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ORIGINAL ARTICLE

Predictors of acute hematologic toxicity attributable to palliative radiotherapy: Analysis of patient characteristics and bone marrow dose-volume parameters

Tetsuo Saito, Ryo Toya, Tomohiko Matsuyama, Satoshi Ninomura, Natsuo Oya

Department of Radiation Oncology, Kumamoto University Hospital, 1-1-1 Honjo, Chuo-ku, Kumamoto-shi, Kumamoto, 860-8556, Japan

Summary

Purpose: *As predictors of hematologic toxicity (HT) after palliative radiotherapy (RT) have been studied insufficiently, we explored predictors of leukopenia, neutropenia, and thrombocytopenia attributable to palliative RT.*

Methods: *We retrospectively assessed patients with various solid tumors who had received palliative RT at our institution. Excluded from our study were patients who had undergone chemotherapy from one month before to one month after the start of RT. To measure the bone marrow dose, all bones were delineated, and the absolute volume of bone marrow that had received 5, 10, 20, and 30 Gy was recorded. Univariate and multivariate logistic regression analysis was performed to identify variables associated with leukopenia, neutropenia, or thrombocytopenia of grade 2 or higher (HT2+).*

Results: *Of 68 patients, 17 (25%) developed HT2+. Grade ≥ 2 leukopenia developed in 13 patients (19%), neutropenia in 8 (12%), and thrombocytopenia in 6 (9%). Only one patient experienced ≥ grade 3 toxicity. The median baseline and nadir white blood cell count (WBC) was 6.950 and 4.650x10^9/l, respectively; the absolute neutrophil count (ANC) was 5.236 and 3.307x10^9/l, respectively, and the platelet count was 249 and 177.5x10^9/l, respectively. Multivariate analysis revealed that female gender and a lower baseline WBC and ANC were significant independent predictors of HT2+. No bone marrow dose-volume parameter was a significant predictor of HT2+.*

Conclusions: *Overall, HT was relatively mild. Female gender and lower baseline WBC and ANC may be predictors of HT elicited by palliative RT.*

Key words: *bone marrow, leukopenia, palliative care, radiotherapy, toxicity*

Introduction

Palliative RT plays an important role in easing the symptoms of cancer patients [1,2]. Although HT due to palliative external beam RT tends to be mild, some patients develop moderate to severe HT [3-5]. Bone marrow (BM) suppression may occur if the treatment portals are large and cover a significant volume of BM, especially in patients heavily pretreated with chemotherapy [3]. Patients receiving palliative RT often need chemotherapy to prolong their lives. The temporary cessation of treatment due to HT elicited by RT may have an adverse effect on the outcome.

In patients undergoing curative RT, BM dose-volume parameters are associated with HT [6-10]. However, predictors of HT in patients treated by palliative RT have been insufficiently studied. Also, most reports on post-RT HT involved patients treated with concurrent chemoradiotherapy [6-10] and few addressed the impact of RT alone on myelosuppression [11,12].

We investigated predictors of leukopenia, neutropenia, and thrombocytopenia attributable to palliative RT. Patient characteristics, baseline blood counts, and BM dose-volume parameters

Correspondence to: Tetsuo Saito, MD. Department of Radiation Oncology, Kumamoto University Hospital, 1-1-1, Honjo, Chuo-ku, Kumamoto-shi, Kumamoto, 860-8556, Japan.
Tel: +81 96 373 5261, Fax: +81 96 373 5342, E-mail: tsaito@kumamoto-u.ac.jp
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were evaluated for their ability to predict HT. To evaluate the impact of RT alone on HT, we excluded patients treated with concurrent chemotherapy.

Methods

Patients

This retrospective study was performed in accordance with the Declaration of Helsinki, and approved by the ethical committee of our institution. Informed patient consent for inclusion in this study was waived. Our inclusion criteria were as follows: palliative RT delivered between October 2010 and June 2013 at our institution; the availability of laboratory data acquired within 2 weeks prior to the start of RT; and of two or more laboratory data obtained within one month after the start of RT, the latest data recorded at least 2 weeks after the start of RT. Excluded were patients with hematologic tumors; patients treated with chemotherapy, molecular targeted therapy, interferon, or RT delivered from one month before to one month after the start of this course of RT; and patients with leukopenia, neutropenia, or thrombocytopenia of grade 2 or higher based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 at the start of RT. Of the 68 included patients, 54 were the subject of our earlier analysis of lymphopenia after palliative RT [13]. Patient and treatment data were acquired from medical records.

Hematologic toxicity

The study endpoints were (1) the WBC, the ANC, and the platelet count at the nadir, defined as the lowest value recorded within one month after the start of RT, and (2) HT including leukopenia, neutropenia, or thrombocytopenia of grade 2 or higher (HT2+) according to CTCAE version 4.0; the highest grade recorded within one month after the start of RT was used for analysis.

Dose-volume parameters

All patients underwent CT simulation in the supine position and three-dimensional treatment planning. We reported the procedure for delineating BM elsewhere [13]. We delineated an organ at risk on planning CT images using commercially available software (Velocity AI, Velocity Medical System, Atlanta, GA, USA). To evaluate the effect of radiation on BM, all bones were delineated by threshold-based segmentation and manual correction by one radiation oncologist. Intervertebral disks and costal, thyroid, cricoid, and tracheal cartilage were excluded from the BM volume. The distal half of the femur and humerus were also excluded because they contain little proliferating BM [14]. The absolute BM volumes that had received 5, 10, 20, and 30 Gy (V5, V10, V20, and V30) were recorded.

Statistics

Data were summarized by using descriptive statistics (frequency, percentage, median, range). The Spear-

Table 1. Patient and treatment characteristics (n = 68)

Characteristics	*Patients, n*	*%*
Patient characteristics		
Male gender	40	59
Age (years)		
Median (range)	69 (39-86)	
Body mass index (kg/m²)		
Median (range)	21.0 (14.1-30.8)	
Body surface area (m²)		
Median (range)	1.5 (1.2-2.0)	
Primary tumor (n=68)		
Lung	16	24
Gastrointestinal	15	22
Skin	5	7
Uterus	4	6
Others	28	41
Prior radiotherapy	22	32
Prior chemotherapy	37	54
Concurrent steroid use	30	44
Bone metastasis	35	51
Brain metastasis	15	22
Interval from tumor diagnosis to radiotherapy (months)		
Median (range)	13 (0-168)	
Symptoms treated with radiotherapy (n=83)		
Pain	45	54
Weakness of an arm or leg	13	16
Dysphagia	6	7
Bladder dysfunction	5	6
Other	14	17
Baseline blood count		
WBC (x10⁹/l)		
Median (range)	6.950 (3.100-36.600)	
ANC (x10⁹/l)		
Median (range)	5.236 (1.714-34.404)	
ALC (x10⁹/l)		
Median (range)	1.209 (0.403-3.468)	
Platelet count (x10⁹/l)		
Median (range)	249 (77-765)	
Hemoglobin (g/dl)		
Median (range)	11.0 (5.9-15.1)	
Treatment characteristics		
Total radiation dose (Gy)		
Median (range)	30 (16-50)	
Number of fractions		
Median (range)	10 (4-25)	
Fraction size (Gy)		
Median (range)	3 (2-5)	
Treatment site (n=75)		
Head and neck	20	27
Chest	29	39
Abdomen	12	16
Pelvis	12	16
Limb	2	3

WBC: white blood cell count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count

man correlation coefficient was calculated between the baseline and the nadir blood count, and between the BM dose-volume parameters and the nadir blood count. For univariate and multivariate logistic regression analysis, the patient age, body mass index, body surface area, the interval from tumor diagnosis, baseline blood counts (WBC, ANC, absolute lymphocyte count, platelet count, and hemoglobin), and BM dose-volume parameters were applied as continuous variables. The categorical variables included the gender, prior RT, prior chemotherapy, concurrent steroid use, bone metastasis, and brain metastasis. All variables with a p value <0.10 at univariate logistic regression analysis were entered into multivariate analysis. We used the backward elimination method with a p<0.05 criterion for retention in multivariate logistic regression analysis. Values of p<0.05 were considered statistically significant. All statistical analyses were performed with SPSS software, version 23 (IBM SPSS, Armonk, NY, USA).

Results

Patients

The study population included 68 patients whose solid tumors had been treated with palliative RT. The patient and treatment characteristics are shown in Table 1. A median of 5 blood samples (range 2-18) was obtained within one month from the start of RT; the median interval between the start of RT and the acquisition of the last blood sample subjected to evaluation was 25 days (range 14-31 days). Of the 68 patients, 22 (32%) had undergone previous RT and 37 (54%) had received chemotherapy earlier.

Hematologic toxicity

The median baseline and the nadir value for WBC were 6.950 and 4.650x10^9/l, respectively; it was 5.236 and 3.307x10^9/l, respectively, for ANC, and 249 and 177.5x10^9/l, respectively, for the platelet count. Of the 68 patients, 17 (25%) experienced HT2+ (Table 2). Grade ≥ 2 leukopenia developed in 13 patients (19%), neutropenia in 8 (12%), and thrombocytopenia in 6 (9%). One sole patient, a 79-year-old male with skin cancer, suffered toxicity ≥ grade 3 (grade 3 leukopenia, grade 4 thrombocytopenia). No patient received granulocyte colony stimulating factor within one month after the start of RT; only the sole patient with grade 4 thrombocytopenia required a platelet transfusion within one month after the start of RT. He was unable to complete RT as planned. None of the other patients required discontinuation of RT due to HT.

Dose-volume parameters

The median (range) V5, V10, V20, and V30 of the BM was 3.28 (0.00-9.74), 2.49 (0.00-9.09), 1.73 (0.00-7.37), and 0.71 (0.00-7.24)x10^2 ml, respectively.

Table 2. Acute hematologic toxicity

Toxicity	*CTCAE Grade, n (%)*				
	0	*1*	*2*	*3*	*4*
Leukopenia	52 (76)	3 (4)	12 (18)	1 (1)*	0 (0)
Neutropenia	49 (72)	11 (16)	8 (12)	0 (0)	0 (0)
Thrombocytopenia	39 (57)	23 (34)	5 (7)	0 (0)	1 (1)*

*A patient with both grade 3 leukopenia and grade 4 thrombocytopenia. CTCAE: Common Terminology Criteria for Adverse Events

Table 3. Spearman's correlation coefficients between the baseline and the nadir blood counts, and between the dose-volume parameters and the nadir blood counts

	Nadir WBC		*Nadir ANC*		*Nadir Platelet Count*	
Variables	*Spearman's Rho*	*p value*	*Spearman's Rho*	*p value*	*Spearman's Rho*	*p value*
Baseline blood count						
WBC (x10^9/l)	0.703	<0.001	0.718	<0.001	0.366	0.002
ANC (x10^9/l)	0.720	<0.001	0.772	<0.001	0.317	0.008
ALC (x10^9/l)	0.021	0.87	-0.060	0.63	0.246	0.043
Platelet count (x10^9/l)	0.522	<0.001	0.473	<0.001	0.698	<0.001
Hemoglobin (x10^9/l)	-0.041	0.74	-0.067	0.59	-0.093	0.451
Dose-volume parameter						
BM V5 (x10^2 ml)	-0.002	0.99	0.081	0.51	-0.117	0.34
BM V10 (x10^2 ml)	0.050	0.69	0.135	0.27	-0.092	0.46
BM V20 (x10^2 ml)	0.023	0.85	0.100	0.42	-0.056	0.65
BM V30 (x10^2 ml)	-0.090	0.47	-0.042	0.74	0.039	0.75

WBC: white blood cell count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, BM: bone marrow

Correlation analysis

As shown in Table 3, there was a significant positive correlation between the nadir WBC and the baseline WBC, ANC, and the platelet count (p<0.001), between the nadir ANC and the baseline WBC, ANC, and the platelet count (p<0.001), and between the nadir platelet count and the baseline WBC, ANC, absolute lymphocyte count, and the platelet count (p<0.05). Lower baseline blood counts were correlated with a lower nadir post-RT blood cell count. There was no significant correlation between BM dose-volume parameters and the nadir blood counts.

Predictors of hematologic toxicity

Univariate logistic regression analysis showed that the gender, interval from tumor diagnosis to RT, baseline WBC, baseline ANC, and baseline platelet count were significant predictors of HT2+ (p<0.05, Table 4). The gender, interval from the tumor diagnosis to RT, baseline WBC, baseline ANC, and baseline platelet count had a p value <0.10 at univariate analysis, and were then used in backward elimination logistic regression. Because the baseline WBC and baseline ANC were highly correlated with each other (Speaman's rho=0.965, p<0.001), they were assessed in two models.

Table 4. Univariate logistic regression analysis to identify variables associated with grade ≥ 2 leukopenia, neutropenia, or thrombocytopenia (HT2+)

Variables	*OR*	*95% CI*	*p value*
Patient characteristics			
Male vs. female	0.27	0.09, 0.86	0.027
Age (per 1 year increase)	0.99	0.94, 1.04	0.67
Body mass index (per 1 kg/m2 increase)	0.96	0.80, 1.15	0.68
Body surface area (per 1 m2 increase)	0.11	0.00, 3.07	0.19
Previous radiotherapy (yes vs. no)	2.35	0.76, 7.30	0.14
Previous chemotherapy (yes vs. no)	1.27	0.42, 3.86	0.67
Concurrent steroid use (yes vs. no)	0.85	0.28, 2.59	0.78
Bone metastasis (yes vs. no)	2.06	0.66, 6.43	0.21
Brain metastasis (yes vs. no)	0.70	0.17, 2.84	0.61
Interval from tumor diagnosis to radiotherapy (per 1 month increase)	1.02	1.01, 1.04	0.012
Baseline blood count			
WBC (per increase of $1x10^9$/l)	0.66	0.49, 0.90	0.009
ANC (per increase of $1x10^9$/l)	0.67	0.48, 0.92	0.013
ALC (per increase of $1x10^9$/l)	0.37	0.11, 1.29	0.12
Platelet count (per increase of $1x10^9$/l)	0.99	0.99. 0.99	0.022
Hemoglobin (per increase of 1 g/dl)	0.83	0.64, 1.08	0.16
Dose-volume parameter			
BM V5 (per increase of $1x10^2$ ml)	1.03	0.83, 1.29	0.77
BM V10 (per increase of $1x10^2$ ml)	0.97	0.77, 1.22	0.79
BM V20 (per increase of $1x10^2$ ml)	0.92	0.72, 1.19	0.53
BM V30 (per increase of $1x10^2$ ml)	1.05	0.77, 1.44	0.77

WBC: white blood cell count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, BM: bone marrow, OR: odds ratio, CI: confidence interval

Table 5. Multivariate logistic regression analysis to identify variables associated with grade ≥ 2 leukopenia, neutropenia, or thrombocytopenia (HT2+)

Variables	*OR*	*95% CI*	*p value*
Model 1*			
Male vs. female	0.23	0.06-0.84	0.027
Baseline WBC (per increase of $1x10^9$/l)	0.63	0.44-0.89	0.009
Model 2†			
Male vs. female	0.22	0.06-0.82	0.024
Baseline ANC (per increase of $1x10^9$/l)	0.63	0.43-0.90	0.012

Only the final models are shown in the Table. *Gender, interval from tumor diagnosis to radiotherapy, baseline WBC, and baseline platelet count were tested with backward elimination. †Gender, interval from tumor diagnosis to radiotherapy, baseline ANC, and baseline platelet count were tested with backward elimination. WBC: white blood cell count, ANC: absolute neutrophil count, OR: odds ratio, CI: confidence interval

Multivariate analysis revealed that the female gender, lower baseline WBC and ANC were significant independent predictors of HT2+ ($p<0.05$, Table 5). No BM dose-volume parameter was a significant predictor of HT2+ by univariate analysis.

Discussion

This study showed that the female gender, lower baseline WBC, and lower baseline ANC were independent predictors of acute HT after palliative RT, while dose-volume parameters of BM were not.

Our finding that the female gender was a significant predictor of HT after palliative RT agrees with past studies that investigated HT in patients receiving curative chemoradiotherapy [15-18]. In patients with anal cancer, the female gender was significantly associated with decreased nadir WBC and ANC [15]; it was a risk factor for leukopenia after concurrent chemoradiotherapy for advanced non-small-cell lung cancer [16]. Among rectal cancer patients receiving concurrent chemoradiotherapy, females were more likely to develop grade ≥ 2 HT than males [17]. In a prospective study that analyzed myelotoxicity in glioblastoma patients during radiation plus temozolomide treatment, the female sex was a predictor of severe myelotoxicity [18]. Female cancer patients treated with chemotherapy alone also manifested a higher incidence of HT than did males [19,20]. To the best of our knowledge, ours is the first study to suggest that among patients treated with RT alone, the female gender is a predictor of HT. Our hypothesis that the predisposition of females for HT may be ascribable to a lower BM reserve in female cancer patients requires confirmation.

As did earlier studies [11,21], the present study showed that the baseline WBC and baseline ANC were predictors of HT. Lower absolute baseline values of WBC, neutrophils, and lymphocytes were predictive of acute and late HT in prostate cancer patients treated by RT with pelvic node irradiation [11]. The baseline WBC and ANC was associated with the nadir values in cervical cancer patients who received concurrent treatment with cisplatin and whole-pelvic RT [21].

There is substantial evidence that BM irradiation contributes to the development of leukopenia and neutropenia [6,15,22-26]. As BM stem cells are highly radiosensitive, the radiation dose and the irradiated BM volume affect the acute response of the BM to therapy [22,27]. However, based on the results of our logistic regression analysis, BM dose-volume parameters were not predictive of HT; by correlation analysis, they were not significantly associated with the nadir WBC, ANC, and the platelet count. As our patients were treated with palliative intent, the total radiation dose was low and the irradiated field was relatively small, and this may explain why the effect of BM irradiation was relatively small and why we could not establish statistical significance. In other studies of HT in patients subjected to curative pelvic RT, the total radiation dose delivered to BM-rich pelvic bones was much higher [6-12,15,17,21,24,25,28]. Also, we delineated the outer contour of bones and did not evaluate the active and inactive BM. Rose et al. [24]. demonstrated that decreased nadir WBC was associated with the radiation dose received by active but not by inactive BM. Functional imaging techniques such as positron emission tomography that can distinguish active from inactive BM could be used to ascertain the risk of HT in patients treated by RT.

Patients receiving palliative RT tend to be vulnerable and affected by prior treatments and advanced cancer. As 54% of our 68 patients had undergone prior chemotherapy, 32% had received prior RT, and 51% presented with bone metastasis, their BM reserve may have been compromised at the start of RT. Effective palliative intervention must offer a proper balance between good treatment effects and minimal detrimental side effects. Overall, HT was relatively mild in our study, suggesting that palliative RT was an acceptable, beneficial treatment mode in our patients.

Our retrospective study has some limitations. The patient population was relatively small and laboratory data were acquired at different points after the start of RT. Consequently, we may not have used the true nadir blood cell counts in our evaluations.

In summary, we retrospectively assessed the development of HT in patients with solid tumors who had received palliative RT. As HT in our study population was relatively mild, we think that RT was an acceptable treatment. We identified the female gender, low baseline WBC, and low baseline ANC as significant predictors of acute HT. As far as we know, ours is the first study to suggest that, in patients treated by RT alone, the female gender is a significant predictor of HT.

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Conflict of interests

The authors declare no confict of interests.

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