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Original article

Dose escalation of cytotoxic drugs using haematopoietic growth factors: A randomized trial to determine the magnitude of increase provided by GM-CSF

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Summary

Background: The magnitude of chemotherapy dose escalation made possible by the use of recombinant haematopoietic growth factors has not been quantified in a randomized trial.

Patients and methods: Patients with refractory or relapsing Hodgkin's disease were randomized to receive the Dexa-BEAM regimen with escalating etoposide doses supported by placebo or granulocyte-macrophage colony-stimulating factor (GM-CSF). Using an adaptive sampling method independently in both arms, the etoposide dose was escalated until the maximal tolerated dose for the first cycle was reached.

Results: Thirty patients were randomized to GM-CSF and thirty to placebo. The etoposide dose could be escalated considerably in both treatment arms. Maximal etoposide dose for the first cycle was 1920 mg/m^2 for patients receiving GM-CSF and 1160 mg/m^2 for patients receiving placebo ($P = 0.045$ one-sided), corresponding to a 65% higher etoposide dose and a 13% higher dose intensity with GM-CSF. Dose-limiting events were similar in both arms, consisting mainly of prolonged neutropenia and consecutive infections. Treatment efficacy was not different in the two treatment groups.

Conclusions: While GM-CSF permits a somewhat higher dose escalation than placebo, the increase in dose intensity provided by GM-CSF is small. The use of CSF for interval reduction rather than dose escalation is the more effective strategy for dose intensification.

Key words: chemotherapy, clinical trials, dose escalation, haematopietic growth factors

Introduction

A positive correlation between dose-intensity of anti-neoplastic drugs and response rate has been reported for several human tumours [1, 2]. As dose and frequency of administration of many effective anti-neoplastic agents are limited by myelosuppression, recombinantly derived haematopoietic growth factors (or colony-stimulating factors (CSF)) that stimulate proliferation and differentiation of haematopoietic progenitor cells into mature effector cells [3–5] were expected to allow for dose-intensification without haematopoietic stem-cell support [6, 7]. Early clinical studies of the effects of the haematopoietic growth factors GM-CSF and G-CSF suggested beneficial effects on neutrophil recovery [8–11] which would allow the administration of larger than usual doses of cytotoxic drugs [12]. However, to date there has been no well-controlled study that has convincingly demonstrated if and to what extent CSF makes dose escalations of myelosuppressive drugs possible. We now report on the first randomized placebo-controlled double-blind dose escalation study to determine and quantify the magnitude of increase in dose escalation that can be attributed to GM-CSF support.

Patients and methods

Patients

The design of the Dexa-BEAM ± GM-CSF protocol was in accordance with the declaration of Helsinki. It had been approved by the local institutional review board at the study center, the University of Cologne. Written informed consent was obtained from all patients prior to randomization.

Sixty consecutive patients, 18–60 years of age (median 31 years) from 25 centers with histologically proven Hodgkin's disease, who had failed to respond to or had relapsed after a remission achieved by multi-drug chemotherapy, were randomized to receive Dexa-BEAM salvage therapy [13] with either placebo or *E. coli*-derived human recombinant GM-CSF (Schering-Plough). Inclusion criteria were: primary treatment with cyclophosphamide, vincristine, procarbazine, and prednisone plus doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP + ABVD), or plus ifosfamide, methotrexate, etoposide,

Table 1. Characteristics of patients randomized to dose escalation with and without GM-CSF.

	Placebo	GM-CSF	All
Evaluable	30	30	60
Sex (male, %)	63	67	65
Age (years)			
Median	29	32	31
Range	19–61	18–59	18–61
Histology			
Lymphocyte predominant	1	0	1
Nodular sclerosis	23	17	40
Mixed cellularity	3	8	11
Not classified	3	5	8
Initial stage			
IIA–B	10	5	15
IIIA–B	11	17	28
IVA–IVB	9	8	17
Stage at relapse			
IA–B	2	1	3
IIA–B	2	8	10
IIIA–B	3	9	12
IVA–IVB	17	12	29
Response to primary therapy			
Progressive disease	6	4	10
< CR	1	2	3
Relapse < 12 months	13	20	33
Relapse > 12 months	9	3	12
Multiple relapses	1	1	2
Organ involvement			
Liver	3	4	7
Bone marrow	3	5	8
Bulky disease (> 5 cm)	4	5	9

and prednisone (COPP + ABV + IMEP) chemotherapy [14, 15], or comparable regimens with and without radiotherapy; progressive disease or relapse for which salvage radiotherapy was not considered to be a curative option; and curative intent. The characteristics of the patients and their response to prior chemotherapy are listed in Table 1.

Treatment

The Dexa-BEAM regimen was given as described [13]: dexamethasone 3 × 8 mg p.o. days 1–10, carmustine 60 mg/m^2 day 2, melphalane 20 mg/m^2 day 3, cytosin arabinoside 100 mg/m^2 every 12 hours days 4–7. Etoposide was given on days 4–7 with a daily dose of 75 mg/m^2 at dose level 1, 100 mg/m^2 at dose level 2, 150 mg/m^2 at dose level 3, 250 mg/m^2 at dose level 4, 250 mg/m^2 at dose level 5, 300 mg/m^2 at dose level 6, 400 mg/m^2 at dose level 7, and 500 mg/m^2 at dose level 8. Patients received placebo or GM-CSF 250 μg/m^2 subcutaneously starting day 8 until neutrophil counts had recovered to > 1000/mm^3 for two consecutive days. Treatment was repeated on day 29. Patients with chemotherapy-sensitive disease (as indicated by the achievement of a complete or partial remission after two cycles of Dexa-BEAM) were offered subsequent high-dose chemotherapy (HDCT) followed by autologous bone marrow or peripheral blood stem-cell transplantation (ABMT). The myeloablative regimen consisted of the CVB regimen [16]. Responding patients who did not undergo HDCT/ABMT received four cycles of Dexa-BEAM.

Dose escalation

The maximal tolerated dose (MTD) was estimated for the first Dexa-BEAM cycle only, because further treatment was not uniform (drop outs due to progressions, continuation with HDCT/ABMT). MTD was defined as the dose level at which patients have a 1/3 probability to experience a dose-limiting event. The following events were defined as dose-limiting: (1) recovery of neutrophils (> 1000/mm^3) later than day 24; (2) recovery of platelet count (> 100,000/mm^3) later than day 32; (3) extramedullary toxicicity of WHO grade 4 (with the exception of emesis and alopecia), including therapy-related deaths.

A generalization to parallel accrual of the up and down sampling scheme described by Storer [17] was developed to determine the etoposide dose level for a new patient. Sampling was done independently for the two randomization arms. The sampling algorithm made use of all the information on toxicities and dose-limiting events observed in the first Dexa-BEAM cycle of patients who had been treated in the respective treatment arm before. Essentially, a patient was assigned to the next higher dose level once two patients in the respective treatment arm, who had been treated at the current or a higher dose level, did not experience a dose-limiting event. The dose level for a new patient was decreased by one step if a patient in the same treatment arm experienced a dose-limiting event at the current or a lower dose level. Toxicity results that did not have an immediate effect on the current dose by these rules were queued to have an effect in case a change in the current dose level rendered them relevant. Using this sampling scheme the current dose level oscillates stochastically around the mximal tolerated dose.

Toxicities were analysed conditionally on the sampling using a logistic regression including dose level and GM-CSF as covariates [17]. White blood counts during the first cycle were determined daily or at least every other day and were analyzed using patient-wise cubic spline interpolation (under visual control) to extract four parameters to characterize the course of the white blood cell counts: (1) first day < 2500/mm^3; (2) day of nadir; (3) level of nadir; and (4) first day > 2500/mm^3. Separate linear regression was used to determine the effect of dose level and GM-CSF on these characteristics.

Relative dose intensities of the maximal tolerated dose levels achieved in each treatment arm were calculated using previously described methods [18].

Evaluation of therapy

The extent of disease was assessed by chest X-ray, abdominal sonogram and/or computerized tomography, bone marrow and liver biopsy. After therapy all disease manifestations were reassessed by adequate methods. All patients who started therapy were considered evaluable for toxicity and response. Complete response (CR) was defined as the disappearance of all measurable disease for at least four weeks after the end of treatment, and partial reponse (PR) was defined as a > 50% reduction of the measurable tumour mass for at least four weeks and disappearance of systemic symptoms. Death within six weeks from the initiation of Dexa-BEAM therapy from causes other than refractory disease was designated as therapy-related death. Survival (SV) and freedom from treatment failure (FFTF) of all patients were determined as the time from the beginning of salvage therapy to death or failure, respectively.

Results

Of the 60 patients included in this trial, thirty were randomized to receive GM-CSF and thirty to receive placebo, respectively, starting day 8 of each Dexa-BEAM cycle. The patients were well balanced for known risk factors such as stage and symptoms, organ involvement at diagnosis and at relapse, number of and response to previous therapies (Table 1).

Maximal tolerated etoposide dose levels and relative dose intensities

The toxicities and dose limiting events of the first Dexa-BEAM cycle were investigated by the study center by a

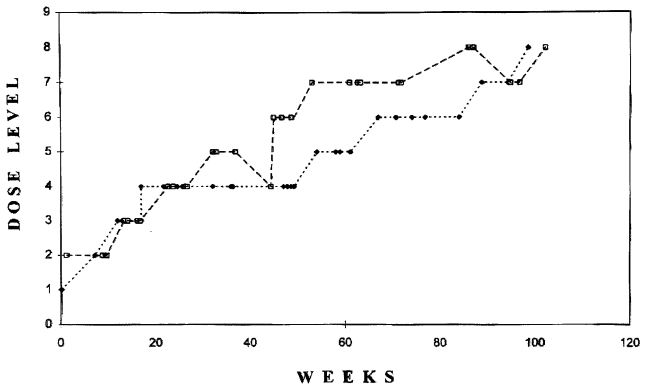

Figure 1. Evolution of the dose escalation of etoposide in the Dexa-BEAM regimen with GM-CSF and placebo during the recruitment phase of the trial. The dose level for a new patient was increased by one step for every two patients in the respective treatment arm treated at the current dose level or above who did not experience a dose-limiting event, while the dose level for a new patient was decreased by one step if a dose-limiting event occurred at the current dose level or below. While four dose-limiting events at levels 5, 7 (two patients), and 8, respectively, occurred in patients who received GM-CSF, seven dose-limiting events were observed at levels 4 (three patients), 5, 6 (two patients) and 8, respectively, in patients who received placebo.

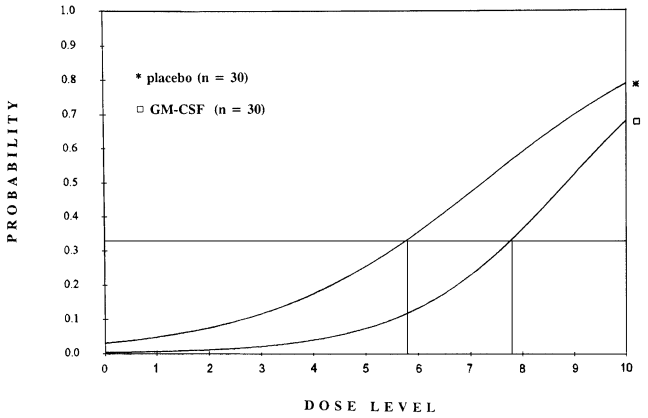

Figure 2. Probability of dose-limiting events. As shown from the logistic regression curves, dose level had a significant ($P < 0.02$) effect on the probability of a toxic event. The curve for patients treated with placebo crossed the 33% probability per cycle for a dose-limiting event at dose level 5.8, while this probability was reached with GM-CSF at a dose level 7.8, demonstrating that GM-CSF allows for an additional dose escalation ($P = 0.045$, one-sided).

phone call to the participating institution three and four weeks after the start of therapy. By adapting the dose based on this information from treated patients, the sampling dose level stochastically approached the maximal tolerated dose in both treatment arms (Figure 1). No dose-limiting event occurred in either treatment arm up to dose level 3. The predominant dose-limiting events were neutropenia and associated infections. Seven dose-limiting events occurred in the 30 patients with placebo: three at level 4 (prolonged neutropenia, prolonged thrombocytopenia, and a fatal infection during neutropenia), one at dose level 5 (prolonged neutropenia), two at level 6 (a fatal pneumonia and a grade 4 infection during neutropenia) and one at level 8 (grade 4 neurological disturbance during neutropenic sepsis). In the group of patients who received GM-CSF, four experienced toxic events at dose levels 5, 7 (two events), and 8. These events consisted of prolonged neutropenia at dose level 5, prolonged neutropenia combined with thrombocytopenia and combined neutro-thrombocytopenia with grade 4 stomatitis at dose level 7, and a fatal staphylococcus sepsis with ARDS at dose level 8.

The probability of experiencing a dose-limiting event at a given dose level was fitted into a logistic regression analysis. Dose level had a significant ($P < 0.02$) effect on the probability of a toxic event (Figure 2). The maximal tolerated dose, which was defined as the probability of 33% per cycle to experience a dose-limiting event was reached by patients receiving placebo at the dose level 5.8 (80% confidence interval (CI): 4.4–7.2), corresponding to 1160 mg/m^2 etoposide per cycle, while the eoposide dose could be increased with GM-CSF support by 65% to 1920 mg/m^2 or dose level 7.8 (80% CI: 6.4–8.7), respectively. This difference was significant in a one-sided test with $P = 0.045$ ($P = 0.09$, two-sided). Thus, a considerable escalation of the etoposide dose was possible with and without GM-CSF, with GM-CSF support allowing for an additional, yet moderate dose escalation when compared to placebo. Using previously described methods for the calculation of relative dose intensities [18], the difference in the dose escalation possible with and without CSF corresponds to an additional increase in dose intensity of 13% with GM-CSF, if the calculation is based on five drugs (including dexamethasone) and 16%, respectively, if only the four cytotoxic drugs included in the four-week Dexa-BEAM regimen are considered.

Severe myelosuppression with temporary neutropenia $< 500/\text{mm}^3$ and thrombocytopenia $< 50{,}000/\text{mm}^3$ was observed at all dose levels. Leukocytopenia occurred earlier ($P = 0.0004$), had a lower nadir and lasted longer with increasing dose levels. The first day $> 2500/\text{mm}^3$ was dose-independent, but recovery was reached 1.5 days earlier with GM-CSF when compared to placebo ($P = 0.04$, two sided; Figure 3).

Patients without a dose-limiting event after the first cycle were to continue at the same dose level to which they had been assigned to for the first cycle. Twenty-eight patients (fourteen in each arm) who responded after two Dexa-BEAM cycles proceeded to high-dose myeloablative therapy followed by ABMT or PBSCT. There was no significant difference in the rate of toxic events in subsequent cycles between patients with GM-CSF or placebo, suggesting that the use of GM-CSF did not result in haematopoietic stem-cell damage or depletion.

Other toxicities

The non-haematological toxicities included mucositis (grades 1 and 2), nausea and vomiting (grade 1) and alopecia (grades 2 and 3) and occurred with the same frequency and severity in the two treatment arms. Anemia

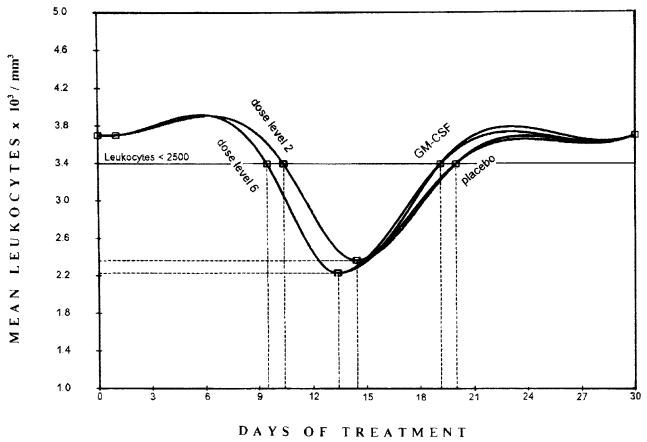

Figure 3. Effect of GM-CSF on neutrophil counts after Dexa-BEAM with etoposide dose levels 2 and 6. The descending arm was not affected by GM-CSF, while the neutrophil recovery was accelerated using GM-CSF by 1.5 days. This effect was observed at all dose levels.

and thrombocytopenia requiring transfusion of packed red cells and platelets, respectively, were not different in the placebo and CSF group; in particular, time to platelet recovery was not prolonged in the patients who recieved GM-CSF when both groups were analyzed according to a given dose level. Injection reaction sites, low-grade fever and flushing were more common in patients receiving GM-CSF, but this did not lead to dose reductions or even refusal of further therapy by the patient.

Response to therapy

There were thirty-one complete remissions (52%) and three partial remissions, with an overall response rate of 57% (95% confidence limits: 43%–69%). No radiotherapy to bulky and/or residual nodal disease was given. Eight patients (13%) died of treatment-related complications (pneumonia, pulmonary embolism, postsurgical death after laparotomy because of suspected ileus, carmustine-induced pneumonia after ABMT, and four septicemias). The response rates were not different between the two treatment arms (Table 2). Similarly, responses to therapy were not different in the 31 patients who were treated at dose level 1–4 when compared to the 29 patients who were treated at dose levels 5–8. Overall survival was affected by the time of failure to primary therapy (one year within diagnosis vs. later; Figure 4a), but not by the addition of GM-CSF (Figure 4b).

Discussion

While there have been randomized trials that evaluated the effect of CSF on dose intensity by shortening treatment intervals with fixed doses of cytotoxic drugs [19, 20], there have been no reports on randomized studies that have determined and quantified the magnitude of dose escalation that can be achieved with haematopoietic growth factor support in comparison to placebo. Several

Table 2. Results of treatment with dose-escalated Dexa-BEAM.

	Placebo	GM-CSF	All
Evaluable	30	30	60
CR (%)	17 (57)	14 (47)	31 (52)
PR (%)	0	3 (10)	3 (5)
No change	0	2	2
Progressive disease	8	8	16
Therapy-related death	5	3	8
	Dose levels 1–4	Dose levels 5–8	All
Evaluable	31	29	60
CR (%)	15 (48)	16 (55)	31 (52)
PR (%)	1 (3)	2 (7)	3 (5)
No change	0	2	2
Progressive disease (%)	12 (39)	4 (14)	16
Therapy-related deaths		8	

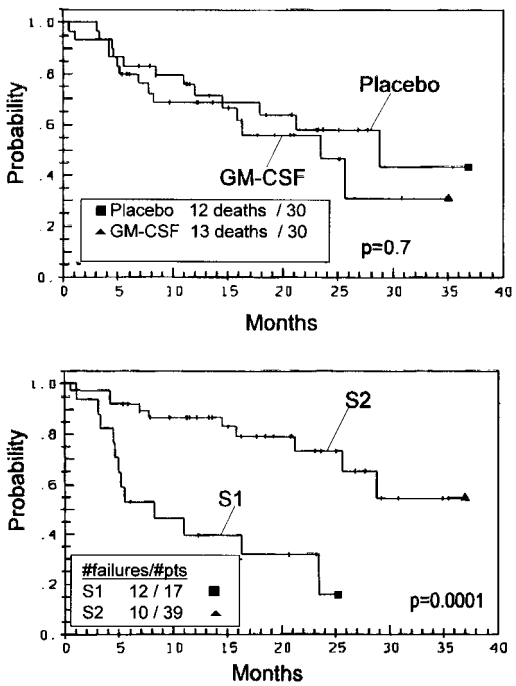

Figure 4. Overall survival of patients treated with escalating doses of Dexa-BEAM. Survival was influenced by response to primary chemotherapy (S1: failure within one year after start of primary chemotherapy; S2: failure after >1 after start of primary chemotherapy) but not by treatment arm (▲ – GM-CSF; ■ – placebo).

prerequisites must be fulfilled for such a study: a regimen with myelosuppression as the dose-limiting side effect and a strict correlation between the dose level and the probability of a dose-limiting event. This was the case in this trial, since the maximal tolerated dose of the Dexa-BEAM regimen was defined by prolonged neutropenia and associated events and not by other side effects that cannot be expected to be ameliorated by the haematopietic growth factor given.

Our Dexa-BEAM dose escalation study shows that by applying liberal, yet predefined criteria for dose-limit-

ing events, which anticipated and allowed prolonged neutropenia, etoposide can be escalated considerably even without GM-CSF support. Etoposide was chosen as the drug to be escalated because etoposide can be given up to a dose of 3.5 g/m^2 without stem cell support [21]. The complete response rate of 52% is encouraging. However, maximally escalated Dexa-BEAM proved to be quite toxic with fatality rates comparable to induction chemotherapy regimens which are given for the treatment of acute leukemias. The toxicity was judged to be acceptable in the light of the dim prognosis of patients with Hodgkin's disease relapsing after primary chemotherapy [22]. As no therapy-related deaths were observed up to dose level 3, this dose level, rather than the maximal tolerated dose levels 5.8 and 7.8 without and with GM-CSF, respectively, would be suggested outside clinical trials.

Compared to placebo, the etoposide dose could be escalated considerably further with GM-CSF, from 1160 mg/m^2 to 1920 mg/m^2 or 65%. However, this reached significance only in a one-sided test ($P = 0.045$) and only if exlusively etoposide dose levels were considered. With regard to the overall dose and relative dose-intensity, the gain provided by GM-CSF was small: 13% more dose intensity based on a calculation that includes all five drugs of the Dexa-BEAM regimen and 16% increase, if only the four cytotoxic drugs are taken into consideration. Even if one considers the earlier leukocyte recovery observed after GM-CSF which would allow recycling of the regimen on day 19.5 instead of 21, this would translate into gains of relative dose intensities of only 14% and 18%, respectively.

While the aim of this study was the quantification of the role of haematopoietic growth factors in permitting dose escalations and explicitly not the evaluation of the role of dose intensification in the treatment of lymphomas, it is not suprising that the small additional gain in dose intensity that was achieved by GM-CSF in comparison to placebo did not translate into higher remission rates, time to treatment failure (data not shown) or overall survival rates.

In contrast to other studies, where CSF-supported dose escalation failed due to reasons other than neutropenia [23–26], the failure of GM-CSF in our study was due to insufficient abrogation of neutropenia, the primary task of this CSF. It might be argued that choosing patients with relapsing or refractory Hodgkin's disease who have gone through prior chemotherapy could have been a bias against the efficacy of GM-CSF, as the bone marrow reserves of these patients might have been compromised prior to the administration of GM-CSF. That this is not the case is demonstrated by the fact that in all 28 attempted cases (14 in each arm) peripheral blood stem cell or bone marrow harvests yielded excellent results after Dexa-BEAM.

The *E. coli*-derived GM-CSF as used in this study was well tolerated and the application scheme was strictly adhered to. Injection reaction sites, low-grade fever and flushing were the only GM-CSF related side effects. They did not cause any dose reductions or even refusal of further therapy by the patient. It is therefore unlikely that results of this study would have been different, had yeast-derived GM-CSF been used instead of the *E. coli*-derived GM-CSF, the former having the advantage of being less toxic than the bacteria-derived product [27].

Even though granulocyte-colony-stimulating factor (G-CSF) has been reported to be more effective than GM-CSF in accelerating haematopoietic recovery after chemotherapy [28, 29], studies on the value of G-CSF in escalating dose or increasing dose-intensity are as controversial as those for GM-CSF [10, 25, 30, 31]. Thus it seems that neither CSF permits a clinically relevant dose escalation of cytotoxic drugs. Considering the suprisingly high-dose escalation possible with placebo alone, one must suspect that many of these studies did not take into consideration that modern supportive therapy other than haematopoietic growth factors allows for a considerable dose escalation that would not have been anticipated previously [12, 32].

Previous randomized and non-randomized studies had come up both with positive [33–37] and negative results [38–41] regarding the efficacy of CSF in dose intensification. Several trials indicate that CSF can contribute to increased dose intensities by permitting shorter intervals between treatment cycles rather than by allowing escalated doses. All positive randomized studies that show a beneficial effect of CSF [19, 20, 42–47] used the haematopoietic growth factors primarily for interval reduction rather than for dose escalation. The time-saving effect of CSF depends on the aggressiveness of the respective chemotherapy regimen and is most pronounced after chemotherapy regimens with low neutropenic risk, where neutrophil recovery can be accelerated by up to 4.5 days [48] compared to placebo, while the difference to placebo after chemotherapy with high neutropenic risk (e.g., the Dexa-BEAM regimen used in this study) or even myeloablative therapy is usually in the range of only one to two days.

With the failure of CSF to permit significant increases in dose escalation without stem cell support in well-controlled, i.e., randomized studies, much of the enthusiasm that accompanied the advent of the recombinant human haematopoietic growth factors several years ago is fading. While CSF is very effective in mobilizing peripheral blood stem cells for stem-cell harvest before high-dose chemotherapy with stem-cell support [49] and has been shown to reduce the likelihood of febrile neutropenia, when the expected incidence is $>40\%$ [50], our study shows that it permits only small-range dose escalations. When increased dose intensity is the goal, reducing treatment intervals rather than dose escalations is the more effective strategy for the use of CSF.

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*Appendix

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