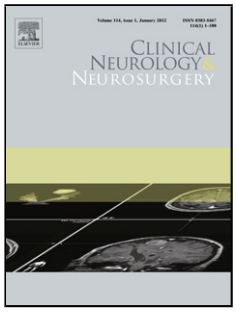

Effect of prophylactic Granulocyte-Colony Stimulating factor (G-CSF) on acute hematological toxicity in medulloblastoma patients during Craniospinal Irradiation (CSI)

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Short title: Prophylactic G-CSF during CSI

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Highlighs

- To see the effect of prophylactic GCSF in medulloblastoma patients during CSI
- Prophylactic GCSF was given during CSI on weekends
- Prophylactic GCSF reduces radiation induced hematological toxicity

Abstract:

Objectives: Haematological toxicity and treatment breaks are common during cranio-spinal irradiation (CSI) due to irradiation of large volume of bone marrow. We conducted this study to see the effect of prophylactic granulocyte colony stimulating factor (GCSF) in reducing treatment breaks.

Patients and methods: The study was conducted over a period of 15 months from August 2017 to November 2018. Histopathologically proven Medulloblastoma patients received prophylactic GCSF during CSI. Acute haematological toxicities and treatment breaks were noted and effect of age and

pretreatment blood counts were analyzed by SPSS (Statistical Package for Social Sciences) version 23.

Results: A total of 28 patients were included in the study. During CSI, hematological toxicity leading to treatment breaks was observed in 11 (39.3%) patients, of which grade 3 and 2 toxicities were seen in ten and one patients respectively. Younger age (<10 years) at diagnosis was significantly associated with the development of hematological toxicity (p=0.028, Chi-Square). No correlation was found with pre-treatment blood counts.

Conclusion: Prophylactic use of GCSF may be effective in preventing radiation induced haematological toxicity and treatment breaks

Keywords: Medulloblastoma, Cranio-spinal irradiation, hematological toxicity, treatment breaks, granulocyte colony stimulating factor, younger age

Introduction

Standard treatment of Medulloblastoma consists of maximum cytoreductive surgery followed by craniospinal irradiation (CSI) and chemotherapy. CSI is considered as an important part of the treatment to reduce the risk of dissemination via CSF and to improve survival. However a significant amount of active bone marrow in spine, skull and pelvis also get radiation during CSI, which leads to hematological toxicities and thus treatment interruption. Although these acute haematological toxicities can be recovered following treatment interruption, it is not desirable as unscheduled break in radiotherapy is associated with poor outcome in Medulloblastoma. [1] Leucopenia has been reported as the commonest hematological toxicity during CSI. In an older study, it was reported that nearly one third of the patients undergoing CSI developed hematological toxicity and younger age, prior chemotherapy and a lower pre-treatment blood count were the predictors of toxicity. [1] Previously published data from our own institute has shown that without GCSF, 75% Medulloblastoma patients had treatment interruption during CSI, out of which >90% interruptions were due to neutopenia.[2] It has been reported that use of granulocyte colony stimulating factor (G-CSF) can prevent haematological toxicity during CSI. [3] However there is no conclusive data on it. Thus we conducted this study to evaluate the impact of prophylactic G-CSF on acute hematological toxicity during CSI for Medulloblastoma and resultant treatment interruptions.

Patients and methods: This prospective study was conducted over a period of 15 months from August 2017 to November 2018 in a tertiary care center in India. The study was carried out in accordance with the declaration of Helsinki and approval was obtained from the Institutional Ethics Committee. Histologically proven Medulloblastoma patients of age more than three years (who do not

require general anesthesia for radiotherapy) with normal blood counts and those who had Karnofsy/Lansky scale of ≥ 70 were enrolled in the study. Written informed consent was taken from all the patients or their guardians. Pre-RT work-up included a post operative Contrast Enhanced Magnetic Resonance Imaging (CEMRI) of the brain which was performed within 3-4 weeks of surgery to allow resolution of post operative changes for better delineation and characterization of the tumour bed. A screening imaging of whole spine was also performed at the same time, if not done previously. Cerebrospinal fluid (CSF) was obtained via lumbar puncture to look for malignant cells. Molecular sub-grouping was performed on histology for integrated diagnosis and prognostication, whenever feasible. Baseline complete blood count (CBC), kidney and liver function tests (KFTs/LFTs) and chests X-Ray were performed as a part of routine pre-treatment work-up. Bone marrow aspiration was not done for staging purpose.

Post-operative radiation therapy (PORT) consisted of CSI (36 Gy/20fractions, 5 days in a week) followed by posterior fossa boost (18Gy/10fractions). CSI was started preferably within 4-6 weeks from surgery using three-Dimensional conformal technique (3D-CRT) or Volumetric Modulated Arc techniques (VMAT). Weekly injection Vincristine (1.4mg/m^2) was given on every Monday while prophylactic G-CSF (15 mcg/kg) was given subcutaneously twice weekly on Saturday and Sunday during CSI. We avoided using prophylactic GCSF on weekdays as we do not have sufficient data on safety of GCSF with radiotherapy. CBC was performed baseline on a weekly basis to monitor for hematological toxicity which was graded as per the RTOG criteria. (Table 1) Spinal RT was interrupted in case of grade 2 or more hematological toxicity while entire CSI was interrupted only when there was febrile neutropenia. RT was resumed after sufficient myelorecovery and the interruption days were calculated. The treatment with GCSF was well tolerated and no patient developed significant bone pain.

Statistical analysis

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 23. Descriptive statistics were used to analyse the qualitative data. Pearson's Chi square test and Fischer exact test were used to look for the association between categorical variables and primary end points. Continuous variables in clinical parameters were compared with logistic regression analysis by using binary logistic regression test. A p value of < 0.05 was considered statistically significant.

Results

A total of 28 patients were included in the study. Of these, 18 patients were males and 10 were females. The median age at presentation was 12 years (3-34 years). Patient and disease related characteristics have been summarised in table 2. Headache and vomiting were the most common

presenting symptoms and the median duration of these symptoms was two months (0.4-36 months). The cerebellar cortex and fourth ventricle were the most common sites of involvement with 11 (39.3%) patients showing disease at these sites each. The cerebellar vermis was involved in five (17.9%) patients. The spinal cord was the primary site in one (3.6%) patient. Twenty (71.4%) patients underwent gross total excision of the tumour, six (21.4%) patients underwent near total excision and two (7.1%) underwent subtotal excision of the tumour. On morphological subtyping, classical, desmoplastic, anaplastic and nodular medulloblastoma was seen in seventeen (60.7%), six (21.4%), three (10.7%) and one (3.6%) patient respectively. Medulloepithelioma was seen in one patient. Molecular subtyping was performed in 14 patients, of which Group 3/4 (non WNT/non SHH) was the most common subtype seen in six patients. WNT and SHH subtypes were observed in four patients each. Spine screening MRI showed metastasis in four patients and CSF cytology was positive in three of them. Post operative CEMRI brain was performed at a median of 4 weeks from surgery and showed residual disease in 16 (57.1%) patients. Confounding factors such as baseline blood investigations and nutritional status were excluded before starting CSI. All patients completed CSI with or without interruption. A total of 54 Gy radiotherapy dose at 1.8 Gy per fraction, five fractions a week was prescribed. Entire craniospinal was irradiated to a dose of 36 Gy followed by a Posterior fossa (PF) boost of 18 Gy. Median PTV volume was 2265.79cc (1699.36-2866.60cc) and median bone marrow volume irradiated was 603.51cc (354.41-975.00cc). Concurrent vincristine during CSI was administered in 26 patients, of which only fifteen patients received the planned 4 cycles. Five patients received 2 cycles and two patients received 3 and 5 cycles each. Hematological toxicity was observed in 11 (39.3%) patients, of which grade 3 and 2 toxicities were seen in ten and one patients respectively. All these eleven patients had breaks in RT. Characteristics of patients who experienced treatment interruption has been shown in table 3. Seven patients had one interruption and three patients had 2 interruptions in spinal RT. One patient had 3 interruptions and the entire course of CSI had to be interrupted in this patient because of development of febrile neutropenia. Nine (out of the 11) patients had treatment breaks of less than or equal to 5 days. Treatment interruptions lasting for more than 5 days were observed in only 2 (7.6%) patients. We observed that younger age (<10 years) at diagnosis was significantly associated with the development of hematological toxicity (p=0.028, Chi-Square), while no correlation was obtained with pre-treatment blood counts.

Discussion:

Bone marrow is an extremely radiosensitive structure located along axial skeleton and long bones of the body. Thus a significant proportion of Medulloblastoma patients undergoing large field radiotherapy like CSI develop haematological toxicity. Unlike chemotherapy, there is a very limited data supporting prophylactic use of GCSF to prevent radiotherapy induced neutropenia. However, few studies have shown that hematopoietic growth factors have a protective role on radiotherapy induced

hematological toxicity. Radiotherapy induced bone marrow suppression may require treatment interruption that may reduce the efficacy of the treatment.

Young patients have relatively high risk of developing hematological toxicity as the greater proportion total marrow is irradiated. Moreover, the additional compensatory mechanism of increase in the activity of previously quiescent marrow areas in the femora and humeri during and after CSI is absent in children. Older studies have shown that GCSF is effective in preventing radiotherapy induced neutropenia without increasing tumor cell proliferation. [4] Marks LB et al recommended GCSF in those patients who develop neutropenia during radiotherapy. [5] The therapeutic use of G-CSF for managing CSI induced neutropenia has been reported in a case series of four consecutive patients receiving CSI who received G-CSF when the absolute neutrophil count (ANC) in peripheral blood fell below 1500/microlitre. Similar daily dose of G-CSF was used as recommended for chemotherapy. The authors concluded that G-CSF therapy is an effective and well-tolerated method to manage CSI induced neutropenia. [6]

Later Kolotas C et al observed that use of prophylactic GCSF is effective in preventing radiotherapy induced neutropenia that ultimately reduces overall treatment time as compared to those who did not receive GCSF. [7]

In another randomized clinical trial, preventive effect of weekly GCSF was assessed with regard to risk of treatment interruption in patients receiving CSI. They found that incidence of treatment interruption was lower in weekly G-CSF therapy group (35%), compared to the control group (55%), although the difference was not statistically significant. [3]

Although there is a concern of tumor cell growth in same way as normal hemopoetic cells, there is no clinical evidence for this as use of GCSF to prevent chemotherapy induced neutropenia has not reported any unexpected tumor progression.

Another concern is that G-CSF use promotes stem cells to differentiate along one lineage, leading to deficiency in other cell lineages. [8]

The results of our study are encouraging. It has demonstrated lower incidence of neutropenia as compared to the historical data and a previous study published by our own institute. However, it is an underpowered study due to its design. Thus a generalization of the results should be done only after further well designed trials.

Conclusion: Haematological toxicity leading to radiotherapy treatment breaks is a common problem during craniospinal irradiation. Small series have shown that prophylactic G-CSF is useful in preventing radiation induced haematological toxicity and treatment breaks. However adequately powered clinical trials should be conducted to establish the guidelines for the routine use of prophylactic G-CSF during craniospinal irradiation.

Credit Author Statement

Kumar N: Conceptualization, Writing - Review & Editing, supervision, Project administration

Gupta A: Methodology, data collection, Formal analysis, Writing - Original Draft

Gupta K: Investigations, Writing - Review & Editing, supervision

Salunke P: Resources, Writing - Review & Editing, supervision

Khosla D: Writing - Review & Editing

Yadav BS: Writing - Review & Editing

Kapoor R: Writing - Review & Editing

Compliance with Ethical Standards

- Non funded project
- Compliance with Ethical Standards was maintained
- Ethical clearance was obtained from Institute ethics committee before starting study.
- Disclosure of potential conflicts of interest: None
- Research involving human participants: Yes
- Informed consent was obtained from all the participants or their guardians prior to the study

Conflict of interest: None

Acknowledgement: None

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Table 1. RTOG grading system for acute hematological toxicity

Grade	Hemoglobin (gm%)	Leucocyte count(per µL)	Platelet count (per µL)
0	> 11	> 4000	> 1,00,000
1	9.5 – 11	3000 – 4000	75,000 – 1,00,000
2	7.5 – 9.5	2000 – 3000	50,000 – 75,000
3	5 – 7.5	1000 – 2000	25,000 – 50,000
4	< 5	< 1000	< 25,000

Table 2. Patient and disease characteristics (n=28, median age at presentation=12 years)

Characteristics	Number of patients (%)
Gender	Males =18 (64.3) Females=10 (35.7)
Tumour site	Cerebellar cortex =11 (39.3) Fourth ventricle =11 (39.3) Cerebellar vermis =5 (17.9) Spinal cord =1 (3.6)
Extent of surgical resection	GTE =20 (71.4) NTE =6 (21.4) STE =2 (7.1)
Morphological subtype	Classical =17 (60.7) Desmoplastic =6 (21.4) Anaplastic =3 (10.7) Nodular =1 (3.6) Medulloepithelioma =1 (3.6)
Spinal metastasis	MRI positive =4 (14.2) CSF positive =3 (10.7)

Table 3: Characteristics of patients who experienced haematological toxicity (n=11)

S. NO	Age (in years)	Histology/ molecular pathology	Type of surgery	Drop Mets[4]	concurrent Vincristine (VCR)	Number of weekly VCR cycles	Highest Grade of haematol--ogical toxicity	T/t [5] Interruption started after fractions of RT (weeks)	Number of T/t breaks	Total duration of T/t interrupt-ion (in days)
1	5	Anaplstic	NTR[1]	Yes	Yes	2	3	7 (2^{nd})	2	3
2	5	Group 3/4	STR[2]	Yes	Yes	4	3	11 (3^{rd})	2	4
3	3	SHH	STR	No	Yes	1	3	7 (2^{nd})	3	20
4	5	Group 3/4	NTR	No	Yes	2	3	12 (3^{rd})	2	2
5	17	WNT	NTR	No	Yes	4	3	12 (3^{rd})	1	5
6	7	Anaplastic	GTR[3]	No	Yes	5	3	11 (3^{rd})	1	15
7	8	WNT	NTR	No	Yes	2	3	10 (2^{nd})	1	2
8	6	Desmopla -stic	NTR	No	Yes	2	3	14 (3^{rd})	1	2
9	26	Group 3/4	GTR	No	No	0	3	12 (3^{rd})	1	2
10	7	Group 3/4	NTR	No	Yes	5	2	18 (4^{th})	1	4
11	10	Group 3/4	GTR	No	Yes	3	3	16 (4^{th})	1	5

[1]NTR- Near total resection

[2]STR- Subtotal resection

[3]GTR- Gross total resection

[4]Mets- Metastasis

[5]T/t- Treatment