Hematological toxicities and treatment interruption due to craniospinal irradiation

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**INTRODUCTION**

CNS tumors especially pediatric tumors with a propensity to seed the neuraxis require the elective or therapeutic use of craniospinal irradiation (CSI) to cover the entire cranial contents and spinal neuraxis at risk. The use of such treatment volumes, encompassing large volumes of bone marrow, can significantly depress hematologic counts(1,2). Leukopenia and thrombocytopenia are very common in patients who receive craniospinal irradiation, especially following multi-agent systemic chemotherapy. Although treatment interruptions may allow recovery from such acute toxicities, it is undesirable; because, reports show that interruptions may compromise tumor control. This appears to be due to more rapid and marked reductions in counts during CSI(3). Since this toxicity may cause treatment interruptions that are potentially therapeutically disadvantageous and aggressive hematologic support with transfusions and growth factors which might be necessary(4). The hematologic toxicities associated with CSI are of particular concern in children, since they are at a greater risk of leukopenia than adults. In the literature, several articles have also reported on significant treatment interruptions resulting from leukopenia and thrombocytopenia(1, 5, 6).

This study was aimed to evaluate the frequency of myelosuppression and treatment interruption in patients treated with craniospinal irradiation to identify patients at high risk of severe myelosuppression and treatment interruption.

**MATERIALS AND METHODS**

Between 1998 and 2002, 45 patients (20 female with mean age of 16 ± 14.5 yrs and 25 male with mean age of 12 ± 7 yrs) received craniospinal irradiation (CSI) to cover the entire cranial contents and spinal neuraxis at risk. The use of such treatment volumes, encompassing large volumes of bone marrow, can significantly depress hematologic counts(1,2). Leukopenia and thrombocytopenia are very common in patients who receive craniospinal irradiation, especially following multi-agent systemic chemotherapy. Although treatment interruptions may allow recovery from such acute toxicities, it is undesirable; because, reports show that interruptions may compromise tumor control. This appears to be due to more rapid and marked reductions in counts during CSI(3). Since this toxicity may cause treatment interruptions that are potentially therapeutically disadvantageous and aggressive hematologic support with transfusions and growth factors which might be necessary(4). The hematologic toxicities associated with CSI are of particular concern in children, since they are at a greater risk of leukopenia than adults. In the literature, several articles have also reported on significant treatment interruptions resulting from leukopenia and thrombocytopenia(1, 5, 6).

This study was aimed to evaluate the frequency of myelosuppression and treatment interruptions in patients treated with craniospinal irradiation to identify patients at high risk of severe myelosuppression and treatment interruption.

**Keywords:** Cranio-spinal irradiation (CSI), treatment interruption, hematologic toxicities, myelosuppression, risk factors.

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craniospinal axis radiotherapy as a part of the treatment of primary CNS tumors at the department of radiotherapeutic oncology in Cancer Institute. Thirty patients had medulloblastoma, 11 patients had ependymoma, 1 patient had germ cell tumour and 3 patients had neuroblastoma (25 male and 20 female). The median age at the time of diagnosis was 10 years (range 2-43 years). Twenty eight of the patients were children aged less than 12 years. Four patients had received neoadjuvant chemotherapy (RT).

Radiotherapy was delivered by megavoltage telecobalt techniques (Theratron 780C at SSD= 80). Patients were treated prone in an immobilization board. 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 depend on spinal involvement 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 to 12 Gy, the gap junction was changed to avoid junction over dosage. Treatment was delivered 5 days per week. The dose to the whole brain ranged from 30 to 40 Gy in 1.5-1.85 Gy/f. The usual dose to the posterior fossa or to the site of primary disease was 50-55 Gy in 6-8 weeks for adults and was reduced to 45-50 Gy in 6-7 weeks for children aged, 3 years. The median tumour dose was 54 Gy (range 40-56 Gy). The dose to the spinal cord was usually a minimum of 30 Gy in 20 fractions over 4 weeks with a boost of 5-10 Gy to the sites of known metastatic disease. The median dose to the spine was 32 Gy (range 24-40 Gy). The median duration of radiotherapy was 42 days (6 weeks, range 5-10 weeks).

Treatment interruptions 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. Any interruption in treatment lasting 2 days was defined as a significant treatment interruption. We excluded week-end from the days of treatment interruption.

Haematological parameters

Complete blood counts (CBC) were obtained during radiotherapy. CBC level within 1 week of the start of radiotherapy was used as the pre-treatment value. Serial measurements were taken during radiotherapy at least once a week. Regular counts, including nadir counts defined as the minimum haemoglobin/white cell/platelet counts within the period. Haematological toxicity was graded according to the WHO criteria and severe haematological toxicity was defined as WHO grades 3 and 4.

The duration of treatment interruption due to toxicity was measured from the onset of grades 3 and 4 toxicity until recovery to grade 2 of complete haematological recovery was also made.

RESULTS

In 45 patients who received craniospinal irradiation (CSI) 19 patients had treatment interruption more than 2 days. The median dose at interruption was 21.6 ± 8.7 Gy (range 9-39 Gy) and the frequency of grade 3, 4 hematologic toxicities occurred with peak incidence during the fourth week of CSI (median day of interruption was day 23, range 8-38) the median White Blood Cell count was 1900(range 100-2140).The mean of interruption period was 7 ± 8 days (one patient died from neutropenic fever then he didn't finish his treatment).

In 19 patients who had treatment interruption 13 were under 12, while 5 were older than 12 years. With Man-Whitney U test showed that the median age of patients with treatment interruption was significantly low; 10.2 years and 16.2 years respectively (P=.059). There was no correlation between spinal dose, tumor dose, dose per fraction and treatment interruption (table 1).

There was no corrolation between spinal dose category (lesser & greater than 32 Gy) and treatment interruption. In patients who had spinal dose <=32 Gy, the treatment interruption was 9 of 24 (37%) and in >32 Gy
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DISCUSSION

Wide field irradiation in the form of CSI radiotherapy for CNS tumors or nodal irradiation in lymphoma may result in myelosuppression with a risk of neutropenic sepsis and treatment interruptions compromising treatment efficacy and hematologic growth factors may well be useful in this setting(7).

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(8). Parmentier et al. cited three mechanisms of physiologic compensation for loss of hematopoietic activity in irradiated areas of the marrow:

1) stimulation of hematopoietic activity in non-irradiated areas;
2) extension of such activity to long bones, which are normally inactive in adult subjects, and extramedullary erythropoiesis; and
3) 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 nonirradiated areas soon after irradiation.

Ferrokinetic studies indicate when 20-30% of the bone marrow is irradiated, the activity of the irradiated areas remains extremely low; an increase in cell proliferation in adjacent nonirradiated tissues is sufficient to maintain a normal number of circulating blood cells. When larger volumes, up to 25-50% of the marrow are irradiated, a release of a humoral stimulus probably "turns on" hematopoietic activity in the remaining portion of the marrow organ. Observations with radiocollodoids and ferrokinetic studies have shown that, there is a high incidence of bone marrow extension into bones that are normally dormant in adults, such as the femora, tibia, humerus, and extramedullary sites of hematopoiesis after extended-field RT. In children, approximately 25% of the active marrow is treated with CSI, whereas in adolescents and young adults, the percentage is clearly higher, approaching 30-40%. Thus, in adults, the activity in the previously quiescent areas of marrow in the

<table>
<thead>
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<th>Category</th>
<th>Treatment Interruption</th>
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<tr>
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<td>&lt;= 32 Gy</td>
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<td>15</td>
<td>P=0.2</td>
</tr>
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<td>&gt;32 Gy</td>
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<td>11</td>
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<td>Dose Fraction</td>
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<td>&gt; 1.6 Gy</td>
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<td>&lt;= 12 yrs</td>
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<td>6</td>
<td>14</td>
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There was no correlation between total dose, spinal dose, age and treatment interruption. The rate of treatment interruption in younger patients (<=12 years) was greater than older patients (>12 years) 50% vs 30% but not significant statistically (P=0.62) (table 2).

Table 2. C. Correlation between treatment interruption period and risk factor categories

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<tbody>
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<td>Spinal Dose</td>
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<tr>
<td>&lt;= 32 Gy</td>
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<td>4</td>
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<td>&gt;32 Gy</td>
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<td>Age</td>
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<td>&gt;12 yrs</td>
<td>2</td>
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femora and humeri is likely increased during and after CSI. This increase in activity may serve as an additional compensatory mechanism that is present in adults but absent in children\(^{(9,10)}\).

The lower proportion of total marrow in the axial skeleton in adults than in children may explain the proportional decrease in the volume of marrow irradiated with age, from a greater percentage in children to a smaller percentage in adults, whose peripheral bones are longer. In turn, the greater proportional volume of total marrow irradiated in children may explain why younger age has been associated with an increased incidence of acute hematologic toxicity. Our results indicate that even within the pediatric population, younger age (\(<=12\) years) is associated with more treatment interruption which directly causes acute toxicities of sufficient severity to warrant treatment interruption. The series by Jeffries which included adults and children from 270 patients reported that 66 (24.5\%) of patients had treatment interruption and that treatment time was extended beyond 12 weeks in 17 (8\%) of patients and the peak of treatment interruption was in second week of CSI and at the dose of 24 Gy\(^{(7)}\). Plowman reported that 5 (22\%) of 23 patients had significant prolongations in therapy (7 days) because of dropping blood counts. Our current study reports a longer treatment interruptions (42\%) and the peak of treatment interruption was longer in patients with d/f >1.6 Gy\(^{(11)}\). As compared with other studies indicating 8-24 Gy treatment interruption, due to CSI, we have more incidence of treatment interruption. On the other hand, according to biological effective dose (BED) formula, the acute toxicity of radiation depend on total dose, dose per fraction (d/f) and alfa /beta ratio and therefore in patients with greater d/f we expect more acute toxicities specialy in bone marrow wich is very radiosensitive. In our study, treatment interruption was longer in patients with d/f >1.6 Gy specialy in young group and the relative risk of longer treatment interruption is 2.4 for patients who had d/f >1.6 Gy. Therfore with lower spinal dose/fraction we expecte lower bone marrow toxicity and treatment interruption.

The haematological consequences of CSI irradiation for medulloblastoma have been studied previously. The nadir white blood cell count (WBC) occurred early or towards the middle of the course of radiotherapy and the pre-radiotherapy white cell count was predictive of a subsequent fall which is similar to our findings. Young age as a predictor of haematological toxicity was suggested in 23 patients receiving CSI radiotherapy for medulloblastoma. In this small cohort treatment interruptions were reported in five patients, all of whom were under the age of 18. Generally in this study 42\% of patients undergoing CSI had treatment interruption. The risk was higher in children and in patients who received higher spinal dose fraction the treatment interruption was longer, but the overall treatment-related morbidity was low.

Prior to developing interventional strategies, it is important to establish consistent criteria for instigating radiotherapy treatment interruptions and to establish whether haematological toxicity by causing treatment interruptions affects overall survival. It would be in this setting that HGFs may have a particularly useful role. However, 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\(^{(5,12)}\). 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\(^{(13)}\). Before employing HGFs around the time of CSI radiotherapy, it is important to document the frequency and severities of haematological toxicity, associated with CSI irradiation and define the most appropriate scenario for the potential use of HGFs. In a population at risk of haematological toxicity further studies of prophylactic HGFs should be targeted.

REFERENCES

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