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Papers

Granulocyte Colony-Stimulating Factor Treatment of Leucopenia during Fractionated Radiotherapy

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11 patients suffering from an isolated leucopenia during fractionated radiotherapy were treated with granulocyte colony stimulating factor (G-CSF). 4 of the patients received radiotherapy alone, and 7 patients received concomitant chemotherapy. G-CSF treatment was initiated at the occurrence of leucopenia and maintained for the duration of radiotherapy. The applied daily dose was 5 μg/kg subcutaneously. 10 of the 11 treated patients reacted with an increased leucocyte count, from an average of 1342 leucocytes per μl (± 502/μl) to 24 568 leucocytes per μl (± 950/μl). Neutrophil counts increased on average from 64.9% (± 13.9%) to 91.1% (± 2.3%) (n = 7). In 1 patient thrombocytopenia occurred during the continued radiotherapy. 1 other patient reacted with an unexplained fall of leucocytes after two doses of G-CSF and one fraction of mediastinal irradiation. Side-effects observed during G-CSF treatment consisted of mild bone pain (1/11) and transient increases of serum alkaline phosphatase levels (4/11). Our observations indicate that G-CSF treatment is well tolerated during continuous fractionated radiotherapy. Therefore, we conclude that G-CSF can be used clinically to alleviate neutropenia caused by radiotherapy or by combined radio-chemotherapy.
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INTRODUCTION

THE EMERGING use of colony stimulating factors (CSF) in the treatment of chemotherapy-induced leucopenia [1–4] has prompted the question as to whether the application of growth factors could be beneficial for patients suffering from myelosuppression under radiotherapy or under a combination of radio- and chemotherapy. Experimental data suggest that there is a radioprotective effect of haematopoietic growth factors against haematological toxicity [5–11]. Isolated leucopenia without a significant thrombocytopenia is not a common problem. However, it is a considerable cause for treatment interruption in the following specific situations: extended field irradiation [e.g. for Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL)], combined modality treatment with chemotherapy or after extensive myeloablative pretreatment. With the increasing clinical use of combined radiotherapy and chemotherapy, myeloablation might become a bigger problem in clinical radiotherapy in the future.

We undertook a pilot study to evaluate the safety and the feasibility of the CSF r-metHuG-CSF (Neupogen^R) for the treatment of neutropenia in patients undergoing radiotherapy. Between September 1991 and May 1992 we found 11 patients eligible for this treatment, as they were all suffering from leucopenia without significant thrombocytopenia.

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PATIENTS AND METHODS

Patients

11 patients were treated in this study: 5 patients received radiotherapy with a curative intent and 6 patients received palliative radiotherapy. 5 patients received concurrent chemotherapy. 2 patients had had extensive chemotherapy pretreatment due to recurrent NHL. Only 4 patients received radiotherapy alone. 1 patient had received ^{131}I treatment in her past. Detailed patient characteristics are given in Tables 1 and 2. The mean age of the patients was 57.3 years, ranging from 22 to 79 years.

Treatment with G-CSF

R-metHuG-CSF was obtained from Amgen-Roche (Basel, Switzerland) and was given by subcutaneous injections with a single daily dose of 5 μg/kg body weight.

Radiotherapy was interrupted when leucocytes fell to a level below 2000 cells/μl. In the first 4 patients, granulocyte CSF (G-CSF) was applied during such a treatment interruption to accelerate leucocyte recovery. Radiotherapy was continued after an increase of leucocyte counts to levels higher than 4000 leucocytes/μl, and G-CSF was given continuously for the further duration of radiotherapy.

In the 7 subsequent patients, treatment with G-CSF was initiated when leucocyte counts were below 2000 cells/μl, and radiotherapy was continued without interruption. In all patients thrombocyte counts had to be higher than 75 000/μl at the initiation of treatment. At thrombocyte levels below 50 000/μl radiotherapy was discontinued. Erythrocytes were substituted at haemoglobin levels below 8 mg per 100 ml.

Blood cell counts including leucocytes, thrombocytes and

Table 1. Patients' characteristics

Patient no.	Age	Sex	Diagnosis	Pretreatment	Concurrent treatment
1	68	F	Hodgkin's lymphoma stage IIA	None	None
2	79	F	Metastatic thyroid cancer (bone metastases)	^{131}I treatment. Previous irradiated areas: lower thoracic spine, right clavicle	None
3	22	M	Recurrent non-Hodgkin's lymphoma stage III	VIM/CHOP (2 cycles) MAP (3 cycles) VIM (1 cycle) Dexa-Beam (1 cycle)	None
4	55	F	Metastatic breast cancer (bone and liver metastases)	Previous irradiated areas: right thoracic wall	Epirubicine Cyclophosphamide
5	60	M	Recurrent non-Hodgkin's lymphoma	Mitoxantrone/ prednimustine (6 cycles) VIM/CHOP (2 cycles) VIM (1 cycle) Previous irradiated areas: abdomen, left inguinal nodes	None
6	34	F	Leiomyosarcoma of the right thigh	None	Ifosfamide, doxorubicin
7	68	F	Uterine sarcoma	None	None
8	52	F	Rectal cancer	None	5-FU
9	65	M	Metastatic chondrosarcoma (lung and bone metastases)	Previous irradiated areas: right thigh	Epirubicine, ifosfamide
10	65	F	Metastatic breast cancer (bone metastases)	Previous irradiated areas: left thoracic wall, thoracic spine	5-FU, methotrexate
11	62	M	Metastatic bronchial carcinoma (cerebral and adrenal metastases)	None	None

Characteristics of the patients including age, sex, diagnosis, pretreatment and concurrent treatment are given.

Table 2. Treatment fields, doses and fractionation in patients treated with G-CSF under radiotherapy

Patient no.	Field	Total dose (Gy)	Daily fractions (Gy)	% of bone marrow in field
1	Mantle field with inclusion of spleen, cervical, paratonsilar and paraaortal nodes	44.0 involved field 36.0 extended field	2.0	37
2	Thoracic spine	37.5	2.5	
	Lumbar spine	30.0	3.0	
	Sacral bone	30.0	3.0	39
3	Mediastinum	50.0	2.0	16
4	Left hip	30.0	3.0	
	Lumbar spine	30.0	3.0	24
5	Mediastinum, supraclavicular and axillary nodes	36.0	1.2 × 2	22
6	Right thigh	64.0	1.6 × 2	4
7	Small pelvis	50.0	2.0	
	boost to the uterus	10.0	2.0	20
8	Pelvis	47.5	1.9	
	boost to the tumour region	5.7	1.9	20
9	Sacral bone	36.0	3.0	14
10	Both hips, left ilium	30.0	3.0	26
11	Mediastinum	50.0	2.5	
	Cerebrum	30.0	3.0	29

The extent of bone marrow in the treatment field has been estimated according to Ellis [12], as a percentage of total active bone marrow.

erythrocytes were performed four to six times per week under G-CSF treatment. Differential blood cell counts, liver enzymes and electrolytes were measured twice per week. Blood samples were drawn several hours before G-CSF application.

RESULTS

Within the 9 months of our study, we found 11 patients with isolated leucopenia eligible for treatment with G-CSF. This corresponded to about 1% of all patients treated in our department during this time period.

Effects on neutrophils and leucocyte counts

After the initiation of daily G-CSF treatment, a rapid increase of leucocyte counts, from an average of 1342 leucocytes per μl (± 502/μl) to an average of 24 568 leucocytes per μl (± 9530/μl), was observed in 10 of the 11 patients treated. The percentage of neutrophils was monitored in 7 patients, and this increased from an average of 64.9% (± 13.9%) before G-CSF treatment, to an average of 91.1% (± 2.3%) during G-CSF treatment. An overview on leucocyte recovery after G-CSF treatment and the necessary interruptions of radiotherapy is given in Table 3 for the individual patients. The speed of leucocyte recovery varied between 1 and 8 days. The peripheral leucocyte counts were kept at normal or supranormal levels during G-CSF application. After discontinuation of G-CSF treatment, leucocyte counts fell back to subnormal levels within 2–3 days.

G-CSF treatment was started in patients 1–4 during an interruption of radiotherapy. Under the daily treatment with G-CSF, all of these patients were able to continue radiotherapy without any further treatment interruptions.

Patients 5–11 received G-CSF as soon as leucocytes fell below 2000/μl so avoiding treatment interruption. Of these 7 patients, 5 were able to receive radiotherapy without any interruption. 1 patient (no. 10) had treatment interrupted due to thrombocytopenia. Patient no. 5 had a pause of 11 days, due to an unexplained fall of leucocytes (see below). The development of leucocyte counts of one representative case (patient no. 1) under G-CSF application is shown in Fig. 1.

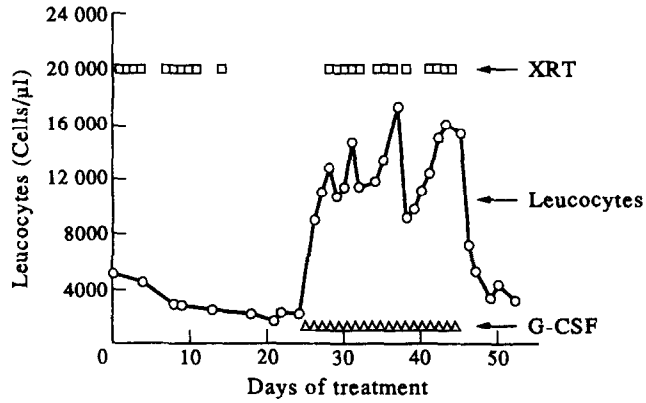

Fig. 1. Leucocyte counts of patients treated with fractionated radiotherapy and G-CSF. The change of circulating leucocyte counts over treatment time from the beginning of radiotherapy is shown for one representative patient (patient no. 1). Leucocyte counts are indicated in open circles. Each dose of G-CSF (5 μg/kg/day) is shown as a triangle. Fractions of radiotherapy are given in open squares. The application of G-CSF induced a rapid increase of leucocyte counts, allowing the continuation of radiotherapy. Similar curves have been obtained for the other patients, apart from patient no. 5 who reacted adversely.

Thrombocytes and erythrocytes

Thrombocyte counts were not influenced by G-CSF application. Patient no. 10 developed severe thrombocytopenia under the G-CSF-supported radiotherapy with platelet counts of less than 50 000/μl at the time when her leucocyte levels had recovered to supranormal levels. This necessitated treatment interruption of 12 days. Palliative chemotherapy had been given to this patient on day 2 of radiotherapy (see Table 1).

Erythrocyte counts and haemoglobin levels in serum were not influenced by G-CSF application (data not shown). None of the patients required a blood transfusion.

Side-effects

Transient rises of alkaline phosphatase levels were observed in 4 of 11 patients which returned to normal values within 2–4

Table 3. Leucocyte counts and treatment interruptions in patients treated with G-CSF under radiotherapy

Patient no.	Lowest WBC before G-CSF (cells/μl)	Highest WBC after G-CSF (cells/μl)	% maximum increase of WBC after G-CSF	Treatment interruptions (days)		Time required for leucocyte recovery to > 4000/μl (days)
				before G-CSF	after G-CSF	
1	1800	17 270	959	13	0	1
2	1300	45 900	3531	3	0	2
3	750	21 700	2893	11	0	1
4	700	22 500	3214	6	0	2
5	1550	170	—	0	11	—
6	1520	23 300	1532	0	0	2
7	1980	18 710	945	0	0	1
8	1590	19 280	1213	0	0	1
9	670	14 530	2168	0	0	4
10	1200	26 620	2399	0	12	8
11	1910	35 870	1878	0	0	3

Patients 1–4 were treated with G-CSF during treatment interruptions to accelerate leucocyte recovery. Patients 5–7 received G-CSF as soon as critical leucocyte levels occurred in order to avoid treatment interruption. Total leucocyte counts are shown. Differential blood cell counts were monitored twice per week.

days after discontinuation of G-CSF. 4 patients had elevated alkaline phosphatase levels before the application of G-CSF due to bone metastases. The remaining 3 patients did not show any changes of these levels. 1 patient complained of transient mild bone pain, which was controlled with paracetamol. Febrile events did not occur during the treatment. Intercurrent infections were not observed.

One of the treated patients (no. 5) had a dramatic fall in leucocytes from 1700 to 170 leucocytes/μl after two applications of G-CSF and one subsequent 1.6 Gy fraction of mediastinal irradiation. Radiotherapy and G-CSF treatment were discontinued for safety reasons. After a treatment interruption of 11 days, the leucocyte counts recovered spontaneously.

DISCUSSION

The therapeutic effect of G-CSF in leucocytopenia after high-dose chemotherapy has been reported and is well established in numerous clinical trials [1–4, 13, 14]. Our observations confirm an isolated effect of G-CSF on the regeneration of granulocytes during the application of radiotherapy with or without chemotherapy. Thrombocytopoiesis and erythrocytopoiesis were not influenced.

The most important observation of this study is that continuous G-CSF treatment is tolerated during fractionated radiotherapy in most patients. Only 4 patients suffered from a purely radiation-induced leucopenia. The majority of our patients (7) had been suffering from chemotherapy-induced leucopenia, either due to pretreatment, or due to simultaneous application of chemotherapy with radiotherapy. The response in both groups was the same.

Initially, G-CSF was given to 4 patients who had an interruption of radiotherapy due to leucopenia. After the therapeutic effects on these patients was observed, G-CSF was given prophylactically as soon as leucocyte counts fell below 2000/μl. In 5 of the 7 patients treated in this group, we were able to continue the fractionated radiotherapy without any interruptions. The impact of this effect on cure rates, infection rates and hospitalisation is not clear, however, there is some indication that G-CSF treatment can reduce the overall treatment time in leucopenic patients.

The patient who responded with a dramatic fall in his leucocyte count after the application of two single doses of G-CSF followed by one fraction of mediastinal irradiation had a severely impaired bone marrow reserve due to previous treatment for recurrent NHL. Furthermore, a major part of his bone marrow has been included in the radiation field in this study.

A transient fall of leucocyte counts 30–60 min after the application of G-CSF has been reported by others [3, 13]. This explanation is not likely to be true in our case, as the blood samples in all patients were drawn several hours after the last dose of G-CSF.

Experimental studies have shown that the therapeutic efficacy of G-CSF under fractionated radiation can be reversed, if a very high proportion of the functioning bone marrow is irradiated at the same time [7]. Similar effects have been observed during concomitant application of G-CSF with chemotherapy [4, 15]. Very few reports have been published to date on the therapeutic effects of G-CSF under fractionated radiotherapy [16, 17]. Most of the clinical and experimental studies on the use of growth factors in radiation-induced leucopenia have been applying colony stimulating factors to reconstitute bone marrow function after total body irradiation, with or without bone marrow transplantation [4, 8–11, 18–20].

The criteria for initiating G-CSF treatment during fractionated radiotherapy are disputable. Fushiki and Abe reported on a phase III study in which G-CSF was applied as soon as leucocytes fell below 3000/μl [16]. With a daily dose of 1 μg/kg leucocyte levels could be maintained above 5000/μl in their study during continued radiotherapy. Our cut-off level was chosen at a leucocyte level of 2000 cells/μl. A daily dose of 5 μg/kg filgrastim induced leucocyte levels of above 20 000/μl in all of the responding patients. It would be valuable to evaluate lower dose levels or altered application schedules of G-CSF in the future.

One of our patients had a treatment interruption due to increasing thrombocytopenia. With the availability of G-CSF for clinical use, the suppression of platelet production remains a major problem in cancer therapy today. The occurrence of isolated leucopenia not accompanied by significant thrombocytopenia might not be a common condition in radiotherapy. It might be for this reason that we found only 11 patients eligible for our study during the 9-month time period. This number of patients corresponds to about 1% of all patients treated in our department during this time.

The overall side-effects observed in our study were low. 1 patient reported mild bone pain, 4 patients showed an asymptomatic and reversible increase of serum alkaline phosphatase. Both side-effects have been reported previously [1–3, 13].

In conclusion, our observations indicate that G-CSF is a feasible and efficient treatment for leucopenia during radiotherapy or radiochemotherapy. Future phase II studies should evaluate the optimal dosage and duration of G-CSF application and define the patient population most likely to benefit from the treatment.

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Surveillance Following Orchidectomy for Stage I Seminoma of the Testis

Hans von der Maase, Lena Specht, Grete Krag Jacobsen, Anders Jakobsen, Ebbe Lindegaard Madsen, Mogens Pedersen, Mikael Rørth and Henrik Schultz

From 1985 to 1988, 261 unselected patients entered a nationwide Danish study of surveillance only for testicular seminoma stage I. The median follow-up time after orchidectomy was 48 months, range 6–67 months. 49 patients relapsed (19%). Sites of relapse were paraaortic lymph nodes in 41 patients, pelvic lymph nodes in 5, inguinal lymph nodes in 2 and lung metastases in 1 patient. The median time to relapse was 14 months, range 2–37 months. The 4-year relapse-free survival was 80%. 37 of the relapsing patients (76%) had radiotherapy as relapse treatment. Of these patients, 4 (11%) had a second relapse and received chemotherapy. 1 died of disseminated seminoma. Of the relapsing patients, 12 (24%) had chemotherapy as relapse treatment because of bulky (11 patients) or disseminated disease (1 patient). None of these patients have had a second relapse. However, 2 patients died of infection due to chemotherapy-induced neutropenia. Thus, there have been three seminoma-related deaths (1.1%). The testicular tumour size had an independent prognostic significance. The 4-year relapse-free survivals were 94, 82 and 64% for tumours < 3, 3 to < 6 and ≥ 6 cm, respectively. Patients with tumours ≥ 6 cm will now be given prophylactic radiation treatment, whereas we will continue to use surveillance only after orchidectomy for patients with tumours < 6 cm.
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INTRODUCTION

CONVENTIONAL TREATMENT for patients with seminoma stage I of the testis has until recently been orchidectomy followed by irradiation to the paraaortic and ipsilateral iliac lymph nodes. This treatment strategy has been difficult to challenge because of the exceptionally good outcome. Thus, in a previous publication from the Danish Testicular Carcinoma Study Group (DATECA), we found that only 13 out of 424 patients experienced a relapse (3%) and there were only four cancer-related deaths (1%) [1]. Similar data were given by Zagars in a recent review based on 2376 patients showing a relapse rate of 4.5% and a seminoma-related death rate of 2.3% [2]. Nevertheless, it seemed likely that prophylactic irradiation following orchidectomy was unnecessary for a substantial proportion of these patients. Therefore, there was an obvious need to investigate the possibility of using a surveillance only strategy following orchidectomy—a study that became acceptable because a safe salvage therapy was available. Thus, we initiated a nationwide Danish study in 1985. Here we report the data from this study which comprises the largest study population hitherto reported for surveillance only following orchidectomy in patients with seminoma stage I.

PATIENTS AND METHODS

During the period from January 1985 to January 1988 all new patients with a diagnosis of testicular seminoma in Denmark had

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