RESEARCH COMMUNICATION

Granulocyte Colony Stimulating Factor for Prevention of Craniospinal Radiation Treatment Interruption among Central Nervous System Tumor Patients

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Abstract

Objectives: In this pilot randomized clinical trial the preventive effects of weekly granulocyte colony stimulating factor (GCSF) injection for patients with central nervous system (CNS) tumors receiving craniospinal irradiation were assessed with regard to risk of treatment interruption. Methods: We randomized 40 CNS cancer patients into two groups (20 patients each), the first receiving GCSF prevention therapy before weekly craniospinal radiotherapy and the control group without this prophylaxis. The main outcome was whether GCSF preventive therapy decreased the rate of interruption of radiotherapy because of leucopenia and thrombocytopenia. We used t -test, and chi-square test statistics to compare the quantitative and qualitative outcomes. Results: there were no significant differences in platelets and WBC loss between the treatment and control groups. Treatment interruption was lower in weekly GCSF therapy group (35%), compared to the control group (55%), although the difference was not statistically significant (P value 0.2). While 8 patients (40%) also received GCSF therapy due to leucopenia in the control group only one patient reached a critical level and needed GCSF therapy because of irradiation complications (p-value 0.02). Among those who received naodjuvant chemotherapy (8 patients in each group), among the GCSF prevention group only in one (12%) we had to interrupt radiotherapy, as compared to 6 in the control group due to WBC loss. Conclusion: Weekly GSCF injections among CNS tumor patients receiving craniospinal therapy may decrease treatment interruption. A larger study with longer follow-up is now needed to confirm our results.

Keywords: CNS tumors - irradiation interruption - prevention - GCSF

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Introduction

Craniospinal irradiation (CSI) is employed to reduce the risk of dissemination of primary CNS tumors through the CSF pathways and thereby improve survival. While it is the way of elective or therapeutic treatment in some patients with cranial ependymoma, primary cerebral lymphoma and germ cell tumors, it is of proven benefit in patients with medulloblastoma and other primitive neuroectodermal tumors (PNETS) of CNS and CSI therefore remains an important part of treatment. The increasing use of chemotherapy in patients with PNETS also means that CSI will be combined with systemic chemotherapy of increasing intensity with potential for more frequent and severe haematological toxicity (Sarah et al., 1998). Also the use of such treatment encompassing large volumes of bone marrow can significantly depress hematologic counts (Brada et al., 1990; Bailey et al., 1995). Although treatment interruption may allow recovery from such acute toxicities, it is undesirable, because interruption may compromise tumor control (Custer and Ahlfeldt, 1932).

With head and neck and uterine cervix cancers, prolongation of the RT treatment course has resulted in an inferior locoregional control (Bataini et al., 1989; Barton et al., 1992; Fyles et al., 1992). Accelerated repopulation of tumor clonogens surviving a protracted treatment course has been postulated as a mechanism for an inferior local control (Withers et al., 1988). In medulloblastoma, there is information that patients with RT treatment duration of >45 days have a better posterior fossa control than those with RT duration of <45 days (DelCharco et al., 1998).

Hematopoietic growth factors and stem cell rescue are increasingly used to overcome dose-limiting myelotoxicity of intensive chemotherapy. similar strategies have been suggested to deal with radiation induced myelo-suppression particularly following radiation which includes a large amount of active bone marrow such as CSI (Marks et al., 1992; Janssen et al., 1994).

In the literature several article have also reported on significant treatment interruption resulting from leukopenia and thrombocytopenia. Also, according to the study of Aghili and in our department and the frequency of treatment interruption in treatment patients with CSI

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method due to leukopenia and thrombocytopenia we decided to evaluate the effect of prophylactic GCSF in these patients.

Materials and Methods

This trial was approved by the research ethics committee of the university to which the performing institution is affiliated. In this prospective study performed from 2006-2009, 40 patients with primary brain tumors who needs craniospinal irradiation as a part of their treatment with pathologies like medulloblastoma, ependymoblastoma,… entered to this trial, in radiation oncology department of cancer institute.

This study was a randomized clinical trial. after written informed consent, patients randomized in two case and control groups. the patients in case group received 1 dose of GCSF subcutaneously per week during treatment of CSI. Complete blood count (CBC) was checked in each group weekly and with onset of leucopenia (WBC<2000), treatment was stopped. After GCSF and rising of WBC>2000 treatment was again continued. In the case PLT the cut off was <100000.

Radiotherapy was delivered by mega voltage tele cobalt techniques (theratron 780 C at SSD=80). Cranial radiation encompassed the whole brain and upper cervical spine to the level of C6 using parallel opposed fields with appropriate lead shielding. the site of primary disease was boosted by limited volume irradiation using two fields. the spinal cord was treated from C6 to S2-S4 via one or two direct posterior field. The field width covered the whole vertebral body and a margin and was occasionally widened in the sacro-iliac region. after each 10-12 GY ,the gap junction was changed to avoid junction overdose. treatment was delivered 5 days per week. the dose to the whole brain was 36 GY in 19-20 fractions .the usual dose to the posterior fossa or to the site of primary disease was 54-56 GYin 6-8 weeks. the dose to the spinal cord was 36 GY over 4 weeks. The median dose to the spine was 36 GY (19-20 fractions).

Treatment interruption were scored in terms of the total number of the days of interruptions that occurred and the duration of days of CSI missed. Treatment interruption and duration were determined directly from the daily treatment records made in the RT chart by the radiation therapy technologist. we excluded week-end from the days of treatment interruption.

Hematological parameters

Complete blood counts (CBC) were obtained during radiotherapy. CBC level in first day of the start of radiotherapy was used as the pre treatment value. Serial measurement were taken during radiotherapy at least once a week.

Results

A total of 40 patents entered to this trial from April 2006 to September 2009. There were 21 males and 19 females, their characteristics being summarized in Table 1. Data for haematological indices at the end of 4 weeks follow-up are shown in Table 2, along with findings for treatment interupption and GCSF therapy. Although T-test showed that intervention group and control group are statistically different from each other with regards to the need for GSCF therapy during the radiotherapy, the effect is modified to some extend with age of participants, the difference was not statistically significant. But this is highly likely due to sample size.

Table 1. Characteristics of Patients by Treatment Group

Variable	GCSF	Control	P value
Male/Female	14/6	7/13	0.02
Age# (year) (± SD)	21.2 (2.3)	15.2 (2.8)	0.1
Dose fraction# (± SD)	179 (0.7)	177.5 (1 .0)	0.2
Hb# (± SD)	13.4 (0.4)	13.3 (0.5)	0.9
Plt# (x 10^5) (± SD)	2.46* (19,045)	2.67 (28,487)	0.5
WBC# (± SD)	6,550 (608)	6,005 (688)	0.5
Neoadj Chemotherapy	8 (40%)	8 (40%)	1
Pathology type			
Disgerminoma	0	1	
Medulloblastoma	16	15	
Pinealoblastoma	0	1	
Epandimo	4	3	

Table 2. Comparison of Hematological Indices and Radiotherapy Complications among GCSF Prevention and Control Groups at the end of Follow-Up

	GCSF	Control	p value
Average Hemoglobin	12.9	12.7	0.5
Average Platelet	142,517	144,400	0.8
Average WBC	4,078	2,988	0.007
Treatment interruption	7 (35%)	11 (55%)	0.2
GCSF therapy	1 (5.3%)	8 (40%)	0.01

In our study, among those who received naodjuvant chemotherapy (8 patient in each group), among the GCSF prevention group only in one (12%) patient we had to interrupt radiotherapy, while out of 8 patients in the control in 6 patients we had to pause the radiotherapy due to WBC loss. The average WBC counts after starting the trial was statistically different in the treatment and control group (see Figure 1).

Discussion

CSI has become part of standard management in brain malignancies over the last 40 years, although the potential long-term squeal constitutes a limiting factor, particularly

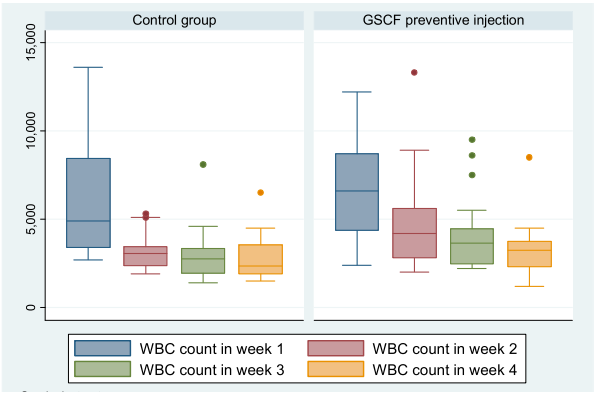

Figure 1. Data for White Blood Cell Counts

in young children(Spiegler et al., 2004; Bowers et al., 2009), but appropriate results made the (CSI)-based radiotherapy (RT) the gold standard for some intracranial lesions likewise intracranial medulloblastoma (Shibamoto et al., 1988; Dearnaley et al., 1990)

That is due to the fact that the bone marrow is extremely radiosensitive; indeed, some degree of injury is produced by any dose. Mauch et al. showed that peripheral blood cells respond acutely by progressively decreasing in number, an effect caused by the destruction of both mature and precursor cells (Mauch et al., 1995) Par mentier et al., cited three mechanisms of physiologic compensation for loss of hematopoietic activity in irradiated area of the marrow: (Sarah et al., 1998) stimulation of hematopoietic activity in non-irradiated areas; (Bailey et al., 1995) extention of such activity to long bones, which are normally inactive in adult subjects, and extramedullary erythropoiesis; and (Brada et al., 1990) partial recovery of hematopoietic activity in the irradiated areas. the depression of the hematopoietic activity in irradiated areas is compensated for by the stimulation of hematopoietic activity in the non irradiated areas soon after irradiation (Parmentier et al., 1983).

Wide field irradiation in the form of CSI for CNS tumors or nodal irradiation in lymphoma may result in myelosuppression with a risk of neutropenic sepsis and treatment interruptions compromising treatment efficacy (Marks et al., 1995). Some patients receiving CSI required a treatment interruption for more than 1 week to recover from hematologic toxicity, thus resulting in a protracted RT course (del Charco et al., 1988) Prohibition to these complications,Haemopoietic growth factors (HGFs) and stem cell rescue are increasingly used to overcome dose-limiting myelo toxicity of intensive chemotherapy. Similar strategies have been suggested to deal with radiation-induced myelosuppression, particularly following radiation which includes a large amount of active bone marrow such as cranio-spinal axis irradiation (Marks et al., 1992; Mac et al., 1993; Janssens et al., 1994). Although Haemopoietic growth factors (HGFs) are increasingly used as supportive treatment in oncology, the use of HGFs should be associated with better survival and quality of life and hematologic growth factors may well be useful in this setting (Marks et al., 1995). Gale et al mentioned that, administration of HGFs such as G-CSF during radiotherapy may increase radiation-induced toxicity by increasing the exposure of proliferating haemopoietic stem cells to radiation. G-CSF also promotes stem cells to differentiate along one lineage which may result in deficiencies in other cell lineages unless other growth factors, such as platelet-stimulating cytokine, were also available (Gale and Butturin, 1990). But in this trial we did not have such complications.

Against up-front chemotherapy, it has been postulated that Neoadjuvant chemotherapy might delay initiation of radiotherapy, resulting in tumor progression (Bailey et al., 1995; Mastrangelo et al., 1999; Zeltzer et al., 1999) and might cause difficulties in completing craniospinal radiotherapy. Cranio-spinal radiotherapy was also reported to lead to a more rapid decline in blood count and to a lower nadir when preceded by chemotherapy, particularly if more than four cycles were used (Marks et al., 1995).

In the study of Sarah et al., (1998) which included adults and children from 270 patient, 66 (24.5%) patients had treatment interruption and that interruption was extended beyond 12 weeks in 17 (8%) of patients and the peak of treatment interruption was in second week of CSI and also 33% of patients developed grade 3 and 4 leucopoenia .

According to some previous studies, on the hematological consequences of CSI for medulloblastoma, The decrease in white blood cell count (WBC) occurred early or towards the middle of the course of radiotherapy(9). the parameters predicting the risk of toxicity were similar to those reported here and a similar model may be applicable to these data. In summary, one-third of patients undergoing CSA radiotherapy developed grades 3 and 4 hematological toxicity. The risk was higher in children and in patients who received chemotherapy prior to radiotherapy, but the overall treatment- related morbidity was low (Marks et al., 1995).

In order to prevent radiotherapy complications, we prescribed 108 doses of GCSF, while only 8 doses of GCSF was injected in the control group. One patient in the treatment arm (preventive GCSF), received GCSF therapy during the study period. so, it seems that prescribing of prophylaxis GCSF is not cost benefit unless in patients who have received neoadjuvant chemotherapy before CSI treatment. in order to get more accurate results we should follow up these patients in longer time to evaluate the effect of interruption of treatment in both survival and recurrence of tumor in each groups and also design a trial with larger sample size to observe the effects of GCSF prophylaxis treatment. It would be in this setting that HGFs may have a particularly useful role. At present the parameters of age, prior treatment and pretreatment blood count identify a population at risk of hematological toxicity where further studies of HGFs should be targeted.

Prior to developing intervention strategies it is important to establish consistent criteria for instigating radiotherapy treatment interruptions and to establish whether hematological toxicity by causing treatment interruptions affects overall survival and define the most appropriate scenario for the potential use of GCSF and also regarding cost benefit.

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