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Safety and efficacy of once-per-cycle pegfilgrastim in support of ABVD chemotherapy in patients with Hodgkin lymphoma

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ABSTRACT

The objective of this prospective study was to examine the safety and efficacy of pegfilgrastim in support of chemotherapy regimens that are administered every 14 d.

Patients with Hodgkin lymphoma receiving standard ABVD (doxorubicin, bleomycin, vinblastine, and decarbazine) chemotherapy every 14 d were eligible for the study. All patients received one fixed dose of 6 mg pegfilgrastim approximately 24 h after each ABVD infusion. Absolute neutrophil counts (ANCs) were measured weekly while on therapy. After completion of therapy, ANCs were measured every 3–4 months for 2 years, and every 6 months thereafter. Twenty-three patients received 115 courses (230 doses) of ABVD. Nadir ANC below 0.5×10^9/L was observed only in two cases (1.1%), and ANC counts on the day of ABVD therapy below 1×10^9/L was observed only once (0.4%). No neutropenic fever was observed. Two hundred and fifteen (93.5%) doses of ABVD were given on time as scheduled. Grade 3/4 bone pain was observed after 0.4% of ABVD doses, and bleomycin lung toxicity was observed in two patients. With a median follow-up of 29 months after completion of ABVD, no myelodysplastic syndrome was observed. Two patients relapsed and subsequently underwent successful stem cell collection and transplantation. Pegfilgrastim was found to be safe in support of ABVD chemotherapy that is administered every 14 d. Pegfilgrastim was also effective in maintaining ABVD dose intensity, and keeping planned dose of chemotherapy on schedule.

1. Introduction

Pegfilgrastim (Neulasta) is a pegylated form of G-CSF that has a long half-life, allowing for a single administration per chemotherapy cycle.[1] Although the safety and efficacy of pegfilgrastim has been established in association with chemotherapeutic regimens that are repeated every 3 weeks, its safety and efficacy in patients receiving chemotherapy regimens every 2 weeks is currently under investigation.[2–5] Of concern is the possibility of stem cell damage that may overlap with subsequent courses of chemotherapy due to the long half-life of pegfilgrastim.

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy is widely used for the treatment of patients with Hodgkin lymphoma (HL), and is administered every 14 d.[6] Many patients receiving ABVD require growth factor support to maintain dose intensity, prevent neutropenic fever, and to prevent delays in chemotherapy administration.[7,8] In this study, we used a single 6 mg fixed dose of pegfilgrastim in first and subsequent doses of ABVD. Although

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the majority of HL patients may not require primary prophylaxis of G-CSF while receiving ABVD therapy, the primary objectives of this study were to determine the safety of pegfilgrastim in supporting chemotherapy regimens given every 14 d, and the efficacy of this approach in preventing dose delays and dose reductions in patients receiving ABVD. The current study provides the longest safety follow-up data using this approach.

2. Patients and methods

2.1. Objectives

The objective of this prospective study was to examine the safety and efficacy of pegfilgrastim in support of chemotherapy regimens that are administered every 14 d.

2.2. Patient Selection

Patients were eligible for this trial if they were at least 18 years of age, and had a new diagnosis of classical HL of any stage requiring treatment with ABVD chemotherapy. Patients were required to have a performance status of less than 2 on the Zubrod scale, an absolute neutrophil count (ANC) greater or equal to 1.5×10^9/L, a platelet count greater or equal to 100×10^9/L, a bilirubin level less than 2 mg/dL, a serum creatinine level less than 1.5 mg/dL, and left ventricular ejection fraction greater than 50%. All patients were required to sign an Institutional Review Board-approved consent form. Patients were excluded if they had human immunodeficiency virus (HIV) infection; lymphoma involving the central nervous system; a history of serious pulmonary or cardiac disease. The study also excluded women of childbearing age who were pregnant or not practicing adequate contraception.

2.3. Study design

The study was approved by M.D. Anderson Institutional Board and all patients were required to sign a consent form prior to participation in the study. All patients received ABVD chemotherapy.[9,10] Patients with stage I or II non-bulky disease were treated with 3–4 courses of ABVD followed by involved field radiation therapy.[11,12] Patients with stage II bulky disease, stage III or IV disease were treated with 6 courses of ABVD followed by involved field radiation therapy to the area of bulky disease.

Pre-treatment evaluation included a complete blood count (CBC) with differential, platelet counts, a chemistry profile, and HIV testing. All patients had a chest X-ray; computed tomographic (CT) scans of the chest, abdomen, and pelvis; a gallium or PET scan; an echocardiogram or MUGA scan; and bilateral bone marrow biopsies and aspirates.

ABVD regimens consisted of doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2, and were all given by intravenous infusions on day one and repeated every 14 d (Day 1 and day 15 schedule).[10] Approximately 24 h after each ABVD infusion, patients received a single 6 mg fixed dose of pegfilgrastim. Each two doses (A and B) are considered as one course. Patients who had disease progression after any course were removed from the study. Tumour status was evaluated every 2 or 3 courses and after the completion of therapy. Follow-up observations after completion of the treatment consisted of a physical examination, CBC, chemistry profile, and imaging studies every 3–4 months during the first years, and every 6 months thereafter. Bone marrow biopsies were repeated if pre-treatment bone marrow biopsy showed involvement with lymphoma, biopsies were repeated at the time of tumour assessment until clearance, and subsequently were performed only if clinically indicated at the investigator's discretion.

Blood samples were collected on the day of chemotherapy administration (or within 24 h before administering the chemotherapy). Nadir blood samples were collected on day 7 (±1 d) of each ABVD treatment. After completion of therapy, blood samples were collected from patients who are in remission every 3–4 months during the first 2 years, and every 6 months thereafter.

2.4. Efficacy and safety measurements

The efficacy end-points were defined as: (1) the incidence of ANC less than 1000 on the day of ABVD therapy, (2) the incidence of dose delays, (3) the incidence of neutropenic fever (defined as fever $\geqslant 38$ °C and ANC $<0.5 \times 10^9$/L), and (4) the incidence of dose reductions. Long- term safety was defined as the incidence of myelodysplastic syndrome (MDS) and the failure rate of stem cell collection in patients subsequently requiring autologous stem cell transplantation.

2.5. Statistical analysis

This was a single institution study. Survival and progression-free survival (PFS) were defined according to the International Workshop to Standardize Response Criteria for NHL, and were analysed using Kaplan–Meier survival estimates.[13] Descriptive statistics of neutrophil counts, box plot analysis and scattered plot analysis, and calculations of mean, median and 95% confidence interval of ANC counts for each cycle of ABVD were performed using Prism 4 for Macintosh statistical software (GraphPad Software Inc.; San Diego, CA).

3. Results

3.1. Patient characteristics

Twenty-five patients were enrolled for the study. Two patients were not compliant with the treatment program and were removed from the study after receiving only 2 courses of ABVD; one patient was lost to follow-up, and the second repeatedly missed appointments and was removed from the study at the request of the treating attendant. Thus, 23 patients completed all planned treatment courses and were evaluable for safety and efficacy analysis. The median age was 26 years (range 19–52 years). Thirteen (57%) had stage I or IIA disease, and 10 (43%) patients had advanced stage disease (Table 1). Thirteen patients received 6 full courses of ABVD and 10 patients received 3–4 courses followed by involved field radiation therapy. Bleomycin was omitted from the last 1 ($n = 6$) or 2 ($n = 3$) courses of ABVD at the discretion of the attending

Table 1 – Characteristics of 23 evaluable HL patients treated with ABVD with pegfilgrastim support

	N	%
Evaluable patients	23	100
Median age (years)	26	
Male/female	13/10	57/43
Ann Arbor stage		
I-IIA	13	57
IIB-IV	10	43
Number of ABVD courses		
3–4	10	30
6	13	57
Total number of ABVD courses delivered	115	
Total number of ABVD doses delivered	230	
Patients received radiation therapy	16	70

physician prophylactically to decrease the potential risk of lung toxicity.

3.2. *Response to therapy and event free survival (EFS)*

All patients initially responded to therapy. Subsequently, two patients had disease progression after 10 and 16 months of starting the therapy. With a median follow-up of 29 months (range 10–41 months), the estimated PFS at 41 months is 91.3% (Fig. 1).

3.3. *Efficacy*

3.3.1. *ANC recovery on the day of ABVD therapy*

Twenty-three patients received a total of 230 doses of ABVD with primary pegfilgrastim support. The median pre-treatment ANC count was 6.4×10^9/L. The median ANC count on the day of ABVD therapy remained above 6×10^9/L throughout the six treatment courses (Fig. 2). Only in one case (0.4%) was the ANC less than 1×10^9/L on the planned day of ABVD administration (Table 2). The highest ANC count on the day of therapy was 22.8×10^9/L. No treatment delays resulted from the elevated ANC on the day of therapy.

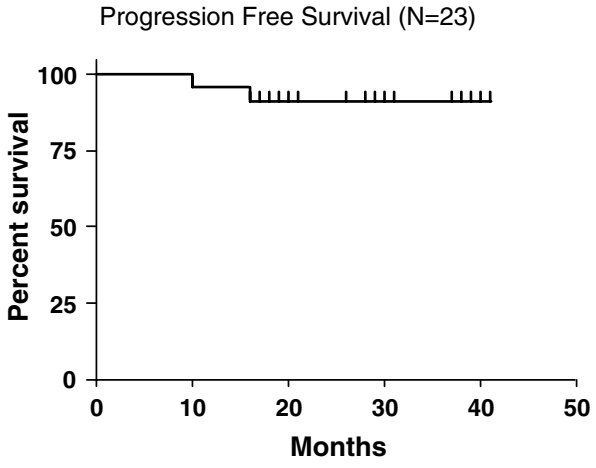

Fig. 1 – Progression-free survival (PFS) in 23 evaluable patients.

3.3.2. *Nadir ANC measurements*

Nadir (day 7 ± 1 d following each dose of ABVD) ANCs were determined in 178 courses. The median mid-cycle ANC after cycle IA of ABVD was 0.73×10^9/L (range, 1.56×10^9/L–27.96×10^9/L), and remained above 4×10^9/L throughout the treatment courses. Only in two cases (1.1%) the nadir ANC was below 0.5×10^9/L (Table 2). The highest nadir ANC count was 58×10^9/L which rapidly declined on the subsequent day of therapy to below 20×10^9/L (Fig. 2).

3.3.3. *Neutropenic fever*

Overall, 408 weekly ANC measurements were performed (230/230 on the day of therapy and 178/230 mid-cycle). Only in three (0.7%) cases, the ANC was below 1×10^9/L and none were associated with fever. Non-neutropenic fever or infection was observed following eight doses of ABVD (in six different patients) and were as follows: one upper respiratory infection, one pneumonia, two of unknown cause, and four catheter associated infection.

3.3.4. *Dose delays and dose reduction*

Although ANC was higher than 1×10^9/L on the planned day of ABVD administration in 229 of 230 (99.6%) of the doses, 15 (6.5%) doses of ABVD were delayed in 12 patients due to a variety of reasons, including catheter-related infection and lack of patient compliance. However, all doses were given without any dose reduction.

3.4. *Safety*

Grades 3 and 4 bone pain were observed in one patient which was prevented during subsequent doses by mild analgesics. Grade 2 bone pain was observed in five patients. Bleomycin induced lung toxicity was observed in two patients, requiring withholding of bleomycin. One additional patient complained of shortness of breath and dyspnea on exertion without evidence of bleomycin toxicity.

Long-term follow-up of ANC after completion of ABVD therapy is determined in all patients. All patients had ANC measurements during the first year of follow-up, 16 patients had ANC measurements during the second year and 12 patients had ANC measurements during the third and fourth years of follow-up (Fig. 3). The mean ANC during this extended follow-up time remained above 3.5×10^9/L. No cases of myelodysplastic syndrome or acute leukaemia were observed.

Two patients had a relapsed disease requiring salvage therapy with platinum-based regimens and stem cell transplantation. In both cases, autologous stem cells were successfully collected and engrafted.

4. Discussion

Chemotherapy regimens that are administered every 14 d, including dose-dense are increasingly being used for treating a variety of cancers.[14–21] Many of these regimens, especially the dose-dense ones, require growth factor support to maintain delivery of planned dose on time. In recent years, the convenience of one dose of pegfilgrastim per chemotherapy cycle has gained acceptance over the use of daily

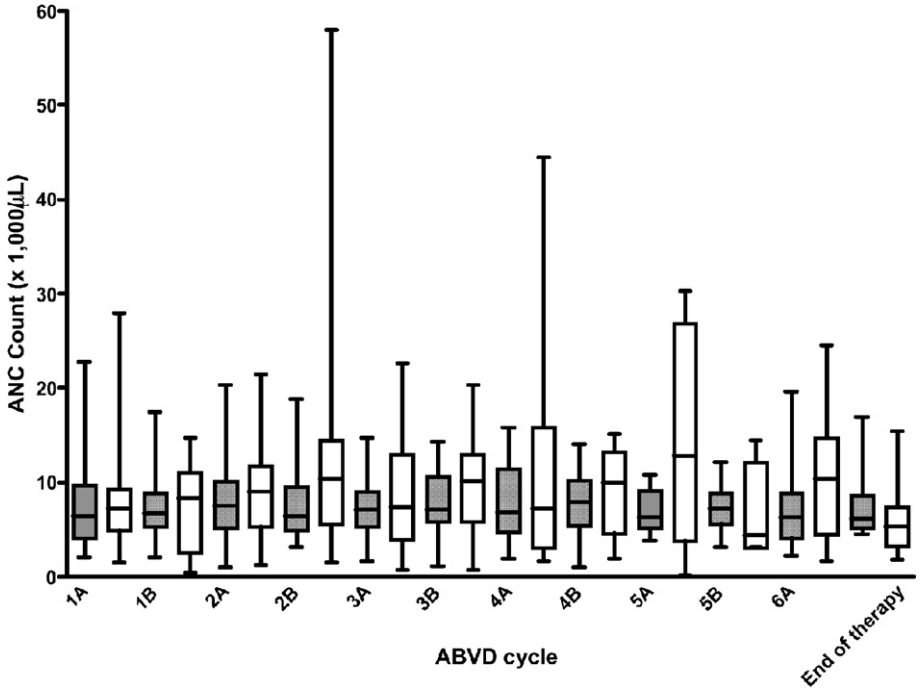

Fig. 2 – Box plot analysis of absolute neutrophil counts (ANC) on the day of ABVD administration (shaded boxes) or day 7 ± 1 d after each ABVD administration (open boxes). The box extends from the 25th to the 75th percentile, with a line at the median (50th percentile). The whiskers are extended to show the highest and lowest values.

Table 2 – Efficacy of pegfilgrastim prophylaxis

Adverse event	Episodes	% ABVD doses
Nadir ANC <500	2	1.1 (178 measurements)
Day of therapy ANC <1000	1	0.4 (230 measurements)
Neutropenic fever	0	0
ABVD dose delays	15	6.5
Reasons for ABVD treatment delays		
Neutropenia	1	6.5
Non-neutropenic infection	8	
Lack of compliance	5	
Other	1	
Combined	15	
ABVD dose reductions	0	0
Bone pain (grades 3–4)	1	0.4

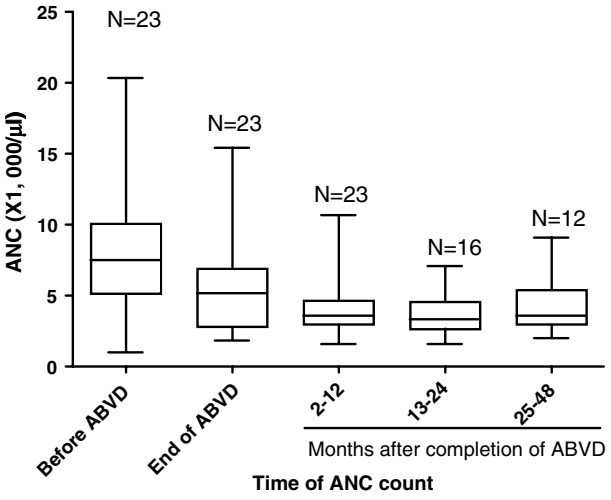

Fig. 3 – Long term follow-up of ANC in patients treated with ABVD plus pegfilgrastim. Box plot data is shown as explained in Fig. 2 legend.

administration of filgrastim in support of regimens that are repeated every 3 weeks.[1,22] Although recent data demonstrated the efficacy of pegfilgrastim in supporting regimens that are given every 14 d, the long term safety of this approach has not been reported. In this study, we examined the efficacy and long term safety of ABVD with pegfilgrastim support in newly diagnosed patients with HL, whereas all patients received primary prophylaxis of a single fixed 6 mg dose of pegfilgrastim. We used ABVD for two primary reasons. First, although ABVD is not considered to be a 'dose dense' regimen, it is a widely used regimen that is administered every 14 d with established curative efficacy.[6] Thus, because it is a curative regimen, the long term safety of this approach needed to be examined in this category of patients population. Second, because up to 75% of the patients receiving ABVD will require growth factor support to maintain dose intensity and delivery of planned dose on time.[7,8] It is widely believed that reducing dose intensity of curative regimens may reduce the cure rate, and therefore maintaining planned dose on time is important.

In this study, prophylactic use of pegfilgrastim in support of ABVD demonstrated excellent efficacy. Only one of the 230 doses was delayed due to low ANC on the planned day of therapy, and no dose reduction was made during the entire study. Although ABVD is not frequently associated with neu-

tropenic fever, the use of pegfilgrastim completely prevented neutropenic fever in all patients, and the ANC nadir was maintained above 500 in 99% of the cycles. Only one patient had grade 3 bone pain, which was controlled with mild analgesics.

One theoretical concern regarding the use of pegfilgrastim in support of regimens that are administered every 2 weeks is the possibility of maintaining high circulating serum levels of pegfilgrastim at the time of chemotherapy administration on day 14. Prior experience of concurrent administration of G-CSF with chemotherapy for several days suggested the potential stem cell toxicity of this approach, as manifested by prolonged neutropenia.[23] In our study, these concerns proved to be clinically irrelevant. We did not observe prolonged cytopenia during the study as neutrophil recovery was achieved by day 14 in 99.6% of the cycles. Furthermore, there was no progressive decline in the nadir mid-cycle ANC throughout the treatment cycles, as nadir ANC was maintained above 0.5×10^9/L in 99% of the cycles. Moreover, in the two patients who had relapsed disease requiring stem cell transplantation, successful stem cell collection was achieved.

Although primary prophylaxis with G-CSF may not be required in the majority of patients with classical HL receiving ABVD therapy, one important aspect of this study is the establishment of long-term safety of this approach. With a median follow-up of 29 months (range 10–41 months), no cases of myelodysplastic syndrome or acute leukaemia were observed. While this data are encouraging, longer follow-up will be required to confirm the safety of this approach.

Although our study established the efficacy and safety of pegfilgrastim in support of ABVD chemotherapy, one should not extrapolate our data to other regimens that are administered every 14 d, including dose-dense regimens. However, Phase II studies of pegfilgrastim in support of a variety of biweekly regimens are currently being conducted, and the available short follow-up data are also encouraging.[24,25]

Conflict of interest statement

The authors declare not to be engaged in any financial or personal relationships with other people or organizations that could inappropriately influence their work. The study was supported by AMGEN.

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