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RADIATION ONCOLOGY—ORIGINAL ARTICLE

Longitudinal study of acute haematologic toxicity in cervical cancer patients treated with chemoradiotherapy

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Abstract

Introduction: Acute hematologic toxicity (HT) limits optimal delivery of concurrent chemoradiotherapy (CRT) for patients with pelvic malignancies. We tested the hypothesis that pelvic bone marrow (PBM) dose-volume metrics were associated with weekly reductions in peripheral blood cell counts in cervical cancer patients undergoing CRT.

Methods: We included 102 cervical cancer patients treated with concurrent cisplatin (40 mg/m^2/week) and pelvic radiotherapy treated at three US centres. No patient received granulocyte-monocyte colony stimulating factor (GM-CSF) or platelet transfusions. Using linear-mixed effects modelling, we analysed weekly reductions in log-transformed peripheral blood cell counts as a function of time (weeks), mean PBM dose and the PBM volume receiving ≥10 Gy (V_{10}), 20 Gy (V_{20}), 30 Gy (V_{30}) and 40 Gy (V_{40}).

Results: Increases in mean PBM radiation dose, V_{20}, V_{30} and V_{40} were all significantly associated with a greater weekly reduction in white blood cell (WBC) and absolute neutrophil counts (ANCs). We estimated that with every 1 Gy increase in mean PBM dose, ln(ANC) was reduced by 9.6/μL per week (95% confidence interval, 1.9–17.3, $P = 0.015$). Subregion analysis also identified significant associations between weekly reductions in ln(WBC) and ln(ANC) within lumbosacral spine, ischium and proximal femora, as opposed to ilium.

Conclusions: PBM radiation dose-volume metrics are significantly associated with weekly reductions in peripheral blood cell counts in cervical cancer patients undergoing CRT, particularly within the lower pelvis and lumbosacral spine.

Key words: acute hematologic function; cervical cancer; chemoradiotherapy; longitudinal analysis.

Introduction

The standard treatment for locally advanced cervical cancer is concurrent cisplatin-based chemotherapy and whole pelvic radiation. Although chemoradiotherapy (CRT) improves tumour control and overall survival compared with radiotherapy alone, patients are subject to higher risk of acute haematologic toxicity (HT),[1,2] due to the myelosuppressive effects of both radiation and chemotherapy. Acute HT, particularly leukopenia and neutropenia, can lead to treatment interruption, limiting optimal delivery of therapy.[3] Therefore, reducing acute HT is an important goal.

The relationship between HT and radiation dose to pelvic bone marrow (PBM) in the context of concurrent chemotherapy has been a subject of investigation. The pelvis contains a substantial portion of the total complement of haematopoietically active bone marrow[2] in proximity to the targeted tumour and pelvic nodal groups. Advanced radiotherapy techniques,

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particularly intensity-modulated radiotherapy (IMRT), have been investigated as a method to reduce PBM dose. Previous studies have indicated that acute HT is associated with increasing mean bone marrow dose and the relative volume of PBM receiving 10–20 Gy,[4–7] especially in the lumbosacral spine and lower pelvic bone subregions.[4,8,9]

Previously, a quantitative relationship between PBM radiation dose-volume metrics with nadir white blood cell (WBC) and absolute neutrophil counts (ANCs) during CRT has been observed.[5] However, nadir counts do not provide information regarding the longitudinal dynamics of toxicity development. An alternative approach would be to study the longitudinal effects of dose-volume metrics on serial blood cell counts. We aimed to test the hypothesis that variations in PBM radiation dose, particularly in certain subregions of the pelvis, are associated with longitudinal reductions in peripheral blood cell counts in cervical cancer patients undergoing CRT. Such studies would help define planning objectives to use in bone marrow sparing radiotherapy.

Methods

Study design, setting and population

This is a retrospective review of 102 patients with stages I–III cervical cancer treated with concurrent cisplatin (40 mg/m^2/week) and pelvic radiotherapy between 2000 and 2010 at three US centres: University of California San Diego (UCSD), University of Chicago and University of Illinois Chicago (UIC). The study was approved by the institutional review boards (IRBs) of each institution. Informed consent was waived. Eligible patients had biopsy-proven clinical stages I–IVA or recurrent cervical cancer undergoing either postoperative or definitive radiotherapy with concurrent weekly cisplatin. Subjects with a previous history of chemotherapy or radiation and those treated with extended-field (para-aortic) radiotherapy were excluded. Patients with pre-existing cytopenias or known pathology of the bone marrow were also excluded.

Treatment

Surgery consisted of either examination under anaesthesia with biopsy or radical hysterectomy. Chemotherapy consisted of five to six planned cycles of concurrent weekly cisplatin (40 mg/m^2; maximum 80 mg). The number of planned cycles was determined by the treating gynaecologic or medical oncologist, independently from the radiation dose and field. Criteria for holding cisplatin were: WBC <2000/mm^3, ANC <1000/mm^3, platelet count (PLT) < 50,000/mm^3, creatinine clearance <50 mL/min, or symptomatic ototoxicity or neurotoxicity. No patients required granulocyte-monocyte colony stimulating factors (GM-CSFs) or platelet transfusions. Packed red blood cells (RBCs) were transfused according to the discretion of the treating gynaecologic or medical oncologist.

All patients underwent CT simulation for radiotherapy planning in the supine position with customised immobilisation. Scans were obtained using a CT simulator with 2.5–3.0 mm slice thickness. Simulation scans covered the abdominal and pelvic regions extending from the L2 vertebral body to the ischial tuberosities. The clinical target volume (CTV) included the cervical mass, cervix and uterus (if present), superior vagina, paracervical and parametrial tissue, and regional lymph nodes (common, internal iliac, external iliac, obturator and presacral nodes). Lymph node regions were defined as the region encompassed by a 5–7 mm margin around the visualised blood vessels. To account for setup uncertainty as well as motion of the tumour and surrounding organs, the CTV was expanded by a 7–15 mm margin to create the planning target volume (PTV). Bladder, rectum, bowel, pelvic bones and femoral heads were delineated for dose-volume calculations and/or conformal avoidance. Pelvic bones were used as an avoidance structure according to the discretion of the treating radiation oncologist. Radiotherapy plans were generated using commercially available treatment planning systems. The prescription dose ranged from 39.6 to 50.4 Gy (median: 45 Gy) in 1.8 Gy daily fractions. Plans were normalised to maintain at least 95% of the PTV receiving >95% of the prescription dose. Subjects requiring boost therapy underwent either high-dose rate (HDR) intracavitary brachytherapy (ICBT) in five fractions of 5.5–6.0 Gy to point A or image guidance per GEC-ESTRO guidelines delivered twice weekly, or low-dose rate (LDR) ICBT in one to two fractions of 35–40 Gy to point A over 2–3 days per insertion.

Measures of haematologic toxicity, covariates and dose-volume metrics

Complete blood counts (CBCs) with differentials were collected for each patient at baseline and roughly every 7 days during CRT. Demographic and clinical characteristics collected were tumour histology, stage, age, body mass index (BMI) and comorbidity. Comorbidity was defined as a binary measure based on whether the patient had a documented chronic medical condition requiring medication. CBC data were missing for two patients (2%) in week 4 of treatment, 18 patients (18%) in week 5 and five patients (5%) in week 6.

Dose-volume measures collected were the mean PBM dose and the volume of PBM receiving ≥10 Gy (V_{10}), 20 Gy (V_{20}), 30 Gy (V_{30}) and 40 Gy (V_{40}). For PBM dose estimation, the PBM volume was delineated using whole bones on the planning CT, consisting of the ilia, L5 vertebral body, sacrum, pubic symphysis, ischia, acetabulae and proximal femora to the level of the

inferior boundary of the ischial tuberosities. Three PBM subregions were contoured based on the previous definitions.[4] Briefly, lumbosacral spine (LSBM) included L5 and the whole sacrum; ilia (IBM) included iliac crests extending to the superior border of femoral heads; lower pelvis (LOWBM) covered the rest of the iliac crests and the other lower pelvic bones down to the inferior border of the ischial tuberosities.

Statistical methods

Longitudinal data were analysed using a mixed-effects, random-intercept-and-slope model where the baseline haematologic function was counted as a known variable, as follows:

$$\ln(y_t) = (\beta_0 + \beta_1 \cdot x) + (\beta_2 + \beta_3 \cdot x) \cdot t \quad (1)$$

where x and y_t represent the measures of dose and haematologic function at time t, respectively, and β_0, β_1, β_2, β_3 represent coefficients associated with the baseline, dose, time and time-dependent dose effects on changes in haematologic function. The parameters β_1, β_3 are fixed, but the 'intercept' and 'slope' parameters β_0, β_2 are patient specific and are assumed random. We also tested the effects of covariates such as age, BMI and comorbidity in the linear mixed-effects models.

To compare this model to a log-linear model, a more concise format of random intercept and slope model, as shown in Equation 2, was developed by taking advantage of the known baseline haematologic function at the beginning of the radiation treatment.

$$\ln(y_t) = \ln(y_{t=0}) + (\beta_2 + \beta_3 \cdot x) \cdot t \quad (2)$$

where y_t is the blood count at time t, and β_2, β_3 represent time and time-dependent dose effects on blood counts. Thus, this analysis using linear mixed effects incorporates both the effects of PBM irradiation and longitudinal variation of haematologic function within each subject. Age, race, BMI and comorbidity were included as covariates. $P < 0.05$ was considered statistically significant.

Logistic regression was used to test relations between PBM radiation doses and interruption of chemotherapy. The reasons for holding one or more cycles of chemotherapy were classified according to haematologic and non-haematologic causes. The data were analysed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and R statistical packages (Free Software Foundation, Boston, MA, USA).

Results

Sample characteristics

A total of 102 patients were analysed (Table 1). Twelve patients were excluded from the analysis due to incomplete records. A plurality of subjects was African American (38.2%) and the stage distribution was roughly equally divided between early (stage I–IIA, 48%) and advanced (IIB–IVA, 52%).

Table 1. Sample characteristics

Institution	
UCSD	51
University of Chicago/UIC	51
Total	102
Mean age, years (SD)	51.1 (14.3)
Race, *n* (%)	
Asian	6 (5.9)
Black	39 (38.2)
Hispanic/Latino	26 (25.5)
White	30 (29.4)
Other	1 (1)
BMI, kg/m^2 (s.d.)	27.8 (6.9)
Comorbidity (%)	60 (58.8)
Histology, *n* (%)	
Squamous carcinoma	82 (80.4)
Adenocarcinoma	15 (14.7)
Adenosquamous carcinoma	5 (4.9)
Clinical stage, *n* (%)	
IA2	1 (1)
IB	3 (2.9)
IB1	13 (12.7)
IB2	23 (22.5)
IIA	8 (7.8)
IIB	36 (35.2)
IIIA	1 (1)
IIIB	17 (16.7)
Brachytherapy, *n* (%)	83 (81.4)

BMI, body mass index; UCSD, University of California San Diego; UIC, University of Illinois Chicago.

Treatment

The percentage of patients completing one, two, three, four, five and six cycles of cisplatin were 4%, 5%, 11%, 22%, 38% and 20%, respectively. Forty-five patients (44%) had at least one cycle of cisplatin held, with 36 (35%) missing chemotherapy due to HT, namely, critically low WBC or ANC as described in the Methods section. Three patients were treated using conventional 4-field box techniques (3D conformal) and the remaining patients were treated with IMRT. The median prescription dose was 45 Gy (range 39.6–50.4 Gy). The majority of subjects (80.4%) received ICBT. There were 51.2% of the patients who received HDR with mean dose 27.9 Gy ranging from 16.5 to 30 Gy in 3–6 applications. There were 48.8% who received LDR with a mean dose 39.4 Gy ranging from 30 to 47.42 Gy in 1–2 applications.

Table 2. Baseline peripheral blood cell counts and pelvic bone marrow (PBM) radiation dose volume metrics

	Mean (SD)	Range
WBC, k/μL	8.2 (3.4)	3.8–27.1
ANC, k/μL	4.9 (3.7)	1.4–21.8
Haemoglobin, g/dL	11.9 (1.5)	7.0–15.3
Platelets, k/μL	303 (95)	109–828
PBM dose, Gy	28.4 (3.1)	22.5–36.7
PBM V_{10}, %	88.9 (5.9)	71.1–98.9
PBM V_{20}, %	72.6 (7.4)	56.7–96.7
PBM V_{30}, %	48.7 (9.0)	31.4–76.5
PBM V_{40}, %	23.2 (9.4)	0.0–47.9

ANC, absolute neutrophil count; PBM, pelvic bone marrow; SD, standard deviation; V_{10}, V_{20}, V_{30}, V_{40}, volumes of pelvic bone marrow that received at least 10, 20, 30 or 40 Gy; WBC, white blood cell.

Measures of haematologic function, covariates and dose-volume metrics

Descriptive statistics of key measures are given in Table 2. All patients' CBC data were collected at an average of 1.0, 2.0, 3.0, 3.9 and 4.9 weeks with standard deviation (SD) 0.3 during the CRT. The mean baseline WBC, ANC, haemoglobin (Hgb) and platelet (PLT) counts were 8.2 k/μL (SD 3.4), 4.9 k/μL (SD 3.7), 11.9 g/dL (SD 1.5) and 303 k/μL (SD 95), respectively. The mean dose of PBM was 28.4 Gy (SD 3.1). The mean V_{10} and V_{20} were 88.9% (SD 5.9%) and 72.6% (SD 7.4%), respectively.

Longitudinal decline in peripheral blood cell counts

The mean reductions in WBC, ANC, Hgb and PLT counts, at 4 weeks relative to the baseline, were 54.8% (SD 20.8%), 45.5% (SD 31.2%), 5.3% (SD 12.7%) and 40.1% (SD 17.7%), respectively. In addition, the weekly reductions of WBC and PLT were significantly different at the beginning and towards the end of CRT (Table 3). Compared with baseline, in the first week of CRT, WBC and PLT on average declined 1.79 k/μL and 15.5 k/μL, respectively. In comparison, the average declines in WBC and PLT between week 4 and week 5 were 0.39 k/μL and 3.1 k/μL, respectively.

Increases in mean PBM radiation dose, V_{20}, V_{30} and V_{40} were all significantly associated with a greater weekly reduction in ln(WBC) (Table 4). For instance, the rate of reduction in ln(WBC) would be 7.8/μL more per week with every 1 Gy increase in mean PBM dose (P = 0.015). However, no statistically significant relationship was

Table 3. Mean weekly reductions in peripheral blood cell counts during chemoradiotherapy

Mean reduction (SD)	Week 1	Week 2	Week 3	Week 4	Week 5	*P*
WBC (k/μL)	1.79 (1.72)	1.21 (2.84)	1.13 (1.92)	0.88 (1.42)	0.39 (0.77)	0.0002
ANC (k/μL)	0.59 (1.58)	0.77 (2.42)	0.96 (1.82)	0.66 (1.34)	0.31 (0.75)	0.19
Haemoglobin (g/dL)	0.27 (0.96)	0.20 (0.95)	0.06 (0.86)	0.24 (0.78)	0.16 (0.94)	0.53
Platelets (k/μL)	15.5 (65.9)	73.3 (70.3)	19.9 (46.9)	19.3 (51.5)	3.10 (44.9)	<0.0001

ANC, absolute neutrophil count; SD, standard deviation; WBC, white blood cell.

Table 4. Univariable analysis of factors associated with longitudinal reductions in log-transformed white blood cell (WBC) and absolute neutrophil count (ANC)

	ln (WBC) (k/μL)			ln (ANC) (k/μL)		
	β†	95% CI	*P*	β†	95% CI	*P*
Mean dose (Gy)	–0.0078	–0.0140, –0.0015	**0.015**	–0.0096	–0.0173, –0.0019	**0.015**
V_{10} (%)	–0.0032	–0.0065, 0.000	0.056	–0.0036	–0.0076, 0.0005	0.084
V_{20} (%)	–0.0038	–0.0064, –0.0012	**0.004**	–0.0047	–0.0079, –0.0016	**0.004**
V_{30} (%)	–0.0024	–0.0046, –0.0002	**0.030**	–0.0030	–0.0057, –0.0003	**0.032**
V_{40} (%)	–0.0026	–0.0044, –0.0005	**0.017**	–0.0032	–0.0058, –0.0006	**0.016**
Age	0.0004	–0.0010, 0.0018	0.593	0.0004	–0.0014, 0.0021	0.688
Race	–0.0087	–0.0303, 0.0129	0.427	–0.0078	–0.0345, 0.0189	0.563
ln(BMI)	0.0299	–0.0506, 0.1104	0.463	0.0577	–0.0409, 0.1564	0.248
Comorbidity	0.0045	–0.0360, 0.0451	0.825	0.0106	–0.0392, 0.0603	0.675

Bold face indicates statistical significance ($P < 0.05$). †β is the coefficient for each covariate in the mixed-effects model: e.g. a reduction in ln(WBC) by 7.8 per μL corresponds to a 1 Gy increase in mean bone marrow dose.

ANC, absolute neutrophil count; BMI, body mass index; CI, confidence interval; V_{10}, V_{20}, V_{30}, V_{40}, volumes of pelvic bone marrow that received at least 10, 20, 30 or 40 Gy; WBC, white blood cell.

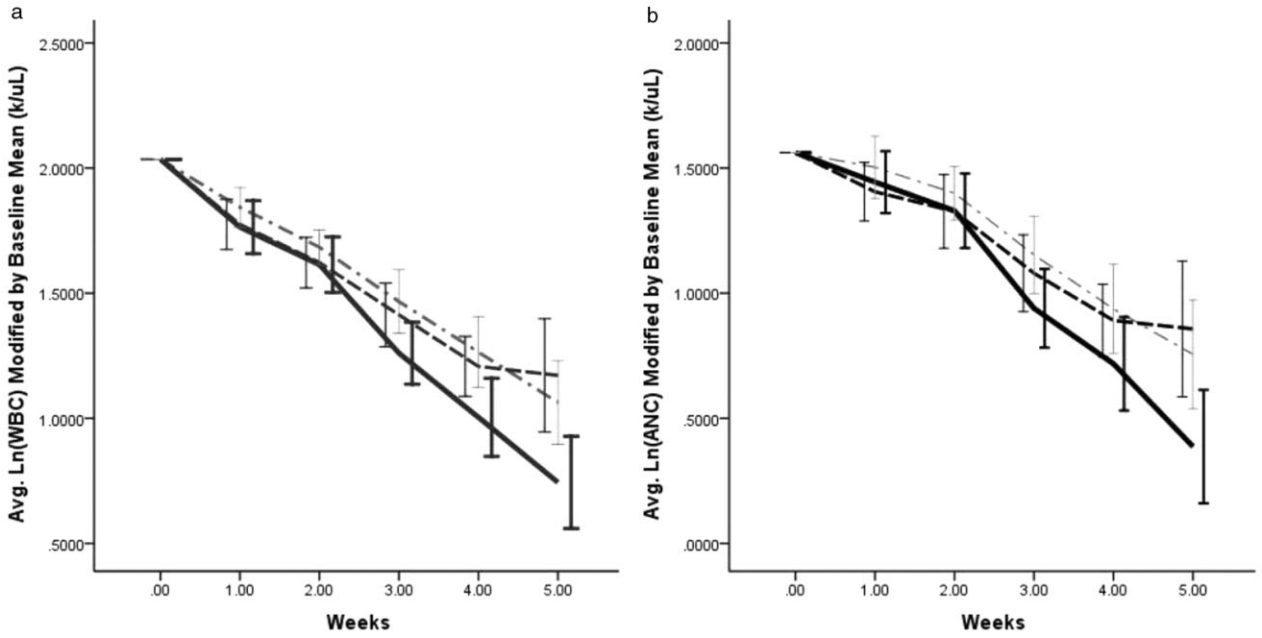

Fig. 1. Relative changes in white blood cell (WBC) (a) and absolute neutrophil count (ANC) (b) over time among low, medium and high pelvic bone marrow (PBM) dose groups, based on mean PBM dose. WBC and ANC values (k/μL) at time 0 were normalised to the baseline mean for all patients, with each week's values adjusted accordingly. Bars represent 95% confidence intervals around the mean. Tertile group of mean dose: ▬ ▪, low; ▬ ▪, medium; ▬, high.

found between V_{10} and WBC (P = 0.056). Effects of confounders on weekly reductions in peripheral blood cell counts were not statistically significant (Table 4). Similarly, radiation dose-volume metrics were found to be significantly associated with weekly reductions in ANC values (Table 4). However, these relationships were not observed for Hgb or PLT counts (data not shown).

Effects of mean PBM dose were further investigated graphically by dividing patients into tertiles according to low, medium and high values. The cut-offs for the low and high tertiles were <26.7 Gy and >29.5 Gy, respectively. The mean values by tertile were 25.3 Gy (SD 1.1 Gy), 28.2 Gy (SD 0.9 Gy) and 31.9 Gy (SD 2.1 Gy), respectively. The relative difference in weekly reductions for WBC and ANC is depicted in Figure 1a,b. The mean ln(WBC) and ln(ANC) were similar for the three groups during the first 3 weeks, whereas divergence in values for the high-dose group was apparent by 5 weeks.

Subregion analysis also identified significant associations between weekly reductions in ln(WBC) and ln(ANC) with irradiation of the lumbosacral spine, ischium and proximal femora, but not with irradiation of the ilium. V_{10} and V_{40} of LSBM significantly affected the weekly reduction in WBC and ANC. V_{20} and V_{30} of LOWBM showed significant correlation with the weekly reduction in WBC and ANC. In comparison, none of the dose-volume metrics mentioned above was associated with IBM (Table 5).

Association between PBM radiation and interruption of chemotherapy

As described above, 44% of the patients had one or more cycles of cisplatin held during CRT, and 35% had one or more cycles held due to critically low WBC or ANC. Patients from all three dose groups experienced low WBC after the third week of CRT; however, patients in the high-dose group had lower mean WBC and ANC values (Fig. 2), providing graphical evidence of the association between mean PBM dose and both leukopenia and neutropenia observed in Table 4. Note that by week 5, in contrast to the low and medium PBM dose groups, over 25% of patients in the high PBM dose group had WBC values below the threshold to withhold chemotherapy.

On univariable logistic regression, withholding at least one cycle of cisplatin was not significantly associated with any dose-volume metric, including V_{20} (OR 1.06, 95% CI 0.998–1.12, P = 0.06) and mean PBM dose (OR 1.06, 95% CI 0.93–1.20, P = 0.39). On multivariable analysis, when controlling for baseline WBC value, interruption of chemotherapy was significantly associated with increasing V_{20} (OR 1.07, 95% CI 1.01–1.13, P = 0.03), a finding that should be viewed as exploratory. However, no dose-volume metrics were significantly associated with HT-related interruption of chemotherapy, including V_{20} (OR 1.06, 95% CI 0.995–1.13, P = 0.07). Withholding chemotherapy was not associated with age, race, BMI or comorbidity.

Table 5. Univariable analysis of dosimetric parameters associated with longitudinal reductions in log-transformed WBC and ANC according to pelvic subregions

	ln (WBC) (k/μL)			ln (ANC) (k/μL)		
	β	95% CI	*P*	β	95% CI	*P*
LSBM						
V_{10} (%)	–0.0046	–0.0092, –.0001	**0.047**	–0.0063	–0.0119, –0.0008	**0.026**
V_{20} (%)	–0.0025	–0.0055, .0005	0.104	–0.0032	–0.0069, 0.0005	0.090
V_{30} (%)	–0.0007	–0.0025, .0010	0.397	–0.0010	–0.0031, 0.0011	0.359
V_{40} (%)	–0.0015	–0.0029, –.0002	**0.029**	–0.0020	–0.0037, –0.0003	**0.022**
LOWBM						
V_{10} (%)	–0.0013	–0.0031, .0005	0.149	–0.0016	–0.0038, 0.0006	0.162
V_{20} (%)	–0.0023	–0.0038, –.0007	**0.005**	–0.0029	–0.0048, –0.0010	**0.003**
V_{30} (%)	–0.0019	–0.0036, –.0002	**0.025**	–0.0023	–0.0044, –0.0003	**0.025**
V_{40} (%)	–0.0018	–0.0039, .0002	0.078	–0.0024	–0.0048, 0.0001	0.063
IBM						
V_{10} (%)	–0.0001	–0.0037, .0036	0.976	–0.0003	–0.0047, 0.0042	0.906
V_{20} (%)	–0.0001	–0.0023, .0022	0.956	–0.0004	–0.0031, 0.0023	0.760
V_{30} (%)	–0.0006	–0.0028, .0015	0.553	–0.0011	–0.0037, 0.0015	0.405
V_{40} (%)	–0.0023	–0.0049, .0003	0.086	–0.0032	–0.0064, –0.0000	**0.050**

Bold face indicates statistical significance ($P < 0.05$). ANC, absolute neutrophil count; IBM, iliac bone marrow; LOWBM, lower pelvic bone marrow; LSBM, lumbosacral bone marrow; V_{10}, V_{20}, V_{30}, V_{40}, volumes of pelvic bone marrow that received at least 10, 20, 30 or 40 Gy; WBC, white blood cell.

Discussion

The aim of this study was to investigate the association between PBM radiation dose-volume metrics and weekly reductions in peripheral blood cell counts in cervical cancer patients undergoing CRT, using a different modelling approach (longitudinal data analysis) than has been applied previously. To our knowledge, this is the first report describing the effects of varying bone marrow radiation dose on longitudinal changes in haematologic toxicity in cervical cancer patients undergoing CRT.

The radiosensitivity of bone marrow has been well described previously. Radiographic, histologic and biochemical changes, including damage of haematopoietic stem cells and adverse modification of bone marrow microenvironment, are known to occur at low doses.[10–12] Early longitudinal studies reported declining peripheral blood cell counts leading only to myelosuppression without the need for medical intervention.[13,14] In contrast, acute HT is a more significant concern in the setting of CRT. Recent studies have indicated that acute HT is dependent on both radiation dose and the volume of the pelvic bones irradiated.[5] However, the extent to which increasing bone marrow dose contributes to acute HT in the setting of CRT is not fully known.

In this study, we observed significant adverse effects of mean PBM dose, V_{20}, V_{30} and V_{40} on weekly reductions in WBC and ANC, lending support to the hypothesis that variations in PBM dose affect acute HT. When patients were divided into tertiles based on mean PBM dose, the effects were most pronounced in the group with the highest levels of PBM irradiation. Therefore, it may be that a sharp threshold exists for mean PBM dose, below which reductions in PBM dose are sufficient to reduce or even prevent HT.

HT can lead to interruption of chemotherapy. In this study, 44% of the patients had at least one cycle of cisplatin held, including 35% of patients as a result of HT. Furthermore, a greater number of chemotherapy interruptions were observed in the high mean PBM dose group. Even though most dose-volume metrics were significantly associated with weekly reductions in peripheral blood cell counts, we could not reject the null hypothesis that these metrics had no effect on whether chemotherapy was held. A previous study by Yang *et al*. showed a strong correlation between baseline CBC and nadir values with partial body irradiation, including the pelvis.[13] In our study, when baseline WBC was controlled for, V_{20} was found to be significantly correlated with interruption of chemotherapy, but the results should be interpreted cautiously because this analysis was exploratory.

Due to the large volume of the pelvis, reducing radiation to the whole PBM is technically challenging; however, functional imaging studies indicate that the haematopoietic activities are mostly concentrated in the lumbosacral bone and lower pelvic bones.[8,9] We have previously identified subregions of the pelvic bones, namely, the lumbosacral spine (i.e. LSBM) and lower pelvic bones (i.e. LOWBM), where lower doses of radiation increased the odds of acute HT during CRT.[4] Recent studies have suggested that HT can be reduced by sparing these metabolically active pelvic regions using functional image-guided IMRT.[8,9] The present study

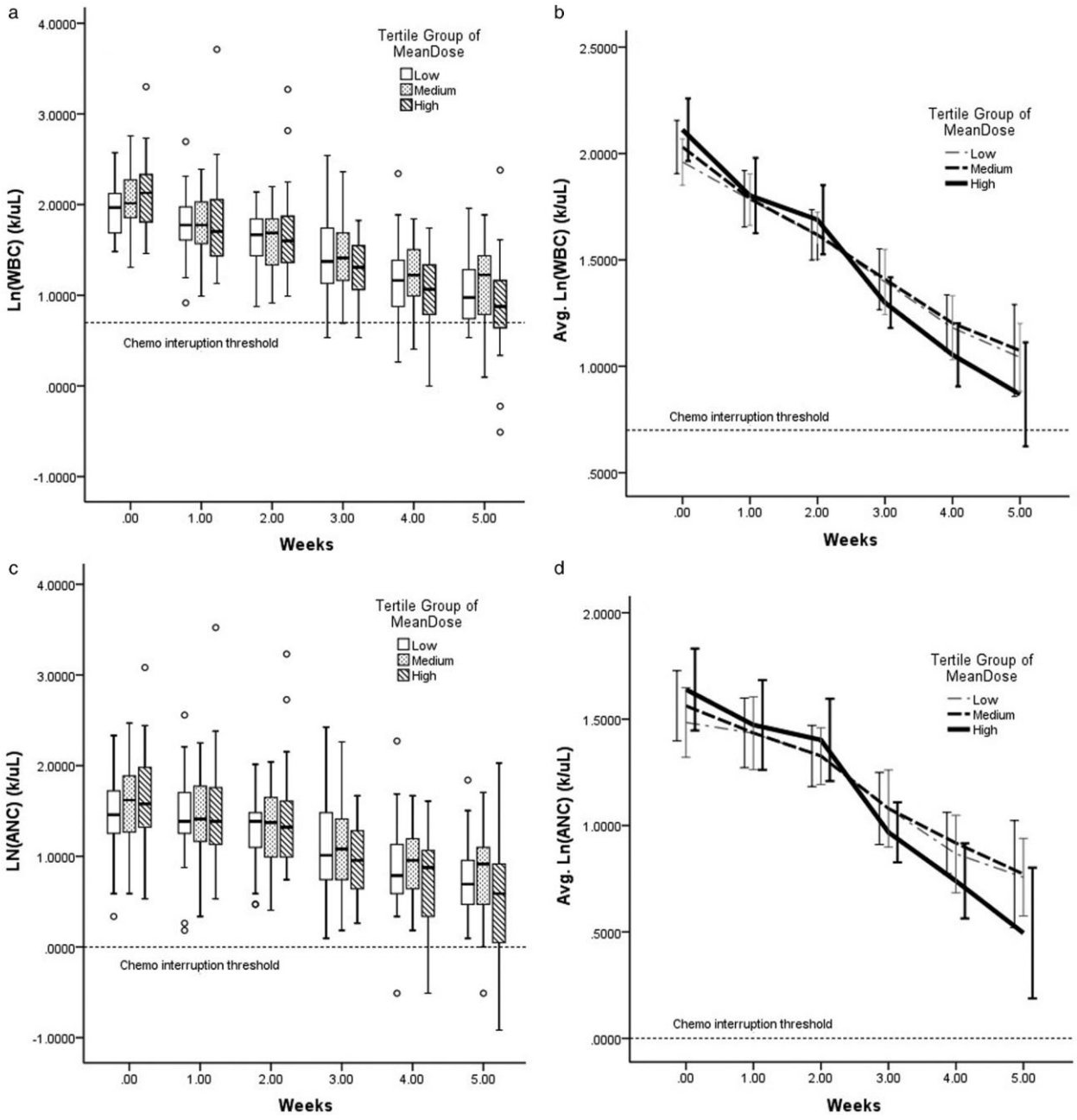

Fig. 2. Absolute changes in white blood cell (WBC) (a–b) and absolute neutrophil count (ANC) (c–d) over time among low, medium and high pelvic bone marrow (PBM) dose groups, based on mean PBM dose. Figure 2a and 2c show boxplot distributions of WBC and ANC levels each week during chemoradiotherapy (CRT), respectively. Figure 2b and 2d show mean WBC and ANC levels, with 95% confidence intervals around the mean. Dashed lines show the critical WBC and ANC levels below which chemotherapy would be held. Tertile group of mean dose: (a and c) ☐, low; ▨, medium; ▨, high; (b and d) —, low; — —, medium; ▬, high.

confirmed the importance of these subregions in affecting weekly reductions in peripheral blood cell counts during treatment. Of note, no significant correlation was found for the iliac crests despite all pelvic subregions receiving comparable doses; however, its clinical significance cannot be ruled out due to the possibility of minimal variance in radiation dose.

A limitation of this study is its retrospective design. A small number of patients in this study missed one or more toxicity collections; thus, variations in the collection of longitudinal outcomes data could have influenced the outcome of statistical analyses, especially those that showed borderline significance. A randomised trial would be the best study design to test the hypothesis that

reducing PBM dose leads to reductions in HT, but such trials are exceedingly difficult to conduct in cervical cancer, placing continued emphasis on the need for well-designed cohort studies. Furthermore, we did not collect information on other forms of toxicity or long-term outcomes; however, we have previously reported detailed toxicity and outcomes data for a virtually identical sample.[15] Lastly, we did not analyse the effects of dose to functional or proliferating bone marrow, which would be an important area for further investigation.

The strengths of this study are that it was hypothesis driven and based on a relatively large sample. We employed methods well established for longitudinal analysis that led us to significantly improve the existing predictive model for acute HT.[5] The bi-institutional study capitalised on natural variations in PBM dose within a broader population, with varying planning approaches and dose prescriptions.

In conclusion, we observed strong associations between PBM radiation dose-volume metrics and longitudinal changes in peripheral blood cell counts in cervical cancer patients undergoing concurrent cisplatin and pelvic RT. Different longitudinal haematologic responses to radiation dose were also observed within individual PBM subregions. Optimal reduction of radiation to PBM is unknown, but bone marrow dose planning constraints could be considered based on externally validated NTCP models.[5] The findings of this paper may assist the design of bone marrow-sparing radiation techniques.

References

1. Green JA, Kirwan JM, Tierney JF *et al*. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001; **358**: 781–6.
2. Kirwan JM, Symonds P, Greene JA *et al*. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. *Radiother Oncol* 2003; **68**: 217–26.
3. Chen S-W, Liang J-A, Hung Y-C *et al*. Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications. *Int J Radiat Oncol Biol Phys* 2006; **66**: 1370–7.
4. Mell LK, Kochanski JD, Roeske JC *et al*. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **66**: 1356–65.
5. Rose BS, Aydogan B, Liang Y *et al*. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2011; **79**: 800–7.
6. Albuquerque K, Giangreco D, Morrison C *et al*. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT. *Int J Radiat Oncol Biol Phys* 2011; **79**: 1043–7.
7. Klopp AH, Moughan J, Portelance L *et al*. Hematologic toxicity on RTOG 0418: a phase II study of post-operative IMRT for gynecologic cancer (abstr.). *Int J Radiat Oncol Biol Phys* 2010; **78**: S121.
8. Liang Y, Bydder M, Yashar CM, Rose BS, Cornell M, Hoh CK *et al*. Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. *Int J Radiat Oncol Biol Phys* 2013; **85**: 406–14.
9. Rose BS, Liang Y, Lau SK, Jensen LG, Yashar CM, Hoh CK *et al*. Correlation between radiation dose to (1)(8)F-FDG-PET defined active bone marrow subregions and acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2012; **83**: 1185–91.
10. Mauch P, Constine L, Greenberger J *et al*. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1319–39.
11. Cao X, Wu X, Frassica D *et al*. Irradiation induces bone injury by damaging bone marrow microenvironment for stem cells. *Proc Natl Acad Sci U S A* 2011; **108**: 1609–14.
12. Blomlie V, Rofstad EK, Skjonsberg A *et al*. Female pelvic bone marrow: serial MR imaging before, during, and after radiation therapy. *Radiology* 1995; **194**: 537–43.
13. Yang FE, Vaida F, Ignacio L *et al*. Analysis of weekly complete blood counts in patients receiving standard fractionated partial body radiation therapy. *Int J Radiat Oncol Biol Phys* 1995; **33**: 617.
14. Sutz FH, Slawson RG. Local radiotherapy and the peripheral white blood cell count: review of 203 treatment records. *Mil Med* 1976; **141**: 390–1.
15. Hasselle MD, Rose BS, Kochanski JD *et al*. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1436–45.