

Acute Haematological Variations in Patients Receiving Radiotherapy and its Correlation with Volume of the Bone Marrow and Radiation Dose

Rajesh Javarappa¹, Ramesh Bilimagga², V. Chendil¹, B.R. Kiran Kumar¹ and Amrut S. Kadam^{1,*}

¹Department of Radiation Oncology, Bangalore Medical College and Research Institute, Bangalore-560004, India

²Bangalore Institute of Oncology, India

Abstract: Purpose: Radiation treatment of all malignancies inevitably includes certain percentage of bone marrow in the site and volume of irradiation. The purpose is to study the magnitude of radiation induced early haematological toxicity in relation to the total dose and volume of the marrow in the field of irradiation.

Materials & Methods: A Prospective analysis was done in 60 patients treated with telecobalt. Haemoglobin, WBC and platelet counts were done before starting treatment and then weekly till the completion of treatment. The volume of bone marrow in the radiation fields was also recorded.

Results: The haemoglobin percentage change between baseline and 5th week was 5.19% (p=0.026) and 7.35% (p=0.049) in <5%, 5-20% & >20% of bone marrow irradiated respectively. The percentage of change between baseline and 5th week total WBC count was 23.79% (p=0.000), 35.53% (p=0.006) and 27.90% (p=0.000) in <5%, 5-20% & >20% of bone marrow irradiated respectively. The percentage change in platelets between baseline and 5th week of 22.14%, 24.66% & 24.80% in patients with <5%, 5-20% and >20% of bone marrow irradiated respectively (overall p=0.000).

Conclusion: The percentage of active bone marrow in the field of irradiation, dose per fraction and the total dose received are the best parameters for the study of haematological variations in patients being treated with radiotherapy. There is significant Haematological variations with decreasing trend in relation to volume of bone marrow irradiated and radiation dose.

Keywords: Acute Haematological variations, Radiotherapy, Bone marrow volume, Radiation Dose, Bone marrow toxicity, Radiotherapy Toxicity.

INTRODUCTION

The cancer burden in the world is estimated to rise to 19.3 million cases and 10 million cancer deaths in 2020 [1]. Radiotherapy is one of the main modalities for cancer treatment but associated associated with acute and late adverse effects.

The Bone marrow is an extremely radiosensitive and dose limiting tissue. Haemopoiesis takes place in the extravascular spaces in the marrow sinuses [2]. Impaired bone marrow function during cancer treatment can be due to the direct injury of stem cells, damage to stroma or microcirculation, injury to accessory cells involved in regulating the proliferation & differentiation and underlying disease itself [3].

Acute effects of radiotherapy on bone marrow depend on dose, dose fractionation and volume of marrow irradiated. The geographical distribution of bone marrow in human body is relevant to understand

the volume effect. Initially the bone marrow distribution was assessed in cadavers [4]. Advances in molecular imaging using FLT PET scan, it is possible to delineate more accurately the active marrow which can help in treatment planning and reduce the toxicities [5]. Majority of bone marrow is in pelvis and vertebrae that make up to approximately 60% of total active marrow [6,7]. Acute effects on marrow are seen as anaemia, leucopenia and thrombocytopenia which are responsible for treatment interruptions, infections (sometimes death), which have a major impact on local control and overall survival [8]. However, the mechanisms through which radiotherapy induced Bone marrow injury occurs remains poorly understood, nor has an effective treatment been developed to reduce the injury [9]. There is limited number of studies on analysing the effects of radiotherapy on bone marrow.

Hence, this prospective study was designed to assess the relationship of acute haematological variations to dose, site of irradiation and volume of bone marrow irradiated in patients receiving radiotherapy.

*Address correspondence to this author at the Department of Radiation Oncology, Victoria Hospital, Bangalore Medical College and Research Institute, Bengaluru-560004, India; Tel: +91-9986545999; E-mail: raysoflife@gmail.com

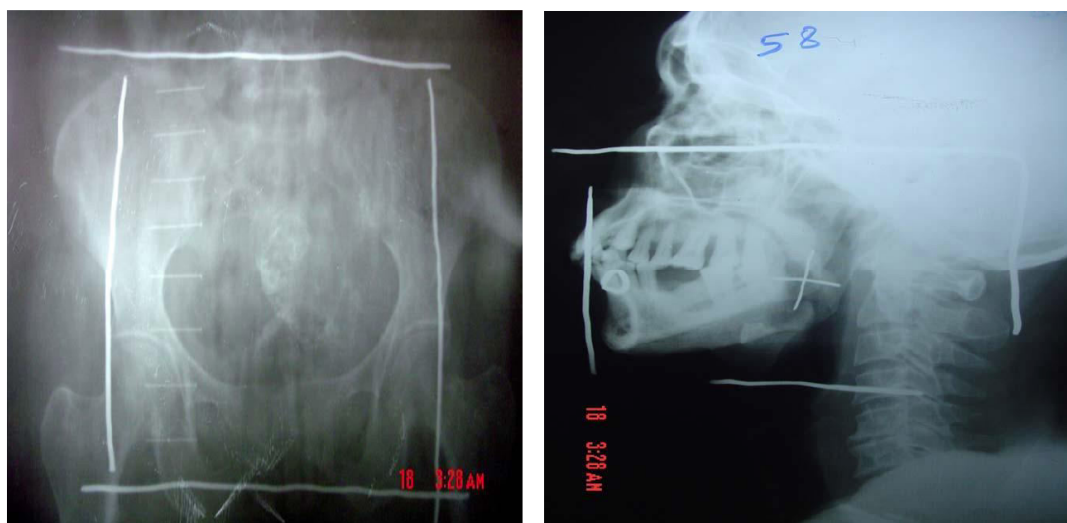


Figure 1: Simulation X ray films of Pelvis and Head and Neck region used to assess the volume of Bone marrow volume irradiated.

METHODS & MATERIALS

A prospective analysis was done on 60 patients who underwent radiation treatment with Telecobalt for various histologically proven malignancies with curative and palliative intent. Patients were excluded if concurrent chemotherapy was received or received chemotherapy less than 4 weeks prior to radiotherapy.

The patient was positioned on a flat table as in the treatment setup and radio opaque markers were placed on the borders of the treatment fields for field localisation. Simulation x-rays or CT scans were taken. The field size was converted into equivalent squares. The bones in the irradiated volume were noted.. Bone marrow volume in the irradiated fields was calculated using the Mechanik data [10] and R.J Eliis distribution of active bone marrow [3].

Haematological parameters (Haemoglobin, Total WBC count and platelet count) was done on the first day of starting radiotherapy as a baseline and then weekly during the course of the treatment.

Statistical Analysis

ANOVA test has been used to find the significance difference of Haemoglobin (Hb), WBC and Platelet counts between the volume of bone marrow irradiated and other treatment parameters. Student t test (paired) has been used to find the significance of Hb, TC and platelet count between week1- week3, week1-week5 and week1-week7. The statistical software SPSS11.0 & Systat 8.0 was used for the analysis.

RESULTS

A total of 60 patients receiving radiotherapy were analysed. The haemoglobin percentage change between baseline and 5th week showed 5.19% decrease in patients with upto 5% of bone marrow in field ($p=0.026$), 6.40% decrease in Hb levels in patients with 5-20% bone marrow in field ($p=0.090$) and 7.35% in patients with >20% of bone marrow in the field ($p=0.049$).

Table 1: Patient Characteristics

Characteristics	
Total Number of patients	60
Age (Mean) years	55.6
Males	25
Females	35
Stage	
Early stage	5
Locally advanced stage	49
Metastatic stage	6
Site of irradiation	
Head & Neck	22
Chest	20
Pelvis	13
Abdomen & Thoraco-lumbar spine	5
Volume of Bone Marrow irradiated	
<5%	25
5-20%	22
>20%	13

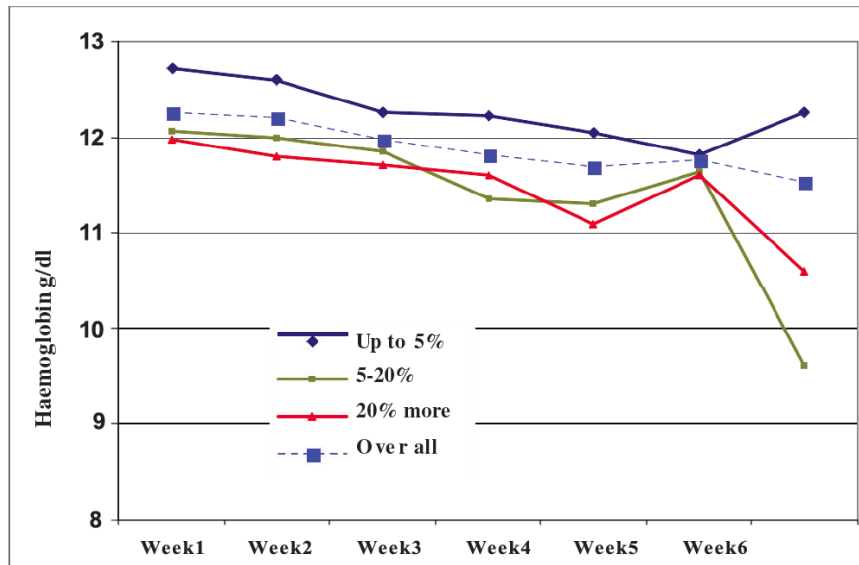


Figure 2: Weekly Hb changes in relation to percentage of Bone marrow irradiated.

Weekly Hb changes in relation to percentage of bone marrow irradiated are shown in Figure 2.

The overall Hb percentage change between baseline and 5th week was 5.76% with a high significant p value ($p=0.001$).

In patients with bone marrow upto 5% in the field of irradiation the percentage of change between baseline and 5th week total WBC count was 23.79% ($p=0.000$). 5-20% bone marrow in field showed a change of 35.53% ($p=0.006$) and for more than 20% of bone marrow in field the change was 27.90% ($p=0.000$). Weekly WBC count changes in relation to percentage of bone marrow irradiated are shown in Figure 3.

There was significant percentage change in platelets between baseline and 5th week of 22.14%, 24.66% & 24.80% in patients with up to 5%, 5-20% and more than 20% of bone marrow irradiated respectively (overall $p=0.000$). Weekly platelet count changes in relation to percentage of bone marrow irradiated are shown in Figure 4.

DISCUSSION

The toxicity of radiotherapy on haematopoietic system depends mainly on volume of bone marrow irradiated. Partial destruction of marrow increases the activity in remaining segments. Therefore, for a

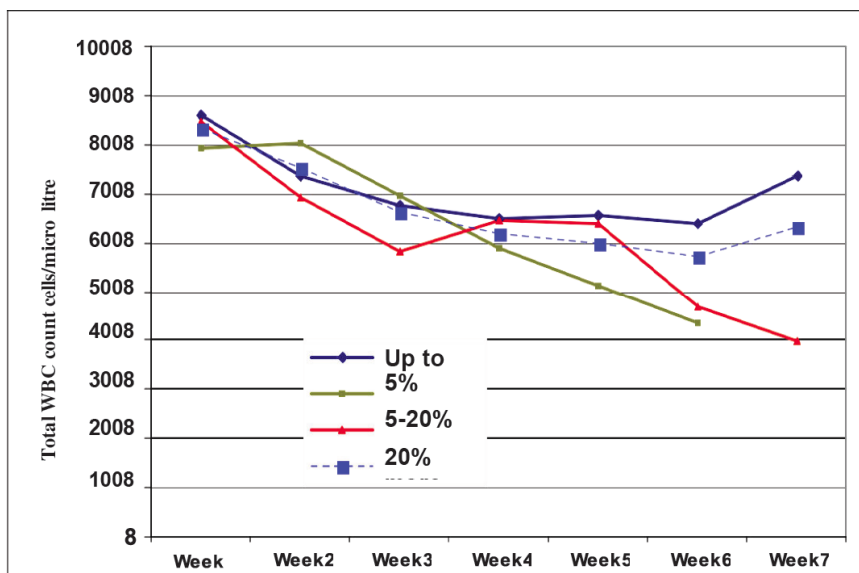


Figure 3: Weekly WBC count changes in relation to percentage of Bone marrow irradiated.

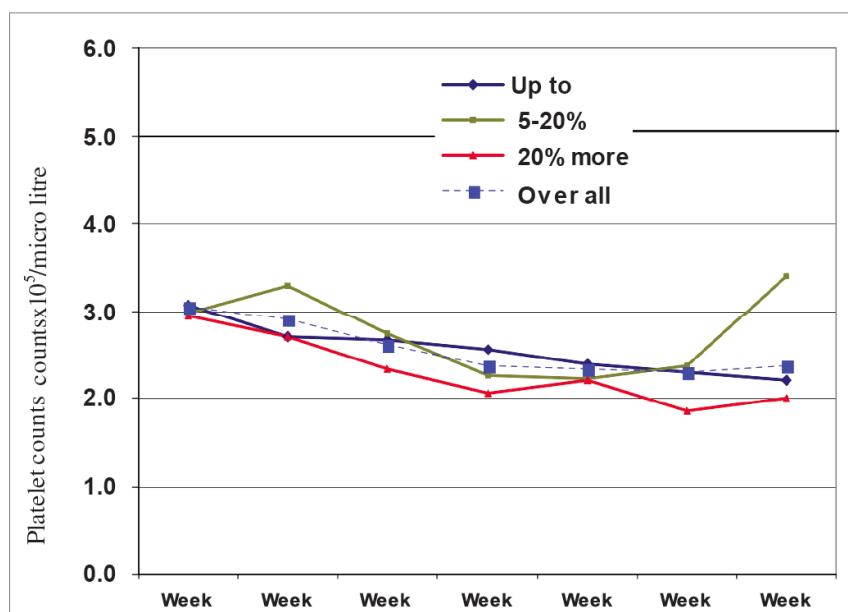


Figure 4: Weekly platelet count changes in relation to percentage of Bone marrow irradiated.

significant haematopoietic toxicity to occur large parts of axial skeleton should be in radiation portals.

In our study, out of 60 patients - 22 patients received radiation to head and neck area, 20 received to thorax, 13 received to pelvis and 5 received to abdomen & thoracolumbar spine. All patients who received radiation to pelvis had more than 20% bone marrow irradiated. Patients who received radiation to other sites had less than 20% bone marrow irradiated.

Zachariah *et al.* analysed the effect of fractionated regional external beam radiotherapy on peripheral blood counts in 299 patients to various sites. Results showed statistically significant declines in WBC and platelet counts but not clinically significant. The greatest weekly interval change in counts occurred during the first week of radiotherapy for all groups of patients. The nadirs for all counts occurred toward the middle to end of radiotherapy [11].

Maria *et al.* studied the effects of conventional external beam radiotherapy on 101 patients with Head&Neck, Chest and pelvis cancer by weekly monitoring of blood counts. The most significant decrease in leukocytes was observed in the fourth week, when total leukocytes and platelets presented a decrease of 26.8% and 14.6%, respectively, in comparison with the values found before the beginning of the therapy. Geometric means for pelvis during the treatment were lower than those for chest, and head and neck [12]. In our study 16 patients had decreased WBC counts compared to baseline, although only 5

patients had it below the normal limit. In relation to volume of bone marrow irradiated percentage change in WBC counts between baseline and week 5 has shown 23.79%, 35.53% and 30.27% for less than 5%, 5-20% and more than 20% bone marrow irradiated respectively.

Overall mean baseline Hb 12.31gm% reduced to 11.6gm% in 5th week with a high significant percentage change of 5.76%. With increase in volume of bone marrow irradiated there was increase in percentage change between baseline & 5th week. Percentage change in Hb between baseline and 5th week was 5.19%, 6.4% and 7.35% in patients with less than 5%, 5-20% and more than 20% of bone marrow irradiated. Only 9 patients had a drop in Hb of more than 2gm%. 4 patients had a drop in Hb below 10gm% during the course of treatment.

20 out of 60 patients who received a total radiation dose up to 40Gy, 3 patients had a drop in Hb level of 2gm% compared to baseline. 40 patients who received radiation dose of more than 40Gy, 6 patients had a drop of 2gm% of Hb. Anaemia occurred more frequently in elder patients and who experience weight loss and large primary tumours [13]. In our study, the mean platelet count at baseline was 3.04lakhs/microliter and dropped to 2.37 lakhs/microliter at completion of the treatment. In relation to volume of bone marrow irradiated there was decreasing trend from 22.14% to 24.66% to 24.80% with increase in percentage of bone marrow from less than 5%, 5-20%

and more than 20% bone marrow respectively. None of the patients had a fall below 1.3 lakhs/micro-litre.

Sacks *et al.* derived a dose response for localized marrow tolerance and concluded that 3000rad in 3 weeks seemed to be the limit above which there is no regeneration of bone marrow cells [14].

With higher the dosage, there is irreversible damage to the medullary stroma associated with permanent marrow aplasia [15].

The addition of chemotherapy concurrently with radiotherapy to improve the survival outcomes, it also increased the acute adverse effects mainly bone marrow toxicity as it affects not only the irradiated marrow in radiation treatment field but also the unirradiated marrow in other segments. Sojourner *et al.* studied the variation in Haematological toxicity in 126 patients undergoing Radiation Therapy with Concurrent Weekly Cisplatin for Head and Neck Versus Cervical Cancer. WBC nadirs and ANC nadirs were significantly lower in cervical cancer patients compared to Head & Neck Cancer patients ($p=.003$ and $p=.001$) respectively [16].

Yang *et al.* [17] conducted a study on 117 patients with Carcinoma Head and Neck, chest and pelvis on conventional external beam radiation therapy, had found the major decrease in the peripheral blood cells count occurred in the first week of treatment and they have recommended a blood cells count prior the initiation of the radiotherapy and in the first week of treatment. Studies in the literature have reported that the decrease in the peripheral blood cells counts starts in the first weeks of conventional external beam radiation therapy [18-20].

Zachariah *et al.* [21] recommend the blood cells count prior the initiation of the treatment, and in the first and third weeks after radiotherapy is initiated. The data found in the present study suggest that complete Haemogram should be requested prior the initiation of radiotherapy, and weekly haemogram could be requested during the course of the treatment on weekly basis especially for patients where a large area of bone marrow is irradiated.

CONCLUSION

Our study showed there was a significant haematological variation in patients receiving regional radiotherapy suggesting weekly monitoring. The percentage of bone marrow in the field of irradiation,

dose per fraction and total dose and its impact on the haematological variation can be best studied by haemograms to recognize and treat radiation induced early haematological toxicities. With the combined modality treatment protocols involving Concurrent Chemoradiation with Myelosuppressive drugs, weekly hemograms are essential to recognize and treat Neutropenia and Thrombocytopenia.

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