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Different doses of granulocyte colony stimulating factor to support a weekly chemotherapeutic regimen in advanced gastric cancer: a randomized study

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It was our intention to verify if increases of granulocyte colony stimulating factor (G-CSF) dose were able to reduce treatment delays due to leukopenia in our weekly regimen of cisplatin (40 mg/m^2), epidoxorubicin (35 mg/m^2), 6S-leucovorin (250 mg/m^2 and 5-fluorouracil (500 mg/m^2), usually supported by G-CSF at a dose of 5 μg/kg. Forty five patients with advanced gastric carcinoma (30 males and 15 females; median age 64 years) were randomized to receive three different doses of G-CSF (5, 8 and 10 μg/kg) by s.c. injection. We did not observe any difference in the mean value of neutrophil counts at each of the 8 weeks of treatment; while we registered a higher incidence of severe neutropenia (<500/mm^3) in patients receiving higher G-CSF doses: two patients in the group at 5 μg/kg, four in the group at 8 μg/kg and seven in the group at 10 μg/kg. Furthermore, low doses of G-CSF allowed a similar number of chemotherapeutic administrations in the eight study weeks. The results arising from our study do not seem to support the use of higher doses of G-CSF, at least in not such a weekly regimen.

Key words: Granulocyte colony stimulating factor, hematological toxicity, weekly chemotherapy.

Introduction

We recently reported the results obtained in advanced gastric cancer with a weekly chemotherapeutic regimen including cisplatin, 4-epidoxorubicin (epiADR), 6S-leucovorin (LV) and 5-fluorouracil (5-FU), and the support of granulocyte colony stimulating factor (G-CSF) from the day after to the day before each chemotherapy administration. This regimen was shown to be highly effective with an overall response rate of about 60% and a complete response rate of 15%.[1,2]

Non-hematological toxicities were uncommon and accounted for a minor proportion of the treatment delays; however, in spite of the use of G-CSF, neutropenia was one of the predominant causes of treatment delays, resulting in some cases in weekly administration being delayed.[1,2]

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Since G-CSF seemed to cause a dose-dependent increase in the number of circulating neutrophils, 3–6, it was our intention to verify if higher doses of G-CSF could produce episodes of neutropenia and treatment delays.

Patients and methods

Patients with a histologically verified advanced gastric carcinoma (stage III–IV) were eligible for the study. Other eligibility criteria included: performance status ECOG grade 0–2, normal liver (serum bilirubun < 1.5 mg/dl), renal (serum creatinine < 1.5 mg/dl), bone marrow (leukocyte count > 4000/mm^3, platelet count > 100 000/mm^3) and cardiac (stable heart rhythm, no active angina and no clinical evidence of congestive heart failure) functions.

Informed consent was obtained from all participants after the nature of the study had been fully explained and the protocol was approved by the institutional review board.

The chemotherapeutic regimen consisted of a 1-day weekly administration of: cisplatin 40 mg/m^2 as a 30 min infusion in 250 ml of normal saline solution; 5-FU 500 mg/m^2 as a 15 min infusion in 100 ml of normal saline solution and epiADR 35 mg/m^2 by i.v. bolus. LV was administered at a dose of 250 mg/m^2 in 250 ml of normal saline solution in 4 h infusion concurrently to hydration. Glutathione was given at the dose of 1.5 g/m^2 in 100 ml normal saline over 15 min immediately prior to each cisplatin administration. Standard i.v. hydration was used: 2 h prior to initiation of the cisplatin infusion patients were hydrated with 1500 ml of 0.9% sodium chloride to which 20 mEq KCl and 15 Meq $MgSO_4$ were added. Post-hydration was continued for 2 h with 1000 ml normal saline.

Patients were randomized to receive G-CSF, by s.c. injection, at three different doses (5, 8 and

10 μg/kg) from the day after to the day before each chemotherapy administration.

One cycle of therapy consisted of eight weekly treatments. Full doses of anticancer drugs were given if the leukocyte count was 4000/mm^3 and if the platelet count was >100 000/mm^3 as well as in the absence of any toxicity of WHO grade 2–3. When the values were less or there was a grade >1 toxicity of any type, the treatment was delayed by a week or until complete recovery.

Patients who did not receive cytotoxic drugs because of chemotherapy-induced side-effects continued to be given G-CSF until the next weekly administration of chemotherapy.

Evaluation of response was performed after eight chemotherapeutic administrations, while toxicity was evaluated weekly according to the standard WHO criteria.[7]

The end-points of the study were: the mean neutrophils count at each weekly administration, and the number of episodes of neutropenia and of chemotherapeutic adminstrations in the eight study weeks.

Randomization, using cards from a computer generated list in sealed envelopes, was performed by a person not involved in the care or evaluation of the patients. The personnel who evaluated the efficacy and tolerability of the treatment did not know the dose of G-CSF because this was done by other staff.

Analysis of variance with repeated measures was used to compare the mean neutrophil counts in the three arms at each week of the 8 weeks of treatment. A χ^2 test and a Wilcoxon test were used to assess the difference in terms of degree of neutropenia and the number of administrations.[8]

Results

Forty five patients were admitted to the study: 15 for each of the treatment groups. The patients' characteristics are summarized in Table 1. All patients completed the treatment. None of the patients were excluded because of violations of the protocol. No modifications in dose of chemotherapeutic drugs were performed.

Objective responses occurred in 10 patients (66.6%) in the 5 μg/kg group, in nine patients (60%) in the 8 μg/kg group and in nine patients (60%) in the 10 μg/kg group.

At baseline, patients were comparable from the hematologic point of view and demographic characteristics.

Table 1. Patient characteristics

	G-CSF dose (μg/kg)		
	5	8	10
No. of patients	15	15	15
Sex (M/F)	10/5	11/4	10/5
Age			
median	61	58	60
range	47–65	39–63	44–68
Prior surgery			
none	3	4	4
curative	8	7	9
palliative	4	4	2
Sites of primary tumors			
gastro-esophageal junction	2	1	2
proximal stomach	2	1	1
body	2	3	3
distal stomach	9	10	9
Histologic type			
well differentiated	4	3	4
moderately differentiated	10	9	10
poorly differentiated	1	3	1
Sites of metastases			
liver	7	8	9
abdomen/peritoneum	5	5	5
lymph nodes	3	3	3
lung	1	1	—
bone	1	1	—

Table 2 reports the mean neutrophils counts for each G-CSF dose at each week of the 8 weeks of treatment. There was no difference at each week among the three different arms.

Patients receiving G-CSF at 5 and 8 μg/kg presented a more regular administration of chemotherapy and less treatment delays in respect to the patients given 10 μg/kg (Table 3). Furthermore, a higher incidence of severe neutropenia was registered in patients treated with higher doses of G-CSF: two episodes in the group at 5 μg/kg; four in the group at 8 μg/kg and seven in the group at 10 μg/kg (table 4).

As regards other toxicities, we did not find a significant difference in terms of gastrointestinal side-effects, thrombocytopenia, anemia or neutrotoxicity (Table 5).

Discussion

Tumor cell resistance can be overcome to some extent by increased dose, although usually at the expense of increased toxicity. Several strategies are being evaluated to permit dose escalation in the hope of obtaining better clinical results with available drugs.[9,10]

Table 2. Mean neutrophilis counts ($\times 10^9$/l) ± SD for G-CSF doses at each of the eight study weeks

Weeks	G-CSF dose (μg/kg)			p^a
	5	8	10	
1	4763 ± 1125	5418 ± 1774	5893 ± 3411	NS
2	13462 ± 8264	12984 ± 9584	7146 ± 6330	NS
3	5862 ± 3945	7072 ± 4004	7520 ± 6870	NS
4	11539 ± 6890	7403 ± 2842	8870 ± 5838	NS
5	9020 ± 8310	10170 ± 3694	9018 ± 8363	NS
6	6934 ± 4959	7911 ± 6271	5717 ± 3848	NS
7	17530 ± 12964	14040 ± 12344	13653 ± 11403	NS
8	20110 ± 13093	18794 ± 13413	19254 ± 10780	NS

[a] ANOVA test; 8 and 10 μg/kg versus 5 μg/kg; NS = not statistically significant.

Table 3. Number of chemotherapeutic administrations in the eight study weeks, number of weeks necessary for eight administrations and received dose intensity

G-CSF dose (μg/kg)	No. of adminstration in 8 weeks					No. of weeks necessary for eight adminstrations							Received dose intensity
	8	7	6	5	4	8	9	10	11	12	13	14	(%)
5	7	5	3	—	—	7	4	3	1	—	—	—	91
8	7	5	2	1	—	7	4	2	2	—	—	—	90
10	3	8	2	1	1	3	4	4	1	—	1	1	77.7

Table 4. Leukopenia severity in the 8 week study

WHO grade	No. of episodes		
	5 μg/kg	8 μg/kg	10 μg/kg
I	8	8	5
II	6	7	7
III	1	2	4
IV	2	4	7

Considerable interest has been shown in the use of weekly chemotherapy since it can allow a higher dose-intensity without at the same time increasing toxicity.[9]

On this basis we designed a weekly regimen containing cisplatin, epiADR, 5-FU and LV for the treatment of advanced gastric cancer patients. In the first five patients, after the third or fourth week of therapy, hematological toxicity, mainly in the form of leukopenia, did not allow the pursuit of the weekly administration (unpublished data). In the following patients, we added G-CSF at the usual recommended dose of 5 μg/kg, from the day after to the day before each weekly administration. The addition of G-CSF reduced the proportion of patients who experienced treatment delays due to neutropenia. Nevertheless this side-effect remained one of the major causes of treatment delays.[1]

The present study tried to address the question of whether an increase of G-CSF dose at 8 μg/kg (about 60% above the standard dose) and 10 μg/kg (100% above the standard dose) could allow a more regular weekly administration, reducing the incidence and severity of leukopenia. Data emerging from our randomized trial are disappointing. No significant differences in the proportion of patients who experienced treatment delays due to neutropenia were found at a certain point during treatment in the three arms. On the contrary, we registered a higher incidence of severe neutropenia ($< 500/mm^3$) in patients receiving higher doses of G-CSF (Table 4).

Although a dose–response relationship of hematological cytokines to marrow stimulation has been demonstrated *in vitro* in the absence of myelosuppressive insult, no dose-dependent increase in neutrophils following chemotherapy was demonstrated.[11,12] Furthermore, no single, systematic controlled trial has yet been conducted with respect to the most effective dose and the optimal schedule for the administration of G-CSF. The only clinical partial information with regard to dose-response for G-CSF can be argued in phase I–II trials, and furthermore

Table 5. Other toxicities

Toxic effect	WHO grade	No. of patients with toxicity		
		5 μg/kg	8 μg/kg	10 μg/kg
Thrombocytopenia	1–2	2	3	2
	3–4	—	—	—
Anemia	1–2	2	3	2
	3–4	1	1	2
Diarrhea	1–2	1	—	—
	3–4	—	—	—
Stomatitis	1–2	—	1	—
	3–4	—	—	—
Nausea vomiting	1–2	2	1	1
	3–4	—	—	—
Neurotoxicity	1–2	1	1	1
	3–4	1	—	—

using different schedules and routes of administrations.[3–5,10,13]

Morstyn demonstrated that 30 μg/kg of rHG-CSF given by i.v. could shorten the duration of leukopenia to 1 day from 8 days of the patients receiving 1 μg/kg only.[5]

In a similar fashion, Bronchud and Gabrilove found that higher doses of i.v. G-CSF were more effective in determining the recovery of neutrophils.[4,6]

Neidhart *et al.* showed that G-CSF shortened the duration of neutropenia with a dose related speed and degree of recovery of granulocytes (20–60 μg/kg) even if, due to the lack of any statistically significant difference, it was not possible to clearly designate the highest dose as the optimal dose.[13]

Even G-CSF, given by s.c., seemed to show a dose–response relationship when doses of 10 μg/kg were compared with the very low doses of 0.1 and 1 μg/kg.[14]

Apart from the different regimen used in our case (G-CSF supported a weekly chemotherapy), some of these results, in contrast with our data, could be accounted for by the different routes of administation or doses of G-CSF. In fact, because *in vitro* data show optimum hematopoietic growth stimulation when growth factors are continuously present, intramuscular or s.c. administrations should produce a more prolonged effect than i.v. injection and the G-CSF dose could be less important in determining neutrophil recovery. rHG-CSF, when administered i.v., has been shown to have a rapid initial phase of distribution (approximately 8 min) and a terminal half-life of approximately 100 min, thus in this short time higher doses could be more effective, stimulating much more neutrophils precursors, as partially reported for GM-CSF.[15]

Furthermore, there could be a plateau in the stimulation of myelopoiesis for doses of G-CSF ranging from 5 to 20 μg/kg, while lower doses (0.1–3 μg/kg) could be suboptimal and much higher doses only (30–60 μg/kg) can produce a faster recovery of neutrophils, as suggested by our results and data from Stahel and Layton.[16,17]

Stahel in fact found that doses of 10 and 20 μg/kg of G-CSF were virtually identical in determining neutrophil recovery in patients undergoing high-dose chemotherapy with bone marrow transplantation, while Layton, on the basis of experimental data, suggested that G-CSF doses higher than 20 μg/kg could saturate plasmatic clearance, thus prolonging half-life and its activity.[16,17]

These latter doses, however, are uncomfortable when given s.c. and require an i.v. route, thus precluding the possibility of supporting a weekly regimen, because of the need to hospitalize the patients.

Moreover, to confirm this hypothesis, although the hemopoietic growth factor was rHuGM-CSF, in a recent randomized trial in small cell carcinoma, three different dosages (5, 10 and 20 μg/kg) were similarly effective in reducing the depth and duration of neutropenia, and increasing the dosage of rHuGM-CSF to 20 μg/kg did not appreciably alter the amount of tolerated chemotherapy.[18]

Even economic reasosn appear to favor in our regimen the use of G-CSF at the lower dose. In fact, since in Italy the price of a vial containing 300 μg/kg of G-CSF costs about $85 for hospital pharmacies, a weekly treatment for a patient weighing 60 kg is about $510 for a dose of 5 μg/kg; $750 for a dose of 8 μg/kg and $1020 for 10 μg/kg.

In conclusion, our results do not seem to shown any advantage in the use of a G-CSF dose higher

than 5 μg/kg, as support for our weekly chemotherapy regimen, at least in the range of 5–10 μg/kg.

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