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ORIGINAL ARTICLE

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Two different schedules for integrating filgrastim as adjuvant therapy in the treatment of patients with advanced stage Hodgkin's lymphoma receiving MOPP/ABV hybrid chemotherapy

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Abstract *Purpose*: Management of advanced-stage Hodgkin's disease with a MOPP/ABV hybrid regimen (mechlorethamine, vincristine, procarbazine, prednisone, Adriamycin, bleomycin and vinblastine) has yielded a high complete response rate (75–85%). However, myelosuppression can limit delivery of treatment. Filgrastim has been shown to reduce chemotherapy-related neutropenia and allow for on-time administration of planned doses of chemotherapeutic agents. The objective of this study was to find the best way to integrate filgrastim with the MOPP/ABV hybrid regimen. *Methods*: Enrolled in this study were 24 patients (aged 18–52 years) with newly diagnosed, histologically documented Hodgkin's disease. In schedule I, patients received filgrastim (5 μg/kg s.c. daily) beginning on day 9, 24 h after administration of ABV. In schedule II, patients received filgrastim concomitantly with procarbazine on days 2–7 (starting 24 h after day-1 MOPP administration and stopping 24 h before ABV administration) as well as after ABV beginning on day 9. Filgrastim after ABV administration was administered until two consecutive ANC readings of 10×10^9/l were achieved. *Results*: All patients were able to complete all six cycles of therapy. There was a trend to fewer dose reductions in schedule II (0.76%) as compared to schedule I (4.2%) with a *P*-value of 0.077 (chi-squared test). Specifically, 11.6% of MOPP courses and 5.5% of ABV courses were dose-reduced in schedule I versus 1.7% and 1.4%, respectively, in schedule II. *Conclusion*: In conclusion, filgrastim was effective in supporting the delivery of the MOPP/ABV chemotherapy. Concomitant administration of filgrastim with procarbazine (days 2–7) appears to be safe and allows the maximum dose intensity of this therapy.

Key words Hodgkin's lymphoma · Growth factors · Chemotherapy

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Introduction

The majority of patients with advanced Hodgkin's disease are curable with multiagent chemotherapy or with a combination of multiagent chemotherapy and radiotherapy. A number of factors correlate as single variables for complete remission (CR), such as B symptoms, stage, number of extranodal sites and involvement of bone marrow. However, there is also a significant

association between the drug dose delivered during the first three cycles of mechlorethamine-vinestine-procarbazine-prednisone (MOPP) chemotherapy and the achievement of CR [1]. The achievement of an early response to chemotherapy in advanced-stage Hodgkin's disease is also an important issue, because survival and disease-free survival are significantly better for patients who achieve CR in the first three cycles of chemotherapy as opposed to those who enter CR at a later stage of therapy [6]. It has also been shown that besides the tumor characteristics, the optimal dose of MOPP chemotherapy is of great importance for survival in the treatment of Hodgkin's disease [10].

A phase I-II study evaluating the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with Hodgkin's disease has shown that it can be administered safely and results in improved hematologic recovery after MOPP chemotherapy [3]. The full dose can be administered on time, resulting in increased overall tolerated dose of myelosuppressive drugs when compared to historical controls. Although the use of CSFs appears to result in less morbidity and hospitalization from chemotherapy administration, it has not been shown to augment the deliverable dose intensity or to result in an improvement in survival. The administration of filgrastim for maintaining dose intensity during conventional dose chemotherapy with Adriamycin, bleomycin, vinblastine, decarbazine (ABVD) in Hodgkin's disease has been shown to significantly lower the incidence of cycle delays and improve dose intensity delivery [11]. However, it has been observed that concurrent administration of CSFs such as G-CSF or GM-CSF with cytotoxic agents can increase the pools of precursors susceptible to destruction by chemotherapeutic agents and paradoxically enhance hematologic toxicity [9].

This multicentre open-label randomized controlled trial is the first study designed to gain experience with the integration of filgrastim in the standard dose MOPP-Adriamycin-bleomycin-vinblastine (MOPP/ABV) hybrid chemotherapy regimen for the treatment of newly diagnosed advanced Hodgkin's disease [5]. MOPP/ABV hybrid chemotherapy has been shown to be a highly effective program for the treatment of advanced Hodgkin's disease [2]. Our objective was to evaluate two different ways of integrating filgrastim in the MOPP/ABV hybrid regimen with respect to the ability to support planned doses given on time. The primary outcomes were the number of cycles given without dose reduction or dose delays and the number of cycles completed, and the secondary outcomes were the incidence of adverse events, duration of grade III and IV neutropenia and frequency of hospitalization.

Patients and methods

This was a phase II open-label controlled multicentre study evaluating two different schedules of integrating filgrastim into the standard dose MOPP/ABV hybrid chemotherapy regimen, where the primary endpoint was the planned delivery of chemotherapy given on time, administered on a 28-day schedule for up to six cycles. After providing signed informed consent, 24 patients were equally randomized to one of the two schedules shown in Fig. 1. In schedule I, filgrastim was administered 24 h after ABV (day 9) up to 24 h before the end of the cycle (day 27) or until the absolute neutrophil count (ANC) was 10×10^9/l or greater on two consec-

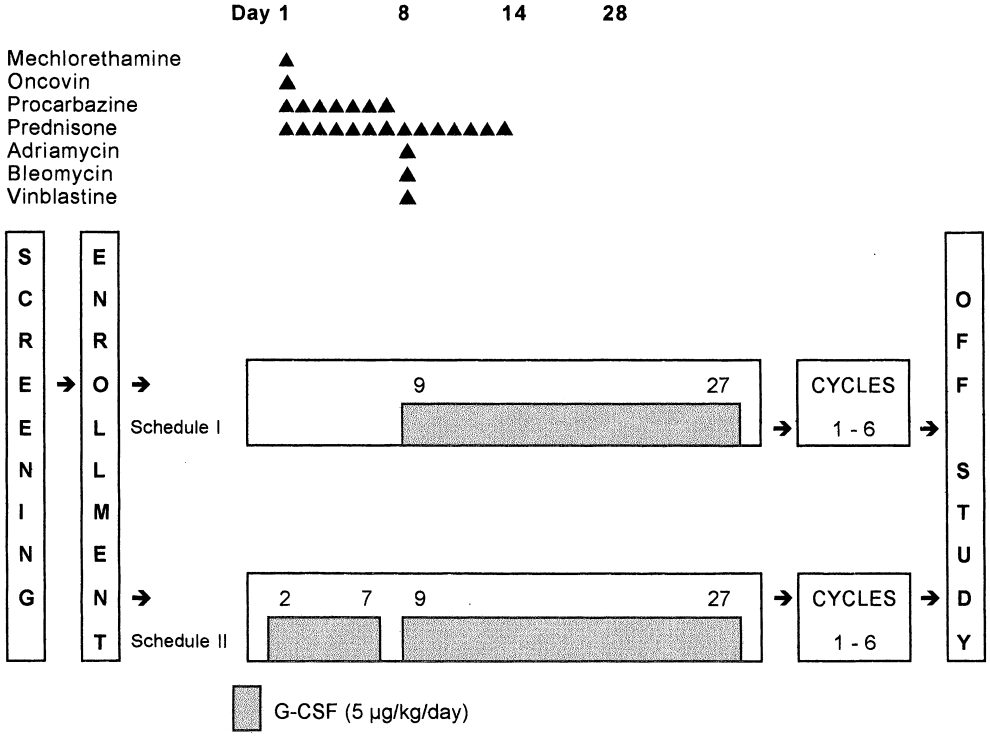

Fig. 1 Study schema

utive occasions at least 24 h apart. In schedule II, filgrastim was administered 24 h after initiation of MOPP (day 2) up to 24 h before ABV (day 7) and from 24 h after ABV (day 9) up to 24 h before the end of the cycle (day 27) or until the ANC was 10×10^9/l or greater on two consecutive occasions at least 24 h apart. The inclusion criteria were as follows: patients with histologically documented stage IIB, IIIA, IIIB, IVA or IVB Hodgkin's lymphoma (Costwolds classification) [7], with no current or other previous malignancy, with no previous radiotherapy, with Karnofsky performance status ≥60%, and with no clinical or bacterial evidence of infection. Patients should not have received lithium within 4 days of the study and no concurrent treatment with other CSFs, immunomodulators or investigational agents.

The dose of filgrastim was 5 μg/kg per day administered by single subcutaneous injection. Chemotherapy was administered as the full dose on day 1 if the ANC was greater than 1.6×10^9/l and the platelet count was greater than 125×10^9/l; for an ANC between 0.8 and 1.6×10^9/l or a platelet count between 75 and 125×10^9/l, a 50% dose reduction was made for mechlorethamine, procarbazine, doxorubicin and vinblastine. Finally, if the ANC and platelet counts were below 0.8×10^9/l or 75×10^9/l, respectively, chemotherapy was postponed for a week.

Informed consent was obtained from the patients after detailed explanation of the purpose of the study, the risks and discomfort involved and the potential benefits. All the analyses are descriptive except for dose delays and reductions where *P*-values and exact χ^2 values were calculated in order to determine statistical significance. The calculations for dose intensity, projected dose, percentage of projected dose and average of projected dose intensity were made according to the methods of Longo et al. [8]. Dose delays were calculated differently for MOPP and ABV. By definition, cycle 1 could not be delayed for MOPP. A MOPP delay was flagged if the difference between cycle start dates was greater than 29 days while an ABV delay was flagged if it was 9 days or more after MOPP. A dose reduction was defined as a dose that was reduced by at least 50% of the intended dose. The total duration of treatment was from the first day of cycle 1 to the final day of cycle 6.

Results

The clinical characteristics of the patients included in this study are shown in Table 1. Results for dose delays and reductions are shown in Tables 2 and 3. As shown in Table 2, there were five dose delays with MOPP chemotherapy on day 1 in both schedules. There was only one dose delay with ABV chemotherapy on day 8 of schedule II. The total numbers of dose delays for the two schedules were not significantly different. There were seven dose reductions on day 1 with MOPP chemotherapy in schedule I as opposed to only one in schedule II (Table 3). There were also four dose reductions on day 8 with ABV chemotherapy in schedule I as opposed to one in schedule II. The total number of dose reductions in schedule I was 11 (4.2%) compared with 2 (0.76%) in schedule II. This difference was of borderline significance with a chi-squared value of 3.41 and a *P*-value of 0.077.

There was no significant difference in the percentage of projected dose administered within each schedule and all patients completed the predicted number of cycles except one in schedule II who did not complete the six cycles because of documentation of CR after the third cycle. A total of eight complete responders and four partial responders were seen in schedule I, while nine complete responders and three partial responders were seen in schedule II.

Table 1 Patient characteristics

	Schedule I	Schedule II
Number of patients	12	12
Sex		
Male	6	9
Female	6	3
Age (years)		
Median	30.5	34.5
Range	18–52	19–50
Clinical stage		
IIB	3	5
IIIA	4	2
IIIB	2	3
IVA	2	1
IVB1	1	1

Table 2 Dose delays (*NS* not significant)

	Schedule I	Schedule II	*P*-value
Number of patients	12	12	–
Total number of cycles			
MOPP	60	59	–
ABV	72	71	–
Delays			
MOPP	5	5	NS
ABV	0	1	NS
Total	5	6	NS

Table 3 Dose reductions

	Schedule I	Schedule II	*P*-value
Number of patients	12	12	–
Total number of cycles			
MOPP	60	59	–
ABV	72	71	–
Delays			
MOPP	7	1	–
ABV	4	1	–
Total	11	2	0.077

Table 4 Days per cycle with ANC ≤ 0.5×10^9/l

	Schedule I (n = 12)	Schedule II (n = 12)
Cycle (28 days)		
1	3	1
2	2	3
3	0	1
4	0	1
5	2	3
6	6	5
Total Events	13	14
Total days of observation	2016	2016

To assess the relative myelotoxicity of the two schedules, we looked at the number of days per cycle with an ANC $< 0.5 \times 10^9$/l or with thrombocytopenia as defined by a platelet count below 50×10^9/l, and also at the transfusion requirements. A total of 13 days with neutropenia were recorded in schedule I and 14 days in schedule II (Table 4). Thrombocytopenia was seen only in one patient in schedule I, during cycles 5 and 6, and it lasted about 15 days each cycle; the same pattern was observed in one patient in schedule II. Packed red blood cells (PRBC) were transfused for hemoglobin below 80 g/l in three patients in each schedule (7 units were given to patients in schedule I and 13 units in schedule II). No major bleeding complications were encountered.

The number of admissions to hospital for treatment of complications were identical in both schedules. It should be underlined that hospitalization for patients in schedule I was not related to neutropenic events. It should also be stressed that none of the patients enrolled in schedule II, in which filgrastim was given concomitantly with procarbazine, experienced adverse events such as significant neutropenia.

Discussion

Although the role of CSFs such as GM- or G-CSF in preventing hematologic toxicity and in accelerating hematopoietic recovery after the administration of chemotherapy regimens such as MOPP, ABVD or cyclophosphamide, adramycin, vincrisline prednisone, (CHOP) has been evaluated in a number of studies, this is the first study designed to gain experience with the integration of filgrastim with the MOPP-ABV hybrid chemotherapy regimen. In the two schedules proposed for integrating filgrastim in this study, of major concern was the concomitant administration in schedule II of filgrastim with the cytotoxic agent procarbazine. Meropol et al. have reported that the concomitant administration of G-CSF and 5-FU could paradoxically induce grade IV neutropenia, suggesting that the concurrent administration of this cytokine with chemotherapy might be responsible for the increased toxicity [9]. Theoretically, administration of chemotherapy concomitantly with the recruitment of marrow progenitors by growth factors can be harmful to the progenitors and induce a grade IV neutropenia. Our study demonstrated that it is possible to administer filgrastim concomitantly with an agent such as procarbazine and not encounter untoward myelotoxicity. However a potential leukemogenic effect has been attributed to the association of procarbazine and mechlorethamine [4], and whether the recruitment of progenitors by filgrastim might potentiate this effect remains to be determined.

The percentages of projected dose, number of cycles completed by patients and dose delays were not statistically significantly between schedules. However, the difference ($P = 0.077$) between the dose reduction in schedule II compared with that in schedule I was of borderline significance, favoring schedule II. The degree of myelotoxicity was assessed in terms of the number of days with severe cytopenia and the extent of transfusion requirements, but the number of patients enrolled in the study did not allow a statistically meaningful conclusion regarding differences between the two groups. It should be underlined though that the degree of neutropenia during therapy was considered less than would normally be encountered with this chemotherapy without filgrastim. Although we cannot favor one schedule of administration over the other at this time, these data are the first reported to address the safety issue.

In conclusion, in our study, all patients supported by filgrastim were able to complete all cycles of therapy. Filgrastim can be safely administered concomitantly with procarbazine without associated induced acute toxicity. Whether or not the addition of filgrastim will result in a better response rate or survival or add a cost benefit cannot be answered by this study and would need a large randomized phase III study.

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