Effect of prechemotherapy filgrastim on the bone marrow toxicity of topotecan

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Summary

Purpose: To investigate the efficacy and safety of single-dose filgrastim administered 24 hours prior to chemotherapy in the prevention of topotecan-related myeloid suppression.

Methods: No medication was given to 21 rats in group I; 1.5 mg/m²/day topotecan was administered intraperitoneally for five days every three weeks to 21 rats in group II; a single dose of 5 μg/kg filgrastim was injected intraperitoneally 24 hours before the intraperitoneal administration of the same dose of topotecan to 21 rats in group III. After completion of six cycles of chemotherapy, the rats were decapitated and blood samples were immediately collected into citrated tubes for complete blood counts.

Results: White blood cell and lymphocyte counts in the control and the filgrastim + topotecan groups were similar ($p > 0.05$) and significantly higher than the counts in the topotecan group ($p < 0.05$). There was no difference in means of neutrophil, monocyte, eosinophil, basophil and erythrocyte counts among the groups ($p > 0.05$).

Conclusion: Filgrastim administration prior to chemotherapy seems to be beneficial and further investigations are needed.

Key words: Filgrastim; Topotecan; Prechemotherapy; Myelosuppression.

Introduction

Although much progress has been made in the development of new chemotherapeutic agents for the treatment of malignant diseases, there are still unresolved toxicity problems, such as myelosuppression. On the other hand, efforts to develop new chemotherapeutic agents with higher efficacies are faced with the problem of higher neutropenia rates as well. A specific topoisomerase-I inhibitor, topotecan, is a novel semisynthetic derivative of camtothecin. It has a high efficacy especially in second-line treatment of neoplasias, but has been reported to cause neutropenia in almost 80% of patients [1, 2].

Filgrastim, a kind of human recombinant granulocyte-colony stimulating factor (G-CSF), induces the proliferation and differentiation of neutrophil progenitors and has been proposed for both the treatment and the prevention of neutropenia [3]. However the 24-hour period before and after the administration of chemotherapy still remains as "no man's land" because of the potential sensitivity of stimulated and rapidly dividing myeloid cells to cytotoxic agents [4].

In this experimental study, we investigated the efficacy and safety of filgrastim in the prevention of myeloid suppression at a single dose of 5 μg/kg, administered 24 hours prior to five days of topotecan at a dose of 1.5 mg/m²/day.

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Materials and Methods

Sixty-three female Wistar rats aged five months and weighing 250 ± 50 g were randomly assigned to three groups with 21 rats in each group. They were housed seven-per-cage and had free access to water and a standard commercial diet under controlled environmental conditions of temperature (23 ± 2 °C).

Group I was the control group without any medication. Rats in group II were administered 1.5 mg/m²/day topotecan intraperitoneally for five days every three weeks. Filgrastim, at a single dose of 5 μg/kg was injected intraperitoneally 24 hours before the intraperitoneal administration of topotecan at a dose of 1.5 mg/m²/day for five days every three weeks in group III. One of the rats in group II died seven days following the last dose of the 3rd course of topotecan and was excluded from the study. After the completion of six cycles of chemotherapy, rats were decapitated and blood samples were immediately collected into citrated tubes for complete blood counts. Blood samples were studied blindly in the haematology laboratory by a Sysmex-NE 8000 counter.

Results were analyzed by the Student's t-test and the level of significance was determined as $p < 0.05$.

Results

White blood cell and lymphocyte counts in the control and the filgrastim + topotecan groups were similar ($p > 0.05$) and significantly higher than the counts in the topotecan group ($p < 0.05$) (Table 1). Platelet count was significantly higher in the filgrastim + topotecan group than in the control group ($p < 0.01$) but the topotecan group did not differ from the other groups ($p > 0.05$). There was no difference in means of neutrophil, monocyte, eosinophil, basophil and erythrocyte counts among the groups ($p > 0.05$).

Table 1. — *Blood cell counts of the rats (Mean ± SD).*

Groups	WBC (cells/mm³)	Neutrophils (cells/mm³)	Lymphocytes (cells/mm³)	Monocytes (cells/mm³)	Eosinophils (cells/mm³)	Basophils (cells/mm³)	Eythrocytes (cells/mm³)	Platelets (cells/mm³)
Control (n=21)	5245.0±2466.1	1417.1±2116.6	3282.3±1501.3	196.9±270.9	192.5±82.5	157.7±206.3	8185000±573033	511500±155034
Topotecan (n=20)	3994.5±1301.9	825.1±911.7	2420.0±809.2	266.5±430.8	219.6±105.3	259.0±392.6	7824000±800969	664450±216120
Topotecan+Filgrastim (n=21)	5643.8±3123.6	707.8±1221.2	3919.5±2917.4	537.6±707.8	208.5±117.4	269.5±259.2	7761428±382364	788238±241494

Discussion

G-CSF is a hematopoietic growth factor that promotes the proliferation and differentiation of neutrophil progenitor cells [3, 5]. Filgrastim does not alter the average half-life of a neutrophil in the circulation, which is 6-8 hours, but shortens the neutrophil maturation time from five days to one day, leading to a rapid release of neutrophils from the marrow into the circulation within 4-6 hours [6-8]. In filgrastim-stimulated bone marrow samples, twofold non-dose dependent increases in lymphocytes and dose-dependent increases in monocytes have been reported [9]. However it did not appear to have any consistent effect on eosinophils, basophils, platelets and erythrocytes [8].

Filgrastim use in patients in whom febrile neutropenia has already been established is called therapeutic administration whereas, prophylactic administration refers to the use of the drug for prevention of chemotherapy-induced febrile neutropenia which is a cost-effective procedure in high risk patients [10]. It is administered 24 hours after chemotherapy for prophylactic purposes, while prechemotherapy and concomitant administration have generally been avoided, based on the theoretical concern that G-CSF-stimulated rapidly proliferating hematopoietic stem cells become highly sensitized to the cytotoxic effects of chemotherapeutic agents [3, 5]. However the postchemotherapy approach requires multiple doses of G-CSF, because it should act on bone marrow that has already faced cytotoxic agents.

In 1998, Tjan-Heijnen *et al.*, administered G-CSF subcutaneously at a dose of 5 μg/kg/day for six days for 48 hours before the chemotherapy course in 12 patients with relapsed small-cell lung carcinoma and they found lower nadirs with prolonged durations for neutrophil and platelet counts [11]. However, the observation of a rapid fall in neutrophil counts following the cessation of 5 μg/kg/day filgrastim treatment has provided another opportunity for the prechemotherapy approach [12]. Probably G-CSF stimulation of unsuppressed stem cells causes an increase in bone marrow cellularity and a transient exaggerated response with high neutrophil count in the circulation [12, 13]. As G-CSF binds to its receptors on progenitor cells, those receptor complexes are internalized and the number of available surface receptors decreases [5, 14]. The mean ± SD elimination half-life of filgrastim at a single dose of 5 μg/kg from the circulation is 163 ± 7.4 minutes and the serum level returns to normal within 14 to 18 hours [8, 15, 16]. Following the rapid clearance of filgrastim from the circulation, the progenitor proliferation rate drops below baseline levels within 48 hours [12, 17]. The thought of this hyperplasic but quiescent bone marrow would make the hematopoietic cells refractory to the cytotoxicity of chemotherapeutic agents has led to two studies. In 1996, de Wit *et al.*, administered filgrastim subcutaneously twice a day for five days with the last dose given 48 hours before chemotherapy and once a day for seven days with the first dose given 24 hours after chemotherapy at a dose of 5 μg/kg/day to 18 patients with locally advanced or metastatic breast cancer and found no advantage in means of neutrophil counts, over another group of 18 patients to whom filgrastim was given only after chemotherapy [18]. Recently, in a controlled study, Aglietta *et al.*, administered granulocyte-macrophage colony stimulating factor (GM-CSF) subcutaneously at a dose of 5 μg/kg from day 7 to day 4 before chemotherapy to 30 patients with stage II - IV Hodgkin's disease [17]. Though the dose intensity (82.5% vs 79.6%) and the overall success in terms of delivery rate (56.7% vs 50%) were higher in the GM-CSF group, these differences did not reach statistical significance. The neutrophil nadirs were higher in the GM-CSF group during the first three courses but were similar in both groups in the subsequent courses.

In our study, we administered a single 5 μg/kg dose of filgrastim 24 hours before chemotherapy to keep progenitor cells in rat bone marrow suppressed during the chemotherapy course. When the half-life of filgrastim was considered, it was obvious that it would have been cleared from the circulation completely at the time of chemotherapy [8, 14, 16].

The chemotherapeutic agent choosen in our study was topotecan, a semisynthetic analog of camptothecin. It is a specific and potent inhibitor of topoisomerase I, with a high potency in cancer treatment, but causes a rather severe myelosuppression as the dose-limiting toxicity. In clinical use, topotecan at a dose of 1.5 mg/m²/day for five days every three weeks was seen to cause grade 4 neutropenia in almost 80% of the patients, while grade 4 thrombocytopenia was reported in 6-25% of the patients [1, 2]. The neutrophil nadir following topotecan treatment was found to develop between 9-14 days of each course with a median duration of 3-5 days [1]. In order to reveal the nadirs, we evaluated the blood cell counts of our rats on the 10th day of the last course of topotecan chemotherapy.

Our results were in favor of prechemotherapy filgrastim administration. Significantly higher white blood cell and lymphocyte counts without a significant decrease in neutrophil and monocyte counts in the filgrastim + topotecan group when compared with the topotecan group, lead us to question the validity of the belief that G-CSF

administration prior to chemotherapy would have detrimental effects on bone marrow. A significant decrease in white blood cells and lymphocyte counts in the topotecan group in comparison with the control group might be the consequence of chemotherapy. Insignificant differences in platelet counts between the control and the topotecan groups were not surprising when the low incidence of thrombocytopenia secondary to topotecan administration was considered [1, 2]. However, we also observed that the platelet count in the filgrastim + topotecan group was significantly higher than that in the topotecan group ($p < 0.05$). Actually this is not in contrast with the literature and both filgrastim and topotecan may cause thrombocytosis in some cases [19, 20].

Conclusion

Our study can be considered as a small step in no man's land. Filgrastim, as a single dose administered 24 hours prior to chemotherapy, would provide a transient myeloid suppression during the course of chemotherapy and hence protect progenitor cells from chemotherapy-induced cytotoxicity. It can also provide sustained levels of myeloid cells in the circulation during the course of chemotherapy. If the prechemotherapy approach of filgrastim proves to be beneficial, patients will have a chance to use highly potent, but highly myelosuppressive chemotherapeutic agents, such as topotecan, as the first-line treatment. Prechemotherapy filgrastim does not seem to deepen chemotherapy-related myelosuppression. On the contrary, it seems to have a beneficial effect that is worth being investigated further.

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