Haematologica 1999; 84:1016-1023 original paper

Prospective, randomized trial of sequential interleukin-3 and granulocyte- or granulocyte-macrophage colony-stimulating factor after standard-dose chemotherapy in cancer patients

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ABSTRACT

Background and Objectives. **Several *in vitro* and animal studies have shown that IL-3 primes hematopoietic stem cells to become more sensitive to later acting growth factors. We wanted to compare the toxicity and the synergistic stimulatory effect of interleukin-3 (IL-3) followed by granulocyte colony-stimulating factor (G-CFS) or granulocyte-macrophage colony-stimulating factor (GM-CSF) on white blood cell (WBC) and platelet counts, after standard-dose chemotherapy (CT) in patients with solid tumors.**

Design and Methods. **Fifty consecutive cancer patients with thrombocytopenia and/or leukopenia registered during a previous course of CT were randomized to receive, after the following course, IL-3 (10 μg/kg/day, s.c., day 1-5) followed by G- or GM-CSF (5 μg/kg/day, day 6-8).**

Results. **The nadir of WBC in the cycles supported with the combination of IL-3 and G-CSF was significantly higher than that observed in the CT cycles not supported by growth factors ($p < 0.005$). Furthermore, severe leukopenia was abrogated in all the cycles supported with IL-3+G-CSF, while in the cycles without cytokines, this event was registered in 62.5% of the cases ($p < 0.0005$). Finally, the recovery of WBC was achieved a mean of 4 days earlier in the cycles supported with IL-3+G-CSF. As for thrombocytoprotection, no significant differences were evidenced, but severe thrombocytopenia was abrogated in all the cycles supported by IL-3+G-CSF ($p < 0.05$). Furthermore, platelet recovery after CT was achieved on average 3.5 days earlier in the IL-3+G-CSF group than in the previous cycles. The nadir of WBC count in the cycles supported by the combination of IL-3 and GM-CSF was significantly higher than that observed in the CT cycles not supported by growth factors ($p < 0.005$). Furthermore, severe leukopenia was abrogated in 40% of the cycles supported by IL-3+GM-CSF, while in the cycles without cytokines, this event was registered in 80% of the cases ($p < 0.005$). Finally, the recovery of WBC was achieved a mean of 3.5 days earlier in the cycles supported by IL-3+GM-CSF. As far as thrombocytoprotection is concerned, there were no significant differences in the nadir between the cycles supported by the association IL-3+GM-CSF and the cycles not supported by cytokines. However, severe thrombocytopenia was registered in 20% of the cycles not supported by growth factors but in only 10% of the cycles supported by IL-3+GM-CSF ($p < 0.05$). Furthermore, platelet recovery after CT was achieved on average 3 days earlier in the IL-3+GM-CSF group. The combination of IL-3 and G-CSF would appear to be more effective than the combination of IL-3 and GM-CSF in the control of both severe thrombocytopenia and leukopenia. Indeed, severe leukopenia was abrogated in all the cycles in arm A, but only in 40% of the cycles in arm B ($p < 0.0005$). Furthermore, considering a platelet count below 49×10^9/L, such a toxicity was avoided in 90% of the cycles in arm B, but in 100% of the cycles in arm A ($p < 0.05$).**

Interpretation and Conclusions. **The sequential administration of IL-3 and myeloid growth factors can be given safely after standard-dose CT programs. The combination of IL-3 + G-CSF seems to be more effective than the association IL-3 + GM-CSF in the control of CT-induced myelosuppression, even though further studies are needed to confirm these results.**

Key words: interleukin-3; G-CSF; GM-CSF; chemotherapy-induced myelosuppression

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Neutropenia and/or thrombocytopenia are dose-limiting toxicities for a number of active chemotherapy regimens, and such toxicities may adversely affect treatment outcome due to consequent dose modification and/or treatment delay.

Although this is not a major problem for treatments given with palliative intent, the clinical impact of such toxicities is much more significant when chemotherapy is given with a curative intent.[1]

Furthermore, myelosuppression may make a patient more susceptibile to infections and hemorrhage with a consequent relevant impact on his/her quality of life and on overall treatment costs.

As far as neutropenia is concerned, the ability of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) to reduce chemotherapy (CT)-induced neutropenia incidence and duration is well documented by a number of clinical studies on patients with both solid and hematologic malignancies.[2-10] Unfortunately, thrombocytopenia is not affected by these late-acting myeloid growth factors.

Interleukin-3 (IL-3), a multipotent hematopoietic growth factor produced by activated T-cells, monocyte-macrophages and stroma cells,[11] was shown to induce thrombocytosis in patients with normal hematopoiesis.[12,13] Furthermore, several *in vitro* and animal model studies[14-19] have demonstrated the synergistic effect of IL-3 and GM-CSF on hematopoiesis, particularly when the two cytokines are given in a sequential mode.[16,17] IL-3 may expand an early hematopoietic cell population that subsequently requires the process of late-acting factors – i.e., G-CSF or GM-CSF – to complete its development.[16]

The aim of this study was to determine whether IL-3 followed by G-CSF or GM-CSF reduces bone marrow depression – in terms of both neutropenia and thrombocytopenia – in heavily pre-treated patients with advanced solid cancer receiving standard-dose CT.

Design and Methods

Patients' enrollment criteria

Patients with different solid cancers receiving antiblastic CT for their disease were eligible for enrollment in this trial. Enrollment criteria included: no leukothrombocytopenia before the chemotherapeutic treatment; CT-induced leukopenia ≥ G3 (WHO criteria[20]) and/or CT-induced thrombocytopenia ≥ G2 in the previous cycle, and/or myelosuppresion-related delay in CT administration in the previous cycle. Furthermore, patients were required to have an adequate performance status, normal renal and hepatic functions, no other causes of myelosuppression (including bone marrow metastases), no concomitant infections, no fever ≥ 39°C and no concomitant autoimmune diseases. Finally, all patients gave their informed consent according to institutional's requirements.

Clinical and laboratory monitoring

Before and during the course of the trial, patients were monitored by a complete medical history, physical examination, laboratory tests (including blood cell count with WBC differential count, serum biochemistry and coagulation profiles), urine analysis and EKG. Blood counts were performed three times per week until the expected nadir was reached and then daily until the count had recovered.

Throughout the study period, patients were examined following each treatment course for evidence of toxicity; all side effects were recorded and graded according to WHO criteria.[20] Acetaminophene was administered for headache, fever ≥ 38°C (measured at the axilla), or myalgia. Patients were taken out of the study if grade 4 cytokine-related toxicity developed.

Chemotherapy administration

All the patients enrolled in this study received first-line standard dose CT as appropriate for their advanced disease; if the CT regimen was changed, the patient was taken out of the study.

Platinum compounds were used in 57.5% of the CT cycles; anthracyclines were used in 50% of cycles, cyclophosphamide/ifosfamide in 37.8%, taxol or VP-16 in 21%, while in the remaining 45% of cycles a combination of other drugs was administered (5-fluorouracil, mitomycin-C, vinca alkaloids); these antiblastic agents were used either alone or together.

Details on the types of chemotherapeutic drug administered are shown in Table 1.

The doses of chemotherapeutic agents were kept fixed during CT cycles to allow a better evaluation of the myeloid restorative effect of the two combinations of cytokines. Platelet transfusions for severe thrombocytopenia and/or hemorrhagic episodes, red blood cell transfusions in case of anemia (Hb < 7 g/dL), and antibiotics for neutropenic fever or when otherwise clinically indicated, were allowed in the study's design.

Treatment protocol

The study period included two CT cycles: the first cycle without cytokines and the second supported by the administration of one of the two combinations of growth factors.

Each patient displaying thrombocytopenia ≥ G2 and/or leukopenia ≥ G3 and/or myelosuppression-related delay in CT administration during the previous CT cycle (performed without cytokine support), was randomized to receive, at the subsequent CT cycle, either IL-3 10 µg/kg/die s.c. days 1 through 5 + G-CSF 5 µg/kg/die s.c. days 6 through 8 (arm A), or IL-3 10 µg/kg/die s.c. days 1 through 5 + GM-CSF 5 µg/kg/die s.c. days 6 through 8 (arm B). The design of the protocol is summarized in Table 2.

The cytokines were administered subcutaneosuly

Table 1. Types of chemotherapeutic drugs administered.

	N° cycles	*%*
Platinum compounds	38	57.5
Anthracyclines	33	50
Cyclophosphamide/ifosfamide	25	37.8
VP-16	14	21
Taxol	14	21
5-fluorouracil	10	15
Vinca alkaloids	10	15
Mitomycin C	10	15

Table 2. Protocol design.

Arm A	
IL-3	10 µg/kg/die s.c. days 1-5
G-CSF	5 µg/kg/die s.c. days 6-8
Arm B	
IL-3	10 µg/kg/die s.c. days 1-5
GM-CSF	5 µg/kg/die s.c. days 6-8

Table 3. Characteristics of enrolled patients.

N° pts. enrolled	50	
N° pts. evaluable for response	47	94%
N° pts. evaluable for toxicity	49	98%
N° cycles administered	66	
N° cycles evaluable for response	63	95%
N° cycles evaluable for toxicity	65	98%
N° cycles with IL-3 + G-CSF	33 (31 evaluable for response)	
N° cycles with IL-3 + GM-CSF	33 (32 evaluable for response)	
Age		
Mean	54	
Range	25-75	
Sex		
Males	23	46%
Females	27	54%
ECOG Performance Status		
0	11	22%
1	30	60%
2	9	18%
Type of neoplastic disease		
Breast	16	32%
Lung (NSLC)	8	16%
Lung (SCLC)	2	4%
Stomach	6	12%
Others	18	36%

in the upper leg, starting 24 hours after the end of CT.

Escherichia coli-derived non-glycosylated, recombinant human IL-3 was kindly supplied by Novartis Pharma (Basel, Switzerland), and each vial, containing 500 µg of lyophilized IL-3, was reconstituted adding 1.1 mL of sterile water.

Response assessment

Hematopoietic response was defined by the occurrence of one of the following:

1. a ≥ 50% reduction in the duration of thrombocytopenia and/or leukopenia (all grades), compared to that after the non-growth factors-supported CT cycle;

2. a ≥ 50% reduction in the duration of severe leukopenia (WBC count ≤ 1.9×10^9/L) and/or thrombocytopenia (platelet count ≤ 49×10^9/L), compared to that after the previous CT cycle.

Statistical methods

The nadir count for both WBC and platelets, the duration of neutropenia and thrombocytopenia, the time to recovery of both WBC (≥ 4×10^9/L) and platelets (≥ 100×10^9/L), the incidence of neutropenic fever, mucositis and hemorrhagic episodes, and the platelet transfusion requirement, were compared between each CT cycle in which cytokines were used and the CT cycle without cytokines, and between the two arms of the study.

Furthermore, hematologic data recorded during the cycles supported by growth factors were compared with those registered in the cycles without growth factors – i.e., the cycles before their inclusion in this study. In all cases, the Student's t-test was used.

Results

Patients

Fifty patients (27 females, 23 males, mean age: 54 years, range: 25-75 years) with different types of solid tumors receiving standard-dose CT were enrolled in this trial. All patients were in performance status 0-2 (ECOG); 16 patients (32%) had breast cancer, 10 (20%) lung cancer, 6 (12%) stomach cancer, 4 (8%) uterine carcinoma or sarcoma, while the remaining 20% had other malignancies (arising from the adrenals, the ovary, the penis and from an unknown primary site). The patients' characteristics are listed in Table 3.

Forty-seven (94%) patients were evaluable for response, 49 (98%) for toxicity. Two patients dropped out of the study after the first administration of IL-3 because of allergic episodes with lipothymia; another patient refused treatment after the first administration of cytokines. The first two patients were considered for the evaluation of toxicity but not for response, while the third patient was not considered for either evaluation of response or toxicity.

IL-3 followed by G-CSF was administered in 33 cycles (31 evaluable for response), IL-3 followed by GM-CSF in 33 cycles (32 evaluable for response), for a total of 66 cycles.

Toxicity

This could be evaluated in 65 of the 66 cycles, while it was not evaluable in one cycle because the patient refused to continue the treatment after the first dose of IL-3.

No side effects were registered in 37.8% of the cycles. The main side effect of the remaining cycles was a flu-like syndrome, accompanied by fever, chills, arthralgia and myalgias, with no significant differences between the two arms of treatment; all these symptoms were mild and reduced by acetaminophene.

In 10 cycles (15.3%) allergic episodes with flushing (9.2%), itching (3%), and in two cases (3%) lipothymia occurred. This last side effect was evident a few minutes after the first administration of IL-3. No specific

Table 4. Cytokine treatment-related toxicity.

	WHO grade	*Arm A*	*%*	*Arm B*	*%*	*Total*	*%*
No. cycles administered		33		33		66	
No. cycles evaluable for toxicity		33	100	32	96.9	65	
No. cycles without side effects		13	39.3	12	37.5	25	37.8
Flu-like syndrome		14	42.4	12	37.5	26	40
Fever	G1	9	27.2	7	21.8	16	24.6
	G2	4	12.1	4	12.5	8	12.3
Arthralgia, myalgia		3	9	4	12.5	7	10.7
Chills		2	6	3	9.3	5	7.6
Allergy		5	15	5	15.6	10	15.3
Flushing		2	6	4	12.5	6	9.2
Itching		1	3	2	6.2	2	3
Lipothymia		2	6	–	–	2	3
Gastrointestinal		1	3	3	9.3	4	6
Nausea/vomiting	G2	–	–	3	9.3	3	4.6
	G3	1	3	–	–	1	1.4

Table 5. Effects of arm A treatment (IL-3 + G-CSF), on CT-induced myelosuppression.

Hematologic parameters	*Cycles without cytokines*	*Cycles supported with IL-3 + G-CSF*	*Increase*	*p*
Mean nadir count				
WBC	1.8×10^9/L	3.2×10^9/L	75%	< 0.005
PLT	81×10^9/L	85.75×10^9/L	6%	n.s.
Severe myelodepression				
WBC (< 1.9×10^9/L)	62.5%	0%		< 0.0005
PLT (< 49×10^9/L)	12.5%	0%		< 0.05
Time to recovery				
WBC (≥ 4×10^9/L)	11	7		n.s.
PLT (≥ 100×10^9/L)	13	9.5		n.s.

treatment was required and all the symptoms receded spontaneously; in these patients, however, the treatment was discontinued.

In Table 4 the toxicities observed in each treatment group are summarized.

Effectiveness of the IL-3 + G-CSF (arm A) combination

This combination of cytokines was used to support 33 CT cycles following chemotherapy, 31 of which were assessable for hematopoietic response (Table 5, Figure 1).

As far as concerns leukocytes, the protective effect of the association of cytokines appeared to be significant. Indeed, the WBC nadir in the cycles supported with the combination of IL-3 and G-CSF was significantly higher than that observed in the CT cycles not supported by the administration of the growth factors (mean nadir with IL-3 + G-CSF = 3.2×10^9/L vs. mean nadir without IL-3 + G-CSF = 1.82×10^9/L , $p < 0.005$). Furthermore, severe leukopenia (WBC < 1.9×10^9/L) did not occur in any of the cycles supported by IL-3 + G-CSF, while this event was registered in 62.5% of the cycles without cytokines ($p < 0.0005$). Finally, the recovery of WBC was achieved a mean of 4 days earlier in the cycles supported with IL-3 + G-CSF than in the previous cycles not supported by growth factors.

As far as concerns platelets, there were no significant differences in the nadir between the cycles supported by the association of IL-3 + G-CSF and the cycles not supported by cytokines (mean nadir with IL-3 + G-CSF = 85.75×10^9/L vs. mean nadir without IL-3 + G-CSF = 81×10^9/L, p = n.s.). However, considering only the cases of severe thrombocytopenia (i.e. platelet count < 49×10^9/L), this occurred in 12.5% of the cycles not supported by growth factors, while it was not recorded in any of the cycles supported by IL-3 + G-CSF ($p < 0.05$). In addition, platelet recovery after CT was achieved on average 3.5 days earlier in the IL-3 + G-CSF group than in the previous cycles.

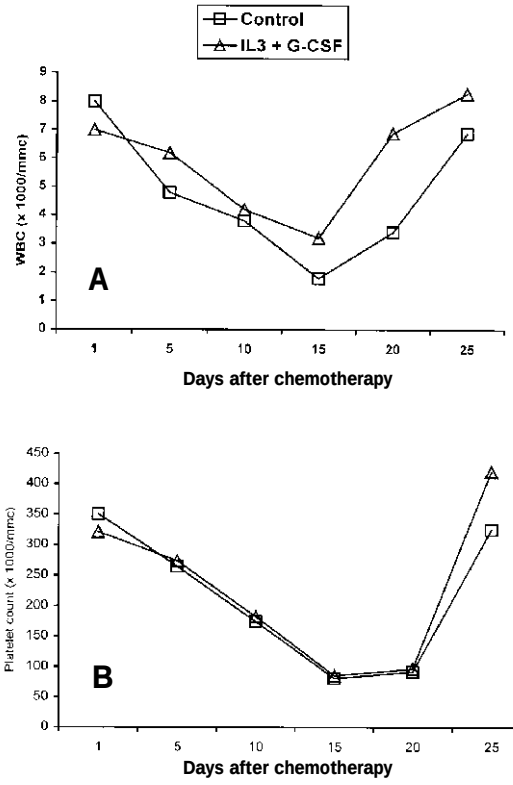

Figure 1. Arm A.
A: median WBC count after chemotherapy with or without IL-3+G-CSF.
B: A: median platelet count after chemotherapy with or without IL-3+G-CSF.

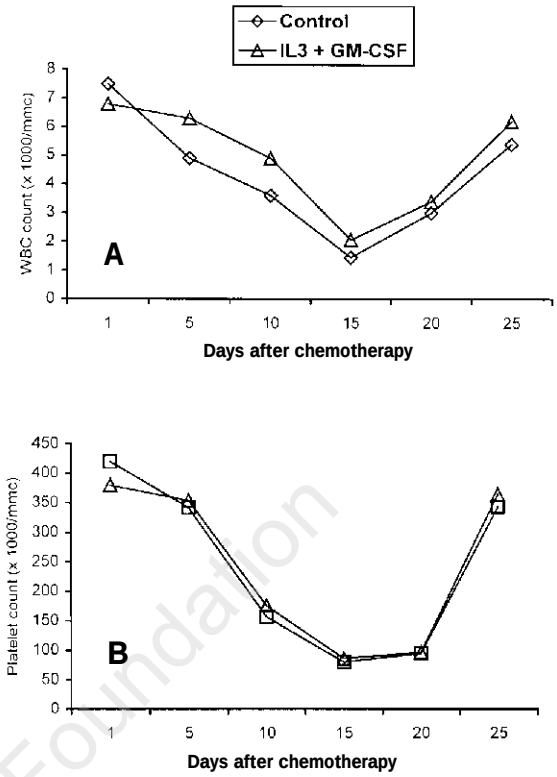

Figure 2. Arm B.
A: median WBC count after chemotherapy with or without IL-3+G-CSF.
B: A: median platelet count after chemotherapy with or without IL-3+G-CSF.

When CT cycles preceeding the inclusion into this trial were analyzed, 62.5% of them were complicated by episodes of severe leukothrombocytopenia (WBC count < 1.9×10^9/L and platelet count < 49×10^9/L), 37.5% by neutropenic fever, 12.5% by hemorrhagic episodes, and 25% by moderate leukothrombocytopenia (WBC count < 2.9×10^9/L and platelet count < 74×10^9/L) leading to delayed chemotherapy, were registered. In net contrast, no such events were recorded in cycles in which IL-3 + G-CSF were administered.

Table 6. Effects of Arm B treatment – i.e., IL-3 + GM-CSF, on CT-induced myelosuppression.

Hematologic parameters	*Cycles without cytokines*	*Cycles supported by IL-3 + G-CSF*	*Increase*	*p*
Mean nadir count				
WBC	1.45×10^9/L	2.06×10^9/L	42%	< 0.005
PLT	79.85×10^9/L	86.1×10^9/L	8%	n.s.
Severe myelodepression				
WBC (< 1.9×10^9/L)	80%	60%		< 0.005
PLT (< 49×10^9/L)	20%	10%		< 0.05
Time to recovery				
WBC (≥ 4×10^9/L)	11.5	8		n.s.
PLT (≥ 100×10^9/L)	13	10		n.s.

Effectiveness of the combination IL-3 + GM-CSF (arm B)

This association of cytokines was administered in 33 CT cycles, 32 of which were assessable for hematopoietic response (Table 6, Graph 2).

The protective effect of this second cytokine association on WBC also appeared to be significant. Indeed, the WBC nadir in the cycles supported by the combination of IL-3 and GM-CSF was significantly higher than that observed in the CT cycles not supported by the administration of the growth factors (mean nadir with IL-3 + GM-CSF = 2.06×10^9/L vs. mean nadir without IL-3 + GM-CSF = 1.45×10^9/L, $p < 0.005$). Furthermore, severe leukopenia (WBC < 1.9×10^9/L) was revoked in 40% of the cycles supported with IL-3 + GM-CSF, while this event was registered in 80% of the cycles without cytokines ($p < 0.005$). Finally, the recovery of WBC was achieved a mean of 3.5 days earlier in the cycles supported by IL-3 + GM-CSF than in the previous cycles not supported by growth factors.

Again, there were no significant differences in the nadir of platelets between the cycles supported by the association IL-3 + GM-CSF and the cycles not supported by cytokines (mean nadir with IL-3 + GM-CSF = 86.1×10^9/L vs. mean nadir without IL-3 + GM-CSF = 79.85×10^9/L, p = n.s.). However, severe thrombocytopenia (i.e. platelet count < 49×10^9/L) was recorded in 20% of the cycles not supported by growth factors), while only in 10% of the cycles supported by IL-3 + GM-CSF ($p < 0.05$). Furthermore, platelet recovery after CT was achieved 3 days earlier on average in the IL-3 + GM-CSF group, than in the previous cycles.

When CT cycles preceding the inclusion into this trial were analyzed, 80% of them were complicated by severe leukothrombocytopenia (WBC count < 1.9×10^9/L and platelet count < 49×10^9/L), 20% by neutropenic fever, 20% by hemorrhagic episodes, and 20% by moderate leukothrombocytopenia (WBC count < 2.9×10^9/L and platelet count < 74×10^9/L) leading to delayed chemotherapy. In contrast, neutropenic fever occurred in only 10% of the cycles supported by IL-3 + GM-CSF.

Comparison between the two treatment arms (arm A vs. arm B)

The combination of IL-3 and G-CSF seems significantly more effective than the combination of IL-3 and GM-CSF in the control of both severe thrombocytopenia and leukopenia.

Indeed, severe leukopenia was abrogated in all the cycles in arm A, but in only 40% of the cycles in arm B; this difference was statistically significant ($p < 0.0005$).

Furthermore, considering severe thrombocytopenia, being defined as a platelet count below 49×10^9/L, this was avoided in 90% of the cycles in arm B, but in 100% of the cycles in arm A; this is another statistically significant difference ($p < 0.05$). No other significant differences were observed between the two arms of treatment. Differences between the two arms of treatment are summarized in Table 7 and Figure 3.

Discussion

The introduction of hematopoietic growth factors, most notably GM-CSF and G-CSF, into oncologic practice has allowed us to manipulate the hematopoietic system in order to lessen toxicity of cancer CT. Clinical studies have evaluated the efficacy of both GM-CSF and G-CSF in reducing myeloid toxicity after conventional-dose or high-dose, non-myeloablative cancer CT. Clinical effects such as a decrease in days on antibiotics, and decrease in number of days spent in hospital, were observed in these heterogeneous phase I and II studies.[21]

Despite these successes, thrombocytopenia still remains a major problem in the management of the cancer CT-induced toxicity.

IL-3 has shown some efficiency in stimulating the production of platelets in animals and in man, with minimal – if any – effect on myelopoiesis.[12,22,23]

Table 7. Effects of arm A vs. arm B on CT-induced myelosuppression.

Hematologic parameters	*Cycles in arm A (IL-3 + G-CSF)*	*Cycles in arm B (IL-3 + GM-CSF)*	*p*
Mean nadir count			
WBC	3.2×10^9/L	2.06×10^9/L	0.05
PLT	85.75×10^9/L	86.1×10^9/L	n.s.
Severe myelodepression			
WBC (< 1.9×10^9/L)	0%	60%	< 0.0005
PLT (< 49×10^9/L)	0%	10%	< 0.05
Time to recovery			
WBC (≥ 4×10^9/L)	7	8	n.s.
PLT (≥ 100×10^9/L)	9.5	10	n.s.

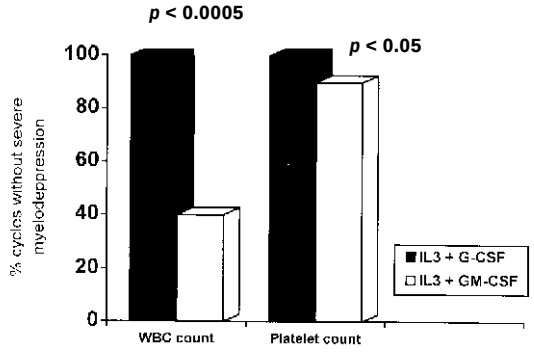

Figure 3. Arm A vs Arm B.

Indeed, in a study on the effect of IL-3 (or GM-CSF) on bone marrow cell proliferation and differentiation, Orazi *et al*. demonstrated that bone marrow cellularity, the myeloid/erythroid ratio and the proportion of bone marrow cells stained for the proliferation-associated nuclear protein (PCNA) by the PC10 monoclonal antibody, were lower in the IL-3 group than in the GM-CSF-treated group (even though in all cases higher than in controls).[24]

Previous studies in normal primates indicated that the combination of GM-CSF and IL-3 promoted a synergistic rise in peripheral WBC and platelet levels when IL-3 was administered before GM-CSF; in contrast, concomitant administration of IL-3 and GM-CSF resulted in a lower WBC production than that following GM-CSF alone.[14] Despite such interesting characteristics and its development as a clinical drug, IL-3 has not yet been extensively used, partly because of its relatively poor manageability in terms of side effects, and partly because of its seemingly disappointingly small effects on thrombocytopoiesis.

The rationale of the sequential administration of IL-3 and GM-CSF is based on the hypothesis that IL-3 will expand GM-CSF-sensitive target cells, thus leading to a more efficient production of neutrophils in addition to an increase in the production and maturation of platelet precursors. Furthermore, we previously demonstrated that sequential administration of IL-3 and GM-CSF is able to induce $CD34^+$ progenitor cells into the cell cycle with a consequent fast and complete hematopoietic recovery.[25]

A study of sequential versus concurrent IL-3 and GM-CSF administration in non-human primates treated for 15 days showed enhanced thrombopoiesis in the animals treated sequentially, with a delayed and modest increase in platelet number in those treated with the two cytokines concomitantly.[26]

The mechanism by which concurrent administration of IL-3 and GM-CSF results in a inhibition of hematopoiesis is not clear. IL-3 and GM-CSF receptors share a common β-subunit and the two cytokines compete in binding to receptors present on a subpopulation of hematopoietic cells.[27,28] Thus, IL-3 and GM-CSF may compete at the cellular level and inhibit megakaryocyte growth and differentation.

In contrast, another study of sequential versus concurrent IL-3 and GM-CSF administration in sublethally irradiated primates showed that twice daily coadministration of the two cytokines was more effective than sequential administration in hastening neutrophil and platelet recovery.[29] The investigators hypothesized that irradiated primate marrow could contain a subpopulation of progenitor cells responsive to both IL-3 and GM-CSF, whereas normal marrow may contain a preponderance of progenitors whose receptors are activated maximally by either IL-3 or GM-CSF; in this case, the competition for binding would be detrimental to normal hematopoiesis.[30]

More recently, Ballestrero *et al*. compared the toxicity and effects on hematologic recovery and circulating progenitor cell mobilization of three cytokine regimens (G-CSF, GM-CSF, and sequential IL-3 + GM-CSF) administered after high-dose cyclophosphamide given as the first step of a high-dose sequential chemotherapy program; despite the fact that the three regimens showed comparable effects in reducing hematologic toxicity and mobilizing circulating progenitor cells, patients treated with sequential IL-3 and GM-CSF had a faster platelet recovery but also definitely more pronounced side-effects.[31]

In a previous study, we utilized, with appreciable results, IL-3 to control thrombocytopenia after standard dose CT.[32] The primary purpose of this randomized study was to evaluate the efficacy of IL-3 followed by either G-CSF or GM-CSF in controlling standard-dose cancer CT-induced bone marrow suppression.

The toxicities of the treatments with growth factors were mild and easily manageable; the sequential administration of IL-3 and G- or GM-CSF can thus be administered safely to patients with malignant diseases. Indeed, the principal side effect was a flu-like syndrome characterized by fever, chills, myalgia and arthralgia.

In summary, IL-3 followed by either G- or GM-CSF can reduce myelosuppression after standard-dose CT administered to heavily-pretreated patients with advanced solid cancer. The sequential administration of IL-3 + G-CSF appears to be more effective than the sequential combination of IL-3 + GM-CSF. As far as regards severe myelosuppression, we observed a reduction in the depth of the WBC nadir, a reduction in neutropenic fever and in the necessity of delaying chemotherapy and/or modifying CT dose in both treatment arms, but once again these favorable effects were more pronounced when G-CSF followed IL-3. However, the combination of these cytokines, at least given in accordance with the schedule we used, is clearly not the ultimate solution with respect to platelet recovery. Further studies are therefore needed to address this topic.

Contributions and Acknowledgments

PS designed the study, wrote the paper and is, therefore, cited first; DM and PC reviewed the manuscript. DV and FS collected and analyzed the data. FG furnished the IL-3. CP, as senior author, is cited last. All co-authors, except FG enrolled patients into the study. The authors wish to thank Mr. M. Biggs for his amending of the text.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous publications.

Manuscript processing

Manuscript received March 30, 1999; accepted July 27, 1999.

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