

## GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) PREVENTS DOSE-LIMITING NEUTROPENIA IN LYMPHOMA PATIENTS RECEIVING STANDARD DOSE CHEMOTHERAPY

Gianpietro Dotti, Carmelo Carlo Stella, Lina Mangoni, Luca Cottafavi, Cecilia Caramatti, Camillo Almici, Vittorio Rizzoli

Department of Hematology, Bone Marrow Transplantation Unit, University of Parma, Parma, Italy

### ABSTRACT

In this study, nine patients with non-Hodgkin's lymphoma (n=6) and Hodgkin's disease (n=3) receiving different cytotoxic chemotherapy regimens were given granulocyte colony-stimulating factor (G-CSF) (5  $\mu$ g/kg/day) from 48 hours after the end of chemotherapy to 48 hours before the next chemotherapy administration. The decrease in mean absolute neutrophil counts (ANC) and in mean platelet (Plt) counts was not significant when pre-therapy counts were compared with post-therapy ones ( $p < 0.375$  and  $p > 0.4$ , respectively). The mean actual dose intensity was 92% (range 68-100%). G-CSF treatment after chemotherapy reduces neutropenia and permits administration of the full chemotherapy program. A wash-out period between G-CSF treatment and chemotherapy administration is needed to prevent the detrimental effect of chemotherapy on leukocyte and platelet recovery when repeated cycles of cytotoxic drugs and G-CSF are administered.

Key words: G-CSF, non-Hodgkin lymphoma, Hodgkin's disease, standard-dose chemotherapy

Standard-dose chemotherapy is the first-line therapy for patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD).<sup>1,2</sup> The concept of dose intensity (as the amount of drug given for unit time) has gained credence as a critical factor in the outcome of treatment.<sup>3</sup>

The definition of dose intensity implies that both delay in drug administration and dose reduction influence dose intensity in the same way. Neutropenia is the most important cause of delay in chemotherapy administration and of dose reduction. Moreover, infections secondary to neutropenia represent the most important cause of death in patients undergoing chemotherapy.<sup>4</sup>

Human recombinant granulocyte colony-stimulating factor (G-CSF) administered *in*

*vivo* induces a dose-dependent increase in circulating neutrophils.<sup>5</sup> G-CSF given after cytotoxic chemotherapy could provide protection from neutropenia-related infections and allow increases in dose intensity. However, G-CSF, by promoting proliferation of hematopoietic progenitor cells, may increase their sensitivity to cytotoxic drugs and thus increase the risk of severe leuko-thrombocytopenia when repeated cycles of chemotherapy plus G-CSF are delivered.<sup>6</sup> In order to prevent hematopoietic toxicity due to detrimental effects on regenerating progenitors, G-CSF should be optimally combined with chemotherapy.

It was the aim of the present study to evaluate the effect on leukocyte and platelet counts of G-CSF given in conjunction with repeated chemotherapy courses.

Correspondence: Prof. Vittorio Rizzoli, Cattedra di Ematologia, Centro Trapianti di Midollo Osseo, Università di Parma, via Gramsci 14, 43100 Parma, Italy. Tel. international +39.521.290787. Fax. international +39.521.292765.

Acknowledgments: this work was supported in part by grants from Consiglio Nazionale delle Ricerche (PF A.C.R.O.), Associazione Italiana per la Ricerca sul Cancro (AIRC, Milano) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, 40%-60%)

Received September 1, 1994; accepted January 23, 1995.

## Patients and Methods

### Patients

Nine patients (6 males and 3 females) aged between 18 and 60 years (median 45 years) with histologically documented NHL (n=6) and HD (n=3) were enrolled in this study. The characteristics of the patients are detailed in Table 1.

### Treatment

Patients with NHL were treated with the CEMP or VACOP-B regimens, while HD patients received the MOPP-ABV regimen (Table 1). A total of 84 chemotherapy cycles were administered in the nine patients. G-CSF, at a dose of 5 µg/kg/day administered as a daily single subcutaneous injection, was started 48 hours after the end of each chemotherapy cycle and discontinued 48 hours before the subsequent chemotherapy treatment. All patients received prophylactic ciprofloxacin 500 mg twice daily and fluconazol 50 mg twice daily. Doxorubicin, cyclophosphamide, etoposide, mitoxantrone, mechlorethamine and procarbazine dosages were reduced by 50% if the

absolute neutrophil count (ANC) on the planned day of treatment was  $>0.5 \times 10^9/L$  and less than  $1.0 \times 10^9/L$ , or if the platelet count (Plt) was  $>60 \times 10^9/L$  and less than  $90 \times 10^9/L$ . If on the planned day of treatment the ANC was less than  $0.5 \times 10^9/L$  or Plt less than  $20 \times 10^9/L$ , chemotherapy was delayed by 7 days. Patients with bone marrow infiltration by lymphoma received 100% of the dose independently of leukocyte and platelet counts.

### Study procedures

On the day planned for the start of chemotherapy, all patients underwent a full blood count including differential, and a biochemical profile evaluation including creatinine and liver function test. World Health Organization (WHO) criteria were used to evaluate toxicity. Chemotherapy dose analysis was performed utilizing the actual dose intensity expressed as a percentage of standard dose intensity.<sup>3,7</sup> Response was evaluated in accordance with standard recommendations.<sup>8</sup>

### Statistical analysis

Analysis was performed with the chi-square test to evaluate statistical significance.

Table 1. Characteristics of the patients included in the study.

Case	Age/Sex	Histology	Status prior to treatment	Stage	Treatment
1	39/F	LnH c.c. <sup>a</sup>	Progression	IV*	CEMP <sup>d</sup>
2	60/F	LnH c. <sup>b</sup>	Recurrence	III	CEMP
3	35/M	LnH c.	Presentation	III	CEMP
4	48/M	LnH c.c.	Progression	III	CEMP
5	52/M	LnH c.c.	Progression	IV*	VACOP-B <sup>e</sup>
6	48/M	LnH c.c.	Presentation	III	VACOP-B
7	59/F	HD n.s. <sup>c</sup>	Presentation	III	MOPP-ABV <sup>f</sup>
8	18/M	HD n.s.	Presentation	IV*	MOPP-ABV
9	48/M	HD n.s.	Presentation	III	MOPP-ABV

<sup>a</sup>c.c.: centrocytic/centroblastic diffuse; <sup>b</sup>c.: centroblastic diffuse; <sup>c</sup>n.s.: nodular sclerosis; <sup>d</sup>CEMP: cyclophosphamide 650 mg/m<sup>2</sup> iv day 1, etoposide 150 mg/m<sup>2</sup> iv day 1, mitoxantrone 12 mg/m<sup>2</sup> iv day 1 and prednisone 60 mg/m<sup>2</sup> orally (po) for 5 days; <sup>e</sup>VACOP-B: doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 350 mg/m<sup>2</sup> iv weeks 1,5, and 9, oncovin 1.2 mg/m<sup>2</sup> and bleomycin 10 U/m<sup>2</sup> iv weeks 2, 4, 6, 8, 10 and 12, etoposide 50 mg/m<sup>2</sup> iv and 100 mg/m<sup>2</sup> po and doxorubicin 50 mg/m<sup>2</sup> iv weeks 3, 7 and 11, prednisone 45 mg/m<sup>2</sup> po for 12 weeks; <sup>f</sup>MOPP-ABV: mechlorethamine 6 mg/m<sup>2</sup> and oncovin 1.4 mg/m<sup>2</sup> iv day 1, procarbazine 100 mg/m<sup>2</sup> po for 7 days, prednisone 40 mg/m<sup>2</sup> po for 14 days, doxorubicin 35 mg/m<sup>2</sup>, bleomycin 10 U/m<sup>2</sup> and vinblastine 6 mg/m<sup>2</sup> iv on day 8.

\*bone marrow involvement

## Results

**ANC.** The mean ANC at the beginning of the first and the last chemotherapy cycles were  $4.5 \times 10^9/L$  (range  $2.5-6.7 \times 10^9/L$ ) and  $4.1 \times 10^9/L$  (range  $1.4-6.3 \times 10^9/L$ ), respectively (Table 2). The decrease in mean ANC was not significant ( $p < 0.375$ ). In the 84 cycles performed during this study, WHO grade III neutropenia was observed in 6 cycles (7%) and grade IV in 7 cycles (8%). During G-CSF administration increases in circulating myelocytes, metamyelocytes and monocytes were observed.

**Platelets.** The mean Plt counts at the beginning of the first and the last chemotherapy cycles were  $261 \times 10^9/L$  (range  $192-338 \times 10^9/L$ ) and  $251 \times 10^9/L$  (range  $104-566 \times 10^9/L$ ), respectively (Table 2). The decrease in mean Plt counts was not significant ( $p > 0.4$ ). In the 84 cycles performed during this study, WHO grade II thrombocytopenia was observed in 7 cycles

Table 2. Mean absolute neutrophil counts (ANC), platelet counts (Plt) and hemoglobin levels (Hb) before the first and last cycles of chemotherapy. Delays in chemotherapy administration and actual dose intensity are shown for each patient.

#	Before first cycle			Before last cycle			Delay (days)	Actual dose intensity (%)
	ANC (x10 <sup>9</sup> /L)	Plt (x10 <sup>9</sup> /L)	Hb (g/dL)	ANC (x10 <sup>9</sup> /L)	Plt (x10 <sup>9</sup> /L)	Hb (g/dL)		
1	2.5	192	13.8	1.4	223	10.5	0	100
2	4.5	309	13.7	3.0	566	10.4	0	100
3	4.5	320	16.0	3.4	254	11.4	0	92
4	3.9	338	13.7	3.4	104	10.6	0	100
5	4.8	236	15.6	5.5	271	9.2	32	68
6	4.8	236	15.4	5.5	271	9.9	2	98
7	6.7	203	10.9	3.7	131	8.7	7	96
8	4.3	236	11.3	6.3	172	9.8	13	93
9	4.8	279	13.5	5.2	270	9.9	7	82
M	4.5	261	13.8	4.1*	251*	10.0 <sup>#</sup>	7	92
R	2.5-6.7	192-338	10.9-16.0	1.4-6.3	104-566	8.7-11.4	0-32	68-100

M: mean. R: range.

\*not significantly different when compared to pre-therapy values ( $p < 0.375$ ). <sup>o</sup>not significantly different when compared to pre-therapy values ( $p > 0.4$ ). <sup>#</sup>significantly different when compared to pre-therapy values ( $p < 0.0005$ ).

(8%) and grade III in 1 cycle (1%). In the 84 cycles performed thrombocytopenia caused a delay or a dose reduction in two cycles. No patient required Plt transfusion for thrombocytopenia.

**Hemoglobin (Hb) count.** The mean Hb counts at the beginning of first and last chemotherapy cycles were 13.8 g/dL (range 10.9-16 g/dL) and 10 g/dL (range 8.7-11.4 g/dL), respectively (Table 2). The decrease in mean Hb counts was significant ( $p < 0.0005$ ). Despite the significant decrease in mean Hb counts in the 84 cycles, none of the patients required blood transfusions for WHO grade III or IV anemia.

**Chemotherapy dose analysis.** The mean actual dose intensity was 92% (range 68-100%). An actual dose intensity  $> 90\%$  was given in 78% of patients. Dose reduction and/or therapy delay for leukopenia and/or thrombocytopenia occurred in two patients (cases 3 and 5). Patient number 5, despite G-CSF administration, experienced a total delay of 32 days. However, this patient had been previously treated with other cycles of chemotherapy. Patient #8 suffered a

delay of 13 days for herpes zoster infection at the time of the second cycle of chemotherapy. Patient #9 received G-CSF only at the end of the third cycle. Before G-CSF administration this patient had required a delay of 7 days for leukopenia, but following G-CSF the same patient experienced no further leukopenia-related delays.

**Infection.** Despite severe neutropenia in 7 cycles, no one experienced fever (temperature  $> 37.5^{\circ}\text{C}$  for 1 hour) or documented infection requiring intravenous antibiotics and hospitalization.

**Safety of G-CSF administration.** G-CSF was well tolerated. No patient required transfusion support. No increased incidence of WHO grade III and IV mucositis was experienced, and no changes in biochemical profile were detected.

**Tumor response.** Seven patients (78%) achieved complete remission, while two (22%) suffered disease progression.

## Discussion

Patients with NHL and HD treated with different combinations of drugs at conventional dosages rarely receive 100% of the planned doses and neutropenia is the most important factor negatively affecting the planning schedule. G-CSF administered after chemotherapy significantly reduces the severity of neutropenia and the incidence of infections.<sup>9</sup> In a recent randomized study, G-CSF not only prevented neutropenia but allowed the full dose of cytotoxic drugs to be delivered without delays.<sup>10</sup>

The timing of G-CSF administration in relation to chemotherapy is still controversial. Kinetic studies have shown that the proliferation status of progenitor cells significantly increases within 48-72 hours of G-CSF treatment.<sup>11,12</sup> After discontinuance of colony stimulating factors (CSFs), progenitor cells become quiescent within 48-96 hours.<sup>12</sup> In addition, several data support the effect of G-CSF on multipotential progenitors *in vivo*.<sup>6</sup> Proliferating progenitor cells are more sensitive to cytotoxic drugs and thus their proliferative status places them at increased risk of massive depletion, primarily when repeated cycles of chemotherapy

and G-CSF are administered. These data suggest that a *wash-out* period between chemotherapy and G-CSF administration is necessary in order to prevent the detrimental effect of chemotherapy on actively proliferating progenitors.<sup>13</sup>

In our study we began giving G-CSF 48 hours after chemotherapy and stopped 48 hours before the subsequent chemotherapy treatment. Using this schedule we found no detrimental effect on neutrophil recovery in 84 cycles except for one patient (#5) who had previously received extensive chemotherapy. The mean decrease in ANC and Plt counts, when pre-therapy and post-therapy counts are compared, was not significant ( $p < 0.375$  and  $p > 0.4$ , respectively).

Due to the high cost of CSF therapy and the existence of a peak leukocyte count (data not reported), the *wash-out* period between G-CSF and chemotherapy should be adapted to each chemotherapy schedule. In particular, when the regimen is based on a 2-3-week interval between cycles and the leukocyte count nadir cannot be predicted, G-CSF should be administered close to the nadir. In contrast, when chemotherapy schedules are based on weekly administrations and the leukocyte count nadir can not be predicted, our schedule of a 48-hour interval between G-CSF and chemotherapy is recommended.

According to randomized trials, chemotherapy and G-CSF administration are able to induce an increase in dose intensity.<sup>10</sup> A recent study in this journal has shown that G-CSF can allow dose intensification even in patients with resistant myeloma.<sup>14</sup> Whether or not this increase will have a clinical effect is still controversial. Although the number of patients included in this study is rather small, on the basis of our results we believe that every attempt to intensify chemotherapy by using CSF even in the standard dose setting, must take into account the

timing of CSF treatment. A *wash-out* period between CSF treatment and chemotherapy is necessary to prevent detrimental effects on myelopoiesis as well as thrombopoiesis.

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