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G-CSF during Large Field Radiotherapy Reduces Bone Marrow Recovery Capacity

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Abstract
Objective: Side effects of chemo- and radiotherapy are granulo- and thrombocytopenia. However, the long-term effects of in vivo granulcocyte-colony-stimulating factor (G-CSF) stimulation of the hematopoietic system during radiotherapy are not yet completely understood. In the present study, we sought to determine the bone marrow effect of G-CSF during radiotherapy.
Material and methods: In a prospective, randomized clinical trial 10 patients (6 *m*, 4 *f,* 30-64 yrs, mean 50.6 yrs) were assigned to large field radiotherapy (RT). 7 patients (pat.) with non-Hodgkin lymphoma, one patient with Hodgkin's disease and 2 patients with small-cell carcinoma of the lung were included. The patients were randomized to either radiotherapy alone (group A) or radiotherapy with simultaneous G-CSF (group B) treatment and assessed for acute and late toxicity. Blood samples were drawn and analyzed before and after G-CSF stimulation. The mobilization effectivity of G-CSF on $CD34^+$ progenitor cells was measured using flow cytometry and colony forming units (CFU) testing on admission and during the complete follow-up period (1, 3 and 18 months post RTx).
Results: Overall, 50 pat. were intended to be included to the protocol. However, the preliminary analysis revealed a significant decrease of thrombocytes and $CD34^+$ progenitor cells in the G-CSF treatment group. According to the study protocol further treatment was stopped. Peripheral leukocyte counts ranged between 2800 - 4375 /µl in 9/10 pat. In group B mean thrombocyte levels dropped below 30.000 mg/l and $CD34^+$ progenitor cells to 50% (interruption criteria, $p<0.02$, Student's t-test). Hemoglobin values did not vary. Differential blood smears showed differences in granulocyte counts and a higher proportion of neutrophils in group B. Lymphocyte counts of patients randomized to group A were significantly decreased when compared to group B. In group A, 3/5 pat. developed an overshooting reaction (4,7 x increase) after G-CSF-stimulation. In arm B circulating $CD34^+$ progenitor cells dropped. In arm A, 3/5 pat. had an initial overshoot reaction when compared to none in group B. CFU (> 40 cells) and cluster (4 -39 cells) showed considerable variations.
Conclusion: Our results demonstrate that simultaneous treatment with G-CSF during radiotherapy reduces the mobilization of $CD34^+$ progenitor cells and exhaust the bone marrow capacity while peripheral leukocyte counts remain at baseline levels.

Key words: chemotherapy, radiotherapy, granulocytopenia, thrombocytopenia, stem cell pool capacity, granulocyte-colony-stimulating factor, myelopoiesis, CD34

Abbreviations:
pat: patient; ALL: acute lymphatic leukemia; AML: acute myeloic luekemia; CFU: colony forming units; s.c.: subcutaneously; G-CSF: granulocyte - colony stimulating factor; FITC: fluorescin isothiocyanate; PE: phycoerythrine; NHL: non-Hodgkin-lymphoma; FSC: forward scatter; SSC: sidescatter; LC: lung cancer; RT: radiotherapy

Introduction

Granulo- and thrombocytopenia are critical side effects of chemo- and radiotherapy [1, 30, 31, 33, 32,]. In the complex hematopoietic system, circulating $CD34^+$ precursor cells are specific indicators for bone marrow injury [30, 34]. Because of the specificity, $CD34^+$ counts are used more frequently or in addition to peripheral blood cell counts.Little is known about the long-term effects of in vivo granulocyte-colony stimulating factor (G-CSF) treatment on the hematopoietic system during fractionated radiotherapy. Although the major effect of G-CSF is restricted to late granulopoietic precursor cells, increased proliferation and amplified differentiation of these cells during fractionated radiotherapy result in release of their reserve capacity. New precursor cells are destroyed during migration into the irradiation volume. A vicious circle of extension and migration further potentiates this expansion phenomenon. As a consequence, myelopoiesis is reduced and an "exhaust phenomenon" on early stem cells is triggered. We designed this prospective, randomized study in an effort to evaluate the effect of G-CSF treatment during fractionated large-field radiotherapy (RT).

Aims of the Study

1. Does G-CSF given during fractionated large volume irradiation cause an improved mobilization effect with rapid recovery of hematopoietic stem cells?
2. Is G-CSF responsible for therapeutic failures due to stimulation of precursor cells leading to an exhaustion of the reserve capacity of the bone marrow?
3. What are the long-term effects on the hematopoietic system?

Material and Methods

We quantified progenitor cells via assessment of the mobilization of CD34+ progenitor cells after G-CSF stimulation. Because of considerable inter-individual variations in control patients and tumor patients, CD34+ cells were measured on admission and during follow-up (1, 3 and 18 months). Since many various parameters influence the mobilization of CD34+ progenitor cells they can only be used as an indirect parameter for bone marrow capacity.

Study Design

Prospective randomized study for large-field radiotherapy with (group B) or without (group A) G-CSF stimulation during therapy. All procedures performed and treatment protocols used were approved by the University of Duesseldorf Institutional Review Board and Ethics Committee on Clinical Trials.

Inclusion Criteria

- Age: 18-75 years
- solid or hematological tumors, except ALL / AML or multiple myeloma
- prognosis > 3 months
- large volume radiotherapy
- chemotherapy within 4 weeks before G-CSF stimulation
- stable hematopoietic recovery, defined as WBC >3000/µl, platelet count > 100 000/µl)
- Signed consent to the protocol

Stopping rules were:

1. The decrease of CD 34+ progenitor cells of more than 50% of the initial base level in 1 arm (A or B)
2. Thrombopenia (< 30 000 /µl) in Arm A or B.

Criteria for Large-field Radiotherapy

To analyze the impact of irradiation on CD34+ progenitor cells, small volume irradiation was excluded because of high hematopoietic recovery in non-irradiated bone marrow. A large volume was defined as a volume including at least eight thoracic vertebrae, the complete vertebral column, abdomen or pelvis. Calculation of the irradiated bone marrow volume was based on measurements according to age, gender and body weight.

Mobilization of CD34+ Progenitor Cells

Hematopoietic precursor cells are located in the bone marrow and peripheral blood. The concentration of circulating CD 34+ cells is low and difficult to detect. Therefore, G-CSF (rhu G-CSF, Filgrastim; Neupogen®; Amgen/Roche Corp., Munich, Germany) was administered to all patients to mobilize CD34+ progenitor cells.

Patients were subcutaneously injected G-CSF 12.5 µg/kg body weight from day 1-4. CD34+ and progenitor cells were determined at day 4. In addition to that, a differential blood cell count (CBC count) was routinely performed.

Assessment of CD34+ Progenitor Cells

The mobilization impact of G-CSF on CD34+ progenitor cells in adults is an indirect parameter for stem cell pool capacity. Therefore, the mobilization of CD34+ cells was measured on admission, 1, 3 and 18 months after therapy.

Immune-specific cell surface antigens were analyzed using an immunofluorescent assay. Detection of CD34+ progenitor cells has been done using specific antibodies conjugated to either Fluorescin Isothiocyanate (FITC) or Phycoerythrin (PE).

Colony Assay

After G-CSF stimulation, peripheral blood samples with progenitor cells were collected and transferred to a methylcellulose-Agar plate. 20 x 103 cells were inoculated. Colony growth was controlled on day 7, 10 and 14. Final counts of the Colony Forming Units (CFU) were performed on day 14. Aggregates with 4 - 39 cells were defined as clusters and more than 40 cells as colonies.

Results

Thirteen patients (pat.) were included in the study protocol within 11 months. Since two patients suffered tumorprogression and succumbed to their disease (high-grade NHL) during therapy and another patient was lost to follow–up after 2 months, these 3 patients were excluded from the study. Six men and 4 women (range 30-64, mean 50.6 yrs.) with NHL (n =7), M. Hodgkin (n = 1) and small-cell lung carcinoma (n = 2) were included in the first interim analysis. Further evaluations of these patients were carried out at 1, 3 and 18 months after radiotherapy. By that time, 5 patients in each arm were assessable. A survey of the patient character is shown in Table 1.

Irradiated mean bone marrow volume was calculated at 22.5% in group A and 25% in group B. In group B the CD34+ progenitor cells dropped below 50% ($p<0.02$, Student's t-Test). All patients received G-CSF to mobilize CD34 progenitor cells.

Results

Hemoglobin values remained unchanged. In group B mean values of thrombocytes dropped down to 20 000/µl . In 9/10 patients, peripheral leukocytes were found in a clinically acceptable range (>2500/µl). In

Table 1. Demographic and clinical data of all patients.

	Arm A			Arm B		
Age (years)*	48 (30-64)			55 (30-64)		
Gender	3 *m* / 2 *f*			2 *m* / 3 *f*		
Initial Chemotherapy	4			4		
Disease	LC 1	NHL 3	M. Hodgkin 1	LC 1	NHL 4	
Irradiated regions	mediast. 2	abd. bath 2	paraaort. lym 1	mediast. 2	abd. bath 3	
Target volume dose (Gy)	1x 39.6 (5x1.8) 1x 50.4 (5x1.8)	1x 30 (5x1.5) 1x 39 (5x1.5)	1x 30 (5x2)	1x 30.6 (5x1.8) 1x 50.4 (5x1.8)	1x 30 (5x1.5) 1x 40 (5x1.5) 1x 39 (5x1.5)	
Percentage of irradiated bone marrow	22.5% of total mount of bone marrow volume			25.3% of total mount of bone marrow volume		
Chemotherapy	mediast. 4x ACO 6x CHOP	abd. bath 6x CHOP 1x none	paraaort. lym 4x ABVD	mediast. 6x ACE 6x CHOP	abd. bath 6x CHOP 3x CHOP 1x none	

*median values and ranges
Abbreviations: m = male; *f* = female; LC = lung cancer; NHL = Non Hodgkin Lymphoma; M. Hodgkin = Morbus Hodgkin; mediast. = mediastinum; abd. bath = abdominal bath; paraaort. lym = paraortic lymphnode; ACO = Adriblastin, Cyclophosphamid, Oncovin; CHOP = Cyclophophamid, Adriblastin, Oncovin, Prednison; ABVD = Adriblastin, Bleomycin, Vinblastin, Darcabacin; ACE = Actinomycin D, Cyclo-phosphamid, Etoposid.

Table 2. $CD34^+$ progenitor cells in the peripheral blood.

Group A	C_0		C_1		C_2		C_3	
	abs	rel%	abs	rel%	abs	rel%	abs	rel%
Patient 1	13.13	100%	1.38	10.51%	10.74	81.80%	12.71	96.80%
Patient 2	1.38	100%	2.07	150%	6.59	477.5%	-	
Patient 3	10.74	100%	14.23	132.5%	6.43	59.8%	6.05	56.33%
Patient 4	35.27	100%	39.39	111.7 %	20.28	57.5%	18.03	51.1%
Patient 5	4.26	100%	2.8	65.72%	3.07	72.06%	-	
Group B								
Patient 1	23.59	100%	1.57	6.6%	8.25	34.97%	-	
Patient 2	24.94	100%	9.92	39.77%	7.23	28.98%	-	
Patient 3	36.25	100%	12.55	34.62%	7.68	21.18%	12.70	35.03%
Patient 4	12.48	100%	4.3	34.45%	6.40	51.28%	-	
Patient 5	6.44	100%	-	-	2.02	31.36%	1.3	20.18%

Absolute und relative counts of $CD34^+$ cells in all patients (n = 5 in each group). The mobilization of $CD34^+$ cells was measured on admission (C_0), one (C_1), three (C_2) and 18 months (C_3) after therapy. Group A: Values without G-CSF Group B: G-CSF treatment

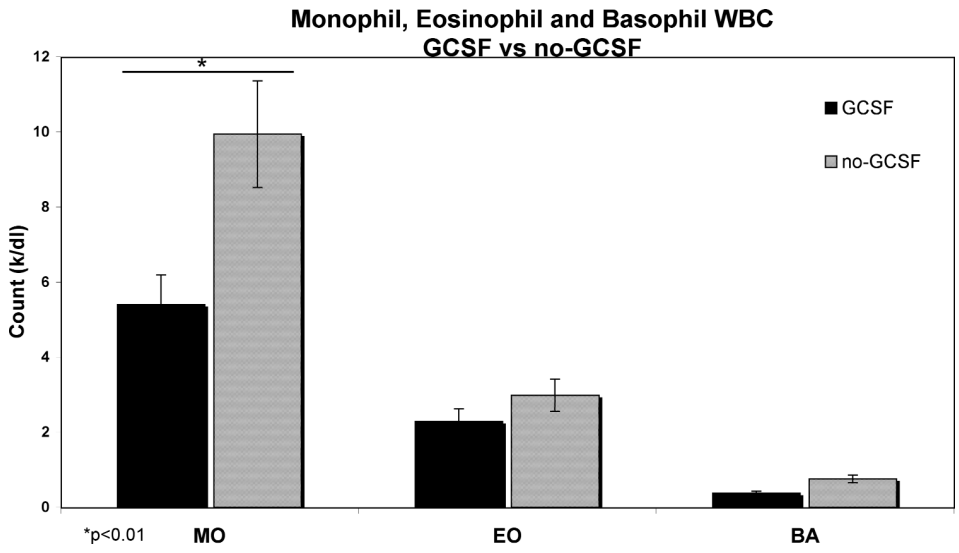

Fig. 1. Differential leukocyte count of the included patients. Numbers indicate absolute counts in 1000/dl. Plotted out are the values for the monophilic, eosinophilic and basophilic subsets. Note the significantly lower monophilic leukocytes in GCSF-treated patients vs. non-GCSF-treatment group. No difference was seen in eosinophilic and basophilic leukocytes. Student's t-Test, $p < 0.01$.

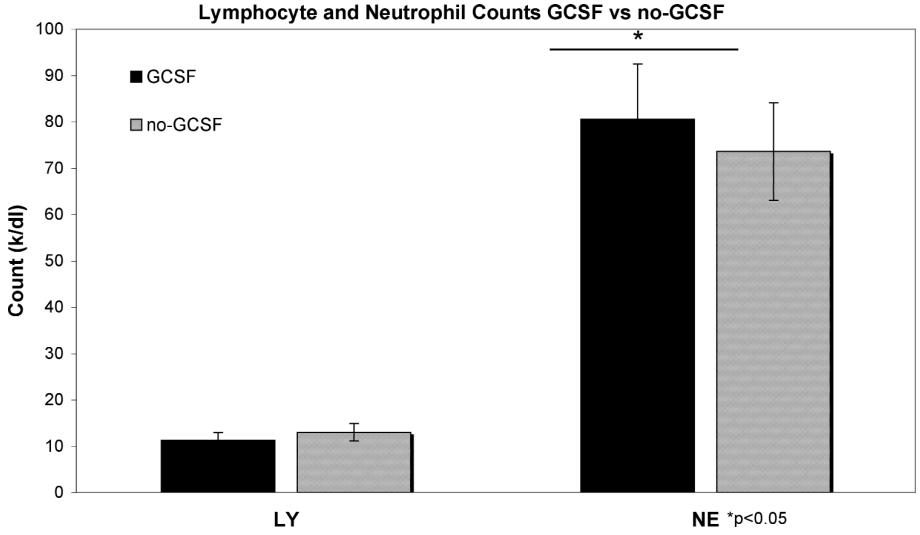

Fig. 2. Lymphocyte and Neutrophil counts of the included patients. Units: 1000/dl. No difference was observed in lymphocyte counts of patients who received GCSF vs. the no-GCSF treatment group. However, we noticed a significantly higher neutrohil count in GCSF-patients vs. no-GCSF thus reflecting a relative neutrophilia compared to the no-GCSF treatment group. Student's t-Test, $p<0.05$.

group A leukocytes ranged from 2800 to 4375/µl. Group B leukocytes showed larger differences. The proportional distribution of the differential blood count showed a significant difference for granulocytes. A higher proportion of neutrophils in group B was detected (>90% in group B, 53% in group A). The lymphocyte subpopulation in group A was found to be significantly lower (Figs. 1and 2). Data of $CD34^+$ progenitor cells in the peripheral blood are shown in table 2.In group A 3/5 pat. developed an overshooting reaction after G-CSF-application. In arm B $CD34^+$ progenitor cells were declining in contrast to arm A, where 3/5 pat. demonstrated an initial overshoot reaction. However, in arm B we observed no increased reaction but values declined to a nadir of 10%. Reaching our stopping rules, we decided to discontinue the study.

Discussion

Our results demonstrate that simultaneous G-CSF application during radiotherapy reduces the capacity of bone marrow recovery. After low-dose radiotherapy an increased endogenous G-CSF production and up-regulation of G-CSF receptors on bone marrow cells were described in literature [2]. Fushiki et al found an increased spleen weight and a rapid recovery from neutropenia when irradiated mice were injected with G-CSF [3]. Other investigators have demonstrated an expansion of early precursor cells after radiotherapy and stimulation with G-CSF [4-6]. All mice survived after the application of growth factors 20 h before and 2 h after a lethal dose of total body irradiation, whereas unprotected, non-treated animals died within 12 days after radiotherapy. The effect of radiotherapy on precursor cells was predominantly analyzed in animal models. Many authors assume that G-CSF has a protective effect against radiation induced myelosuppression [7-9]. Neta and co-workers described a significant radio-protective effect of G-CSF when treatment with Interleukin-1 and Interleukin-6 was initiated simultaneously with radiotherapy [10, 11].

In clinical studies G-CSF was used for the treatment of radiation-induced neutropenia. A rapid recovery of leukocytes was observed and a treatment recov-

ery interval was not necessary [12, 13]. Fushiki and Abe demonstrated in a randomized trial that G-CSF significantly reduces incidence and extent of radiation-induced neutropenia [14]. However, even though initial results encouraged further investigations, during the course of further evaluation of this novel therapeutic strategy, further progress to clinical application was hampered by various side effects. Documented risk factors when using G-CSF in connection with radio-chemotherapy. After the treatment of lung carcinoma with G-CSF and radio-chemotherapy long lasting thrombopenia was observed [15-17].

For the treatment of patients the timing, duration and dosage of G-CSF application are crucial factors for a successful treatment and a favorable outcome,. G-CSF applied after radiotherapy has accelerated the recovery of the hematopoietic system [7, 8]. One single application of 1-2 μg G-CSF before or directly after radiotherapy did not protect against the hematopoietic syndrome [18, 19]. A dose-response relationship was seen after G-CSF application in the overall survival time of mice. Optimal results were achieved when G-CSF was administered at 3h and 24h after radiotherapy [5].

Application of 3μg G-CSF on day 1 to 4 followed by total body irradiation with 6.5 Gy three hours after the last administration of G-CSF results in a myelopoietic depression in mice. For the first time we saw an adverse effect of G-CSF in combination with radiotherapy [20]. Immediately after radiotherapy, precursor cell counts were found to be increased in spleen and bone marrow of animals that had been pretreated with G-CSF. Fourteen days after radiotherapy the precursor cells significantly decreased. At the same time the spleen could only compensate for reduced granulopoiesis in the early phase of irradiation. Erythroid cells predominantly repopulated the irradiated spleen. After radiotherapy the number of peripheral neutrocytes in the pretreated animals declined on day 14 and the monocyte count dopped on day 18 [20].

The mechanism of decreasing circulating $CD34^+$ progenitor cells after radiotherapy is not yet fully understood. The administration of G-CSF in combination with radiotherapy induces an amplified damage for precursor cells which is limited to the granulocyte subpopulation. Additionally, G-CSF is a potent stimulator of CFU-G formation from the pluripotent CFU-GM cells. Baird and coworkers postulated that radiation stimulates the normal bone marrow with an enlarged differentiation of granulocytes. It was hypothesized that increased differentiation and loss of self renewal capacity followed radiation induced bone marrow stimulation [21]. Other investigators found that the multi-potent, early precursor cells (CFU-GEMM) were extremely sensitive to radiotherapy and did not have any recovery capability [22]. Further studies demonstrated that during G-CSF application the GM-CFC (granolucytes - macrophages colony forming cells) had a decreased sensitivity to radiotherapy [23]. The D0 values for GM-CFC were 1.98 Gy for controls and 2.47 Gy in animals that were preconditioned with G-CSF [20]. In a clinical setting, no direct measurement of $CD34^+$ cells is feasible. Peripheral circulating $CD34^+$ cells were counted after previous stimulation with G-CSF. Under steady state conditions effectiveness depends on the G-CSF dose, the mode of application and the interval between G-CSF-administration and blood sample [24-26]. Subcutaneous injection of G-CSF is generally preferred for pharmacodynamic reasons [27]. The highest proportion of CD 34+ cells is expected 4-7 days after G-CSF injection [24, 25, 28]. Even in healthy individuals a variation of $CD34^+$ cell production depending on age, dose and therapeutic timing is seen. Increased interindividual variation is documented in tumor patients [27]. In our study, variables such as age, gender, and previous treatment modalities were comparable in both groups. For stimulation of $CD34^+$ cells all patients received 12,5 μg G-CSF per kg body weight subcutaneously for 4 days [27, 29]. 4/5 patients in each group underwent prior chemotherapy. To minimize interindividual variations, $CD34^+$ progenitor cell counts were assessed on admission and all further values were later compared to this baseline value. Long-term follow-up (18-25 months after the end of radiotherapy) was possible in 3/ 5 pts. in group A and in 2/ 5 pts. in group B. Results did not show any recovery of $CD34^+$ cells in group B. A long-time reduction of the progenitor cell mobilization after radiotherapy was demonstrated. Some investigators observed a recovery up to 40 days after radiotherapy. Their hematologic values remained at 50 - 60% of the baseline level and were comparable to our results [30].

A rapid decrease of the GM-CFC-population was observed in dogs who received a partial or total body irradiation without G-CSF. After 24 hours and during the week following total body irradiation, the values for the GM-CSF population decreased more compared to lymphocytes. Bone marrow recovery was evident by both expansion of GM-CFC- and BFU-E population 14 days after total body irradiation. Several months after radiotherapy these values remained on a low subnormal level [30]. In further experiments, 3 dogs received 2 x 15 μg of rhu–G-CSF/kg/day on seven consecutive days following partial body irradiation. When compared to the control group, the G-CSF-group demonstrated an early expansion of the GM-CSF population. The regeneration of the GM-CSF and of BFU-E compartments was accelerated by early expansion of precursor cells, migration and settlements into the irradiated bone marrow. G-CSF resulted in an expansion of precursor cells [30].

Our results are not directly comparable to these studies due to the experimental conditions of the above mentioned studies. The irradiated bone marrow volumes were smaller and the applied radiation doses were higher. Also, G-CSF was given over a longer time period. However, some parallel effects were seen. In summary, we found a significant decrease of circulating peripheral progenitor cells in the G-CSF treatment group. This effect became clinically evident at the first $CD34^+$ count determination which was performed 4 weeks after the end of the therapeutic course and persisted for more than one year. In contrast to the described animal models we did not find an adequate decrease of circulating peripheral granulocytes. Decreased $CD34^+$ levels persisted even 3 and 18 months after termination of radiotherapy. This was compara-

ble to experiments that have been performed using animal models.

REFERERENCES

1. Zhang HL. Stimulation of low dose radiation on hematopoietic system. Chung Hua I Hsueh Tsa Chih 1993; 73 : 99-100, 127
2. Fushiki M, Ono K, Sasai K, Shibamoto Y, Tsutsui K, Nishida T, Takahashi M, Abe M. Effect of recombinant human granulocyte colony-stimulating factor on granulocytopenia in mice induced by irradiation. Int. J. Radiat. Oncol. Biol. Phys. 1990; 18: 353-7
3. Schuening FG , Storb R, Goehle S et al. Effect of recombinant human granulocyte colony stimulating factor on hematopoiesis of normal dose and on hematopoietic recovery after otherwise lethal total body irradiation. Blood 1989; 74: 1308-1313
4. Uckun FM, Souza L, Waddick KG, Wick M and Song CW. In vivo radioprotective effects of recombinant human granulocyte colony stimulating factor in lethally irradiated mice. Blood 1990; 75: 638-645
5. MacvittieTJ, Monroy RL, Patchen ML et al. Therapeutic use of recombinant human G- CSF (rhG-CSF) in a canine model of sublethal and lethal whole - body irradiation. Int. J. Radiat. Biol. 1990; 57: 723-36
6. Tanikawa S, Nakao I, Tsuneoka K, Nara N.Effects of recombinant Granulocyte-Colony-Stimulating Factor(rG-CSF) and recombinant Granulocyte-Macrophage –colony-Stimulating Factor (rGM-CSF) on acute radiation hematopoietic injury in mice. Exp. Hematol. 1989; 17: 883-888
7. Patchen ML, Mac Vittie TH J, Solberg BD, Souza LM: Therapeutic administration of recombinant human Granulocyte Colony-Stimulating Factors accelerates hemopoietic regeneration and enhances survival in murine model of radiation-induced myelosuppression. Int. J. Cell. Clon. 1990 ; 8 : 107-122
8. Hosoi Y, Kurishitta A, Ono T, Sakamoto K. Effect of recombinant human Granulocyte Colony-Stimulating Factor on survival in lethally irradiated mice. Acta Oncol. 1992; 31: 59-63
9. Neta R, Douches SD, Oppenheim JJ. Interleukin-1 is a radioprotector. J. Immunol. 1986; 136: 2483-2485
10. Neta R. Radioprotection and therapy of radiation injury with cytokines. In: The Biology of Hematopoesis Wiley-Liss Inc. 1990; pp 471-478
11. Bamberg M, Schmidberger H, Hess C. F. G-CSF in the management of neutropenia during radiotherapy. Tumordiagn. u. Ther. 1992; 13: 125-6
12. Schmidberger H, Hess CF, Hoffmann W, Reuss- Borst MA, Bamberg M. Granulocyte colony - stimulating factor treatment of leucopenia during fractionated radiotherapy. Eur. J. Cancer. 1993; 14: 1927-1931
13. Fushiki M, Abe M, Phase III study of recombinant human granulocyte colony-stimulating factor (rhG-CSF) on neutropenia in radiation therapy (Abstract) Rad. Oncol. 1992; 24 : 62
14. Bunn PA jr, Crowly J, Hazuka M et al. A randomized study of VP16/ cisplatin / chest RT ±GM- CSF in limited stage small cell lung cancer: preliminary results of a SWOG study. Lung Cancer 1991; 7 (supp) : 139
15. Bunn PA, Crowley J, Kelly K, Hazuka MB, Beasley K, Upchurch C, Livington R. Chemoradiotherapy with or without granulocyte- macrophage colony-stimulating factor in the treatment of limited-stage small- cell lung cancer: A prospective Phase III randomized study of the south west oncology group. J.Clin. Oncol. 1995: 13: 1632-41
16. Momin F, Kraut M, Lattin P et al. Thrombocytopenia in patients receiving chemoradiotherapy and G- CSF for locally advanced non small cell lung cancer (NSCLC). J. Clin. Oncol. 1992, Proc. of ASCO 11: (Abstract 983)
17. Neta R, Oppenheim JJ, Douches SD. Interdependence of the radioprotective effects of human recombinant interleukin1__, tumor necrosisfactor _ , granulocyte colony-stimulating factor , and murine recombinant granulocyte-macrophage colony-stimulating factor. J. Immunol. 1988; 148: 108-111
18. Neta R, Oppenheim JJ: Cytokines in therapy of radiation injury. Blood 1988; 72: 108-111
19. Popísil M, Hofer M, Netíkova J, Holá J, Znojil V, Vácha J and Vacek A. Pretreatment with Granulocyte Colony-Stimulating Factor reduces myelopoiesis in irradiated mice. Radiat. Res. 1999; 151: 363-367
20. Baird MC, Hendry JH, and Testa NG. Radiosensitivity increases with differentiation status of murine hemopoietic progenitor cells selected using enriched marrow subpopulation and recombinant growth factors. Radiat.Res. 1990; 123: 292-294
21. Uckun FM, Song CW. Radiobiological features of human pluripotent bone marrow progenitor cells (CFU-GEMM). Int. J. Radiat. Oncol. Biol. Phys. 1989; 17: 1021- 1025
22. Uckun FM, Gillis S, Souza L, Song W. Effects of recombinant growth factors on radiation survival of human bone marrow progenitor cells Int. J. Radiat. Oncol. Biol. Phys.1989; 16: 415-435
23. Dührsen U, Villevall JL, Boyd J et al. Effects of recombinant human granulocyte colony-stimulating factor on hematopoietic progenitor cells in cancer patients. Blood 1988; 72: 2074-2081
24. Schwinger W, Mache C, Urban C, Beaufort F, Toglhofer W.: Single dose of filgrastim (rhG-CSF) increases the number of hematopoietic progenitors in the peripheral blood of adult volunteers. Bone Marrow Transplant. 1993;11: 489-492
25. Dreger P, Haferlach T, Eckstein V et al. G-CSF mobilized peripheral blood progenitor cells for allogeneic transplantation : safety, kinetics of mobilization, and composition of the graft. Br. J. Haematol. 1994; 87: 609-613
26. Haas R, Murea S. The role of granulocyte colony-stimulating factor in mobilization and transplantation of peripheral blood progenitor and stem cells. Cytokines Mol. Ther. 1995; 1 (4): 249-270
27. Matsunaga T, Sakamaki S, Kohgo Y et al. Recombinant human granulocyte colony- stimulating factor can mobilize sufficients of peripheral blood progenitor cells in healthy volunteers for allogeneic transplantation. Bone Marrow Transplant. 1993; 11: 103 -108
28. Kobbe G. Einflussfaktoren auf die G-CSF-vermittelte Mobilisation hämatopoetischer Progenitorzellen bei Patienten mit hämatologischen Neoplasien und gesunden Stammzellspendern. Dissertation der Medizinischen Fakultät der Heinrich Heine Universität Düsseldorf. 1999.
29. Nothdurft W, Kreija L. Hemopoietic progenitor cells in the blood as indicator of the functional status of the bone marrow after total body irradiation: experiences from studies in dogs. Stem Cells 1998; 16 (Suppl.): 97-111
30. Mazur G, Wrobel T, Wlodarska-Polinska I, Lacko A, Bojarowska K, Jagas M, Kuliczkowski K. Assessment of hematopoiesis regeneration in patients with solid tumors after radiotherapy Pol Arch Med Wewn. 2004 Jan;111(1): 53-6
31. Wang TJ, Liu LL, Cheng GH, Liu XL, Qu YQ, Wu ZF, Zhang CF. A brief report on effect of rhG-CSF in treating leukopenia after radio-and chemo-therapy of patients with breast cancer Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2004 Jun;12(3):381-2

32. Qiu HY, Wu DP, Sun AN, Chang WR, Jin ZM, Miao M, Tang XW, Shen YM, Fu ZZ. Mobilization of peripheral blood stem cells with mitoxantrone and high-dose cytarabine chemotherapy and rhG-CSF in patients with hematopoietic malignancies Zhonghua Xue Ye Xue Za Zhi. 2004 Aug;25(8):462-5.
33. Movsas B, Hudes RS, Schol J, Mellenson M, Rosvold E, Nicolaou N, Litwin S, Wang H, Keenan E, Curran WJ Jr, Langer CJ. Induction and concurrent paclitaxel/carboplatin every 3 weeks with thoracic radiotherapy in locally advanced non-small-cell lung cancer: an interim report Clin Lung Cancer. 2001 Nov;3(2):125-32
34. Takeyama K, Ohto H. PBSC mobilization Transfus Apheresis Sci. 2004 Dec;31(3):233-43

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