<sup>1-12</sup>

CSFs are glycoproteins that bind to specific cell surface receptors and promote the proliferation, differentiation, and maturation of circulating blood cells.<sup>6-8</sup> Recombinant human granulocyte colony stimulating factor (rhG-CSF) specifically affects neutrophils, resulting in an initial brief neutropenia after subcutaneous administration, and later an increase in circulating neutro-

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phils.<sup>4,9,11</sup> At higher doses, lymphocytes and monocytes may also be affected. Recombinant human G-CSF appears to be fairly well tolerated, the most common adverse effect being bone pain.<sup>4,6-9,11</sup>

Recombinant human G-CSF is the only CSF listed on the Saskatchewan Cancer Foundation (SCF) formulary. The cost of these agents is a major concern. Guidelines for the use of CSFs have been established in order to reduce their budgetary impact.

In spring of 1992, an approach to the use of CSFs was instituted for the SCF. Studies from Japan indicate that the administration of subcutaneous rhG-CSF at doses of 50 to 90  $\mu\text{g}/\text{m}^2/\text{day}$  (1 to 3  $\mu\text{g}/\text{kg}/\text{day}$ ) is sufficient to reduce the degree and duration of granulocytopenia associated with cytotoxic chemotherapy.<sup>1,3,5</sup> Use of the lower dose has a major impact on reducing cost compared to the standard recommended dose of 5  $\mu\text{g}/\text{kg}/\text{day}$ , approximately 230  $\mu\text{g}/\text{m}^2/\text{day}$ . A modified low-dose regimen of rhG-CSF (50 to 90  $\mu\text{g}/\text{m}^2/\text{day}$ ) (1.5 to 3  $\mu\text{g}/\text{kg}/\text{day}$ ) has been employed at the Saskatoon Cancer Centre (SCC). The pharmacy prepares four doses from 480  $\mu\text{g}$  vials sufficient for 4 days therapy at 120  $\mu\text{g}$  per day; i.e., approximately 60 to 70  $\mu\text{g}/\text{m}^2$ , depending on the size of the patient.

To date, little information has been published on the clinical effect of low-dose rhG-CSF in the North American patient population. This study was designed to evaluate the benefits of low-dose rhG-CSF in patients treated with this regimen in Saskatchewan. Benefit was defined as a decrease in the degree or duration of neutropenia, the number of hospital admissions, the number of days spent in hospital for infectious complications, the use of antibiotics for treatment of prophylaxis, and chemotherapy dosage reductions or treatment delays due to initial neutropenia or complications.<sup>1-16</sup>

## METHODS

### A. Patients

All patients who received low-dose rhG-CSF as defined above from either the SCC or the Allan Blair Cancer Centre (ABCC) between April 1992 and April 1993 were included in this study. Patients were excluded from the study if they had not completed at least two consecutive cycles of chemotherapy, however, descriptive information for all patients is presented. Patient characteristics include age, sex, diagnosis, stage of disease, performance status (ECOG 0-4/4)<sup>†</sup> and chemotherapy treatment.

### B. Study Design

Data were collected retrospectively from inpatient and outpatient charts in all cases. In order to evaluate the use

of low-dose rhG-CSF, chemotherapy treatment with rhG-CSF was compared to chemotherapy treatment without rhG-CSF, each patient was used as his/her own control.

### C. Endpoints

The effect of rhG-CSF on myelosuppression was determined by comparing the treatment cycle prior to intervention with rhG-CSF with the first treatment cycle with rhG-CSF, to minimize the cumulative effect of repeated cycles of chemotherapy.<sup>3</sup> The degree and duration of neutropenia, measured by absolute neutrophil count (ANC) < 1.0 × 10<sup>9</sup> neutrophils/L and ANC < 0.5 × 10<sup>9</sup> neutrophils/L, were determined.

Each patient was also evaluated to determine the number of days hospitalized due to infectious complications including febrile neutropenia, requirement for treatment or prophylaxis with antibiotics, chemotherapy dosage changes, and delay in all chemotherapy treatments both with and without rhG-CSF. Toxicities of rhG-CSF were recorded as documented in the patient's chart.

### D. Cost Savings

The use of low-dose rhG-CSF was compared to standard-dose rhG-CSF only with respect to drug cost. Total body weight was used to determine the dose of rhG-CSF that a patient would have received in a standard-dose regimen. It was assumed that patients would have received the same number of days of rhG-CSF treatment regardless of the rhG-CSF regimen used. Hospital stay and antibiotic use were included with drug cost in the comparison between low-dose rhG-CSF and no rhG-CSF.

### E. Statistical Analysis

Comparisons were made between rhG-CSF and non-rhG-CSF cycles of treatment. The degree and duration of neutropenia, the number of days hospitalized for infectious complications, the number of days of antibiotic use (either as treatment or prophylaxis), the number of days delay in chemotherapy treatment and the number of chemotherapy dosage changes were compared using a two-tailed paired t-test. Differences were considered statistically significant when  $p \leq 0.05$ . Dose intensity was calculated as the ratio of administered dose to planned dose in  $\text{mg}/\text{m}^2/\text{treatment cycle}$ . At the end of this study, data were used to estimate the number of patients needed for a prospective study.

## RESULTS

Characteristics of the patients treated with low-dose rhG-CSF are described in Table I. Three males and seven females with a median age of 37.5 years were reviewed for this study. Eight were treated at the SCC and two patients at the ABCC. The dose of rhG-CSF ranged

<sup>†</sup> ECOG, Eastern Cooperative Oncology Group, on a scale of 0 to 4 out of 4.

from 1.46 µg/kg/day to 2.44 µg/kg/day for all patients (Table II).

Four patients were excluded from statistical analysis. Patients G and H died due to their disease before completing the first treatment cycle. Patient I received standard-dose rhG-CSF for three cycles prior to receiving low-dose rhG-CSF and, therefore, was excluded from further evaluation. Patient J had incomplete bloodwork that precluded assessment of the ANC nadir.

The effects of rhG-CSF on the degree and duration of chemotherapy-induced neutropenia in six patients over six cycles with and without rhG-CSF were evaluated (Table III). The degree of neutropenia for treatment cycles without rhG-CSF (i.e., mean nadir of the ANC) was similar to those with rhG-CSF [paired t-test,  $p > 0.05$ ]. The duration of neutropenia below an  $ANC < 1.0 \times 10^9$  neutrophils/L and  $ANC < 0.5 \times 10^9$  neutrophils/L was significantly greater for cycles without rhG-CSF as to those with rhG-CSF [paired t-test, 11.6 days versus 3.3 days, 6.7 days versus 0.6 days;  $p < 0.5$ ]. For treatment cycles without rhG-CSF

**Table I: Patient Characteristics**

Patient	Age	Sex (M/F)	Diagnosis	Stage	PS <sup>3</sup>	Drug Treatment
A	54	M	? extra-gonadal germ-cell tumour	n/a <sup>4</sup>	2	CDDP/VP-16 <sup>5</sup>
B	82	F	Ovarian	3	2	Carbo/Cyclo <sup>6</sup>
C	31	M	Testicular	1	0	CDDP/VP-16
D	33	F	Breast	1	0	CMF <sup>7</sup>
E	61	F	Non-Hodgkin's Lymphoma	4	1	CHOP/CytaBOM/ESHAP <sup>8</sup>
F	41	F	Breast	2	0	CMF
G <sup>1</sup>	34	F	Breast	2	0	FEC <sup>9</sup>
H <sup>1</sup>	46	M	Non-Hodgkin's Lymphoma	3	3	ESHAP
I <sup>2</sup>	27	F	Ewing's Sarcoma	n/a	n/a	VP-16/IFOS <sup>10</sup> /MESNA
J <sup>2</sup>	18	F	Rhabdomyosarcoma	2	0	CCG Protocol <sup>11</sup>

1 Deceased after one cycle of treatment

2 ABCC Patients

3 PS = Performance Status

4 n/a = not available

5 CDDP = Cisplatin, VP-16 = Etoposide

6 Carbo = Carboplatin, Cyclo = Cyclophosphamide

7 CMF = Cyclophosphamide, Methotrexate, 5-Fluorouracil

8 CHOP = Cyclophosphamide, doxorubicin, vincristine, and prednisone

CytaBOM = Cytarabine, bleomycin, vincristine, and methotrexate

ESHAP = Cisplatin, Cytarabine, Etoposide

9 FEC = 5-Fluorouracil, Epirubicin, Cyclophosphamide

10 IFOS = Ifosfamide

11 CCG Protocol = Vincristine, doxorubicin, cyclophosphamide, MESNA, ifosfamide, and etoposide

**Table II: Cost Comparison between Low-Dose rhG-CSF and Standard-Dose rhG-CSF**

Patient	Weight (kg)	Dose (µg) of rhG-CSF dispensed per kg	# of Doses rhG-CSF Dispensed per patient	Cost of Low-Dose rhG-CSF Dispensed per patient (\$)	Projected Cost of Standard-Dose rhG-CSF per patient <sup>2</sup> (\$)
A	49.0	2.44	6	300.00	612.50
B	79.5	1.50	31	1600.00	5134.38
C	82.0	1.46	20	1000.00	3416.67
D	62.8	1.91	51	2550.00	6672.50
E	61.3	1.95	36	1800.00	4597.50
F	69.7	2.30	21	1800.00	3049.37
G <sup>1</sup>	54.5	2.20	6	300.00	681.25
H <sup>1</sup>	75.0	1.60	12	600.00	1875.00
I	48.3	2.48	20	1026.00	2064.83
J	55.0	1.80	32	1374.84	3666.67
Total			235	12350.84	31770.67
Savings with Low-Dose rhG-CSF			19419.83		

1 Patient deceased after one cycle of treatment

2 Projected cost of rhG-CSF is based on patient's weight (kg), dose = 5 µg/kg and 1993 cost of rhG-CSF which is \$205.20 per 480 µg vial

the percentage of time with an ANC  $<1.0 \times 10^9$  neutrophils/L and ANC  $<0.5 \times 10^9$  neutrophils/L was significantly greater than when rhG-CSF was added [paired t-test, 40.4% versus 14.5%, 23.6% versus 2.8%,  $p < 0.05$ ].

The effects of rhG-CSF on the sequelae of chemotherapy-induced neutropenia are listed in Table IV. In two patients without rhG-CSF support, hospitalization and IV antibiotics for infectious complications of neutropenia were required. Patient cycles where rhG-CSF was not used did not result in a significantly greater number of days in hospital or a greater number of days of IV antibiotic therapy. The IV antibiotics used in hospital included tobramycin, piperacillin and cefotaxime. The need for prophylactic oral antibiotics, outside of the hospital, was significantly greater in patients where rhG-CSF was not employed [paired t-test, 9.2 days versus 0 days;  $p < 0.001$ ]. The antibiotics used for prophylaxis were Septra® and cephalexin. Chemotherapy treatment delay for patient cycles without rhG-CSF was greater than with rhG-CSF [paired t-test, 10.8 days versus 1.3 days;  $p < 0.05$ ]. With respect to administering a planned dose of chemotherapy, there was no apparent effect of the use of rhG-CSF on dosage reductions or dosage increases.

Toxicities attributable to rhG-CSF were evident in two patients. These included complaints of bone pain (two patients) and migraine headaches (one patient). Migraine headaches have not previously been reported as an adverse effect of rhG-CSF and no definite relationship could be established between the injections of rhG-CSF and the headaches.

There was no significant difference in the total cost of treatment cycles for six patients treated with rhG-CSF or without rhG-CSF (\$8,031.07 versus \$9,050.00). The largest cost for patients not treated with rhG-CSF was the cost of hospitalization. Other costs to those patients treated without rhG-CSF include the costs of IV antibiotics and oral antibiotics. No hospitalizations or use of antibiotics occurred in the rhG-CSF treated cycles, therefore, cost for rhG-CSF treated cycles only includes the drug cost (Table IV). For the total of 235 doses of low-dose rhG-CSF administered compared to standard-dose rhG-CSF, the cost saving was estimated to be \$19,419.83 for the ten patients. The cost of using standard doses of

**Table III: Summary of the Degree and Duration of Chemotherapy-Induced Neutropenia<sup>1</sup>**

Parameter	Treatment cycle without rhG-CSF <sup>2</sup>	Treatment cycle with rhG-CSF <sup>2</sup>	Statistical Significance <sup>3</sup>
Degree of Neutropenia (Mean Nadir ANC $\times 10^9$ /L)	0.37 (0.02 to 0.9)	1.24 (0.22 to 3.56)	NS
Mean Duration of Neutropenia per cycle (days ANC below $1.0 \times 10^9$ /L)	11.6 (2.1 to 21.8)	3.3 (0 to 9.5)	$p < 0.02$
Mean Duration of Neutropenia per cycle (days ANC below $0.5 \times 10^9$ /L)	6.7 (0 to 13.7)	0.6 (0 to 2.1)	$p < 0.05$
Mean Percentage of Time patients are neutropenic per cycle (ANC below $1.0 \times 10^9$ /L)	40.4% (3.3 to 68.1)	14.5% (0 to 39.6)	$p < 0.05$
Mean Percentage of Time patients are neutropenic per cycle (ANC below $0.5 \times 10^9$ /L)	23.6% (0 to 42.8)	2.8% (0 to 10.0)	$p < 0.05$

1 Six patients were evaluated with and without rhG-CSF for the degree, duration and severity of neutropenia. The degree of neutropenia is reported as the median nadir for each cycle. The duration of neutropenia is reported as the average duration of neutropenia per cycle and as the percentage of time that patients are neutropenic per cycle. The severity of neutropenia is ranked as moderate if neutrophils are  $<1.0 \times 10^9$ /L and severe if neutrophils  $<0.5 \times 10^9$ /L.

2 Range appears in parenthesis.

3 Probability values from paired t-test, NS = not statistically significant,  $p > 0.05$ .

rhG-CSF would have been \$31,770.67, compared to \$12,350.84 for the low-dose rhG-CSF actually dispensed, a cost saving of 61% (Table II).

## DISCUSSION

This evaluation suggests that low-dose rhG-CSF is useful in alleviating sequelae of chemotherapy-induced neutropenia. The patient population was a nonrandomized selected group of individuals with varied diagnoses who received rhG-CSF after demonstrating prior significant hematological toxicities from chemotherapy. No patient received rhG-CSF prophylactically unless they had demonstrated significant toxicity by requiring hospitalization for febrile neutropenia, or having severe or prolonged neutropenia causing delay in chemotherapy treatment.

A number of studies have found statistically significant reductions in the degree and duration of neutropenia with use of rhG-CSF.<sup>1-8,10,12</sup> Although our patients did not show a significant difference in the degree of neutropenia (Table III), there was a trend in favour of rhG-CSF. Other studies using low-dose rhG-CSF in larger numbers of patients have shown a statistically significant reduction in the degree of neutropenia associated with chemotherapy.<sup>1,3,5</sup> Many published studies of both low-dose and standard-dose rhG-CSF have demonstrated a reduced duration of neutropenia, as did we (Table III).<sup>1-5,12</sup>

Prevention of infectious sequelae of chemotherapy-induced neutropenia has been a major benefit of rhG-CSF therapy. There were no hospitalizations and no IV

**Table IV: Summary of Sequelae and Associated Costs due to Chemotherapy-Induced Neutropenia<sup>1</sup>**

Parameter	Treatment without rhG-CSF <sup>3</sup>	Treatment with rhG-CSF <sup>3</sup>	Statistical Significance <sup>5</sup>
# of patients evaluated (cycles)	6 (23)	6 (21)	—
Mean # of days of hospital stay per patient	2.3 (0 to 9)	0	NS
Mean # of days on IV antibiotics per patient	1.5 (0 to 6)	0	NS
Mean # of days on PO antibiotics per patient	9.2 (7 to 14)	0	p<0.001
Mean # of days delay in chemotherapy treatments per patient	10.8 (5 to 22)	1.3 <sup>4</sup> (0 to 8)	p<0.05
Mean # of chemotherapy dosage reductions per patient <sup>1</sup>	0.3	0.3	NS
Mean # of chemotherapy dosage increases per patient <sup>1</sup>	0	0.3	NS
Total cost of IV antibiotics	\$278.98	0	
Total cost of PO antibiotics	\$77.09	0	
Total cost of Hospital Stay <sup>2</sup>	\$7675.00	0	
Cost of rhG-CSF (low-dose)	—	\$9050.00	
Total	\$8031.07	\$9050.00	

1 A dosage reduction was considered to be a decrease in dose intensity below 1 whereas an increase in the dose was only considered to happen if the dose intensity was greater than 1. Dose intensity was calculated as the ratio of the dose administered to the dose that was planned in mg/m<sup>2</sup>/treatment cycle.

2 Cost for Hospital stay per diem = \$635.00.

3 Range appears in parenthesis.

4 One cycle was delayed after 3 consecutive cycles of rhG-CSF where the dose had been increased consecutively on all 3 cycles.

5 Probability values from paired t-test, NS = not statistically significant, p>0.05.

or PO antibiotic drug use required for patients that received low-dose rhG-CSF in this study. Although the difference in hospitalizations is not statistically significant, the costs for those few patients who were hospitalized resulted in rationalization of the cost of use of low-dose rhG-CSF for patients A to F (Table IV). As an independent evaluation, it was important to confirm that reductions in these sequelae yielded not only a cost-saving to the health care system but also an increase in the benefits to the patient. To our knowledge, no study using low-dose rhG-CSF has reported a direct benefit in terms of decreased hospital stay and IV or PO antibiotic use.<sup>1,3,5</sup>

The ability to administer chemotherapy treatments without dosage reductions or delay is important to optimize response to chemotherapy.<sup>6</sup> The capability to administer higher doses of chemotherapy and to deliver treatments on time has been reported in several studies using the low-dose regimen.<sup>1,13-16</sup> Although we were unable to show any difference in either dose reductions or increases in our study, we were able to demonstrate a statistically significant reduction in

treatment delays when rhG-CSF was used compared to no rhG-CSF (Table IV).

Statistical significance was not achieved with some of the desired endpoints: degree of neutropenia (nadir), days of hospitalization, days of IV antibiotic use, chemotherapy dosage reductions and dosage increases. Based on data in this study, the number of patients needed to detect a 50% difference would be approximately 16 for the degree of neutropenia, 32 for the number of days of hospitalization and IV antibiotic therapy, and 98 for the number of dosage increases. This will take approximately three years assuming the same rate of utilization of rhG-CSF in the future at the SCC.

Budgetary realities are forcing more responsible utilization of expensive pharmaceutical agents. With rhG-CSF, this means that the drug is being used for patients who have docu-

mented prior significant toxicity to chemotherapy. By utilizing the lower dose of rhG-CSF, the cost savings for our institution was \$19,419.83 and therapeutic benefits have been demonstrated in all patients evaluated so far, with hospitalizations, antibiotic use, degree and duration of neutropenia, and chemotherapy treatment delays. Further data will have to be collected in order to determine if there is any benefit in terms of survival. A prospective study should be undertaken to compare low-dose rhG-CSF and standard-dose rhG-CSF to confirm equivalent benefit. ☒

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