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Dynamics and predictors of hematologic toxicity during cranio-spinal irradiation

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ABSTRACT

Background: Craniospinal irradiation (CSI) is a complex radiotherapy (RT) technique required for treating specific brain tumors and some hematologic malignancies. With large volumes of hematogenous bone marrow (BM) being irradiated, CSI could cause acute hematologic toxicity, leading to treatment interruptions or severe complications. We report on the dynamics and dose/volume predictors of hematologic toxicity during CSI.

Materials and methods: Pediatric patients (≤ 18years) undergoing CSI in a tertiary cancer center were included. Medical records were retrospectively reviewed for clinical data and blood parameters were collected at baseline and weekly, until four weeks after the end of RT. The BM substructures were contoured, and dose-volume parameters were extracted. We used Wilcoxon rank-sum test to compare quantitative data, Chi square test for qualitative data and receiver operating characteristics (ROC) curves for dose/volume thresholds.

Results: Fifty-one patients were included. Severe toxicities (grade 3–4) were recorded as follows: 2% anemia, 8% thrombocytopenia, 25% leukopenia, 24% neutropenia. Ninety-eight percent of patients had lymphopenia (grade 1–4) at some point. Twenty-nine percent required granulocyte-colony stimulating factor, 50% had an infection and 8% required a blood transfusion. Dmean > 3.6 Gy and V15 Gy > 10.6% for Pelvic Bones were associated with a higher risk of developing any ≥ G3 toxicities. Dmean > 30–35 Gy to the thoracic and lumbar spine was predictive for G3–4 anemia and thrombocytopenia, and Cervical Spine Dmean > 30 Gy was associated with ≥ G3 neutropenia.

Conclusion: CSI was well tolerated, without life-threatening complications in our cohort, but hematologic toxicity was frequent, with severity increasing with higher mean doses delivered to the hematogenous BM and larger volumes of BM receiving 30–35 Gy.

Key words: craniospinal irradiation; radiotherapy; pediatric oncology; medulloblastoma; toxicity

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Introduction

Craniospinal irradiation (CSI) is a complex radiotherapy (RT) technique often required for treating malignant disease prone to disseminate within the cerebro-spinal fluid, such as specific central nervous system (CNS) tumors, selected cases of hematologic malignancies or other rare cancers in both children and adults, including lepto-meningeal metastasis [1–5]. Including such a large volume in the radiotherapy field, concerning a large number of critical healthy tissue, could lead to several toxicities, such as fatigue, gastro-intestinal and neurological symptoms, as well as hematologic toxicity [6–10].

During CSI, a large volume of hematogenous bone marrow (BM) is irradiated, with radiation-induced changes in BM structure being observed as early as the first week of treatment, translating in abnormal blood parameters, such as anemia, leukopenia, and thrombocytopenia. These could subsequently determine severe complications, such as infections or bleeding and could lead to treatment interruptions with prolonged overall treatment time, that might compromise outcome [11, 12]. This effect could be even more important in younger patients or when chemotherapy is added to the treatment [13, 14]. The distribution of active bone marrow varies with age, with children having a larger proportion of active hematogenous tissue than adults [15]. Main centers of hematopoiesis are the axial and long bones, with the pelvis and spine responsible for approximately 70% of the hematopoietic activity, and other regions having smaller contribution: skull 3–6%, sternum 2-3%, ribs, clavicles and scapulae 10–15% [16, 17]. BM is also highly sensitive to radiation, with doses as low as 40mGy capable of inducing senescence in medullary cells, thus being one of the main acute responding tissue, but it might be also subject to late effects with long-term consequences [18].

In prepubertal patients undergoing CSI a common, recommended practice is including the entire vertebral body in the irradiation field to avoid sharp dose gradients that could cause late spinal asymmetry [19–22]. Moreover, the skull is always partially included in the cranial planning target volume (PTV); therefore, these structures usually get almost the total prescribed radiotherapy dose. Other hematopoietic areas get less or no radiation during CSI, depending on the treatment technique, with proton beam therapy (PBT) offering some advantages in bone marrow sparing [4, 23]. Bone marrow sparing techniques could also be approached using photon therapy, with promising results shown in different tumor sites [24–27].

However, there is insufficient data on dose-volume effects for these critical structures involved in hematopoiesis, especially in the pediatric population. Identifying dose constraints could lead to better treatment planning strategies, potentially reducing side effects and improving treatment outcomes [26, 28, 29]. The aim of this study is to report on the incidence and dynamics of hematologic toxicity in pediatric patients undergoing photon CSI, as well as to identify clinical and dose/volume predictors for the occurrence and severity of these side effects.

Materials and Methods

Pediatric patients (≤ 18 years) undergoing CSI between 2011–2023 in a tertiary cancer center were included. Medical records were retrospectively reviewed for clinical data. Laboratory (complete blood count, CBC) results were collected at baseline (before the start of CSI) and weekly, up to four weeks after the end of treatment. The toxicities were scored according to the RTOG criteria [30]. Hematogenous bone marrow was contoured using manual and semi-automatic methods as shown in Figure 1A and dose-volume-histogram (DVH) parameters were extracted from original treatment plans, as follows: Volume (cm^3), Dmean (Gy), V5 Gy (%), V10 Gy (%), V15 Gy (%), V20 Gy (%), V25 Gy (%), V30 Gy (%), V35 Gy (%), V40 Gy (%). Wilcoxon rank-sum test was used to compare quantitative data, Chi square test for qualitative data and ROC curves for dose/volume thresholds. A multivariate logistic regression analysis was performed to identify independent predictors of severe hematologic toxicities. Due to the small number of observations, overfitting was necessary in the regression model. A Significance level alpha was set as $p \leq 0.05$ for all tests.

Results

Patients

Fifty-one pediatric patients (65% male and 35% female) underwent CSI in the 12-year

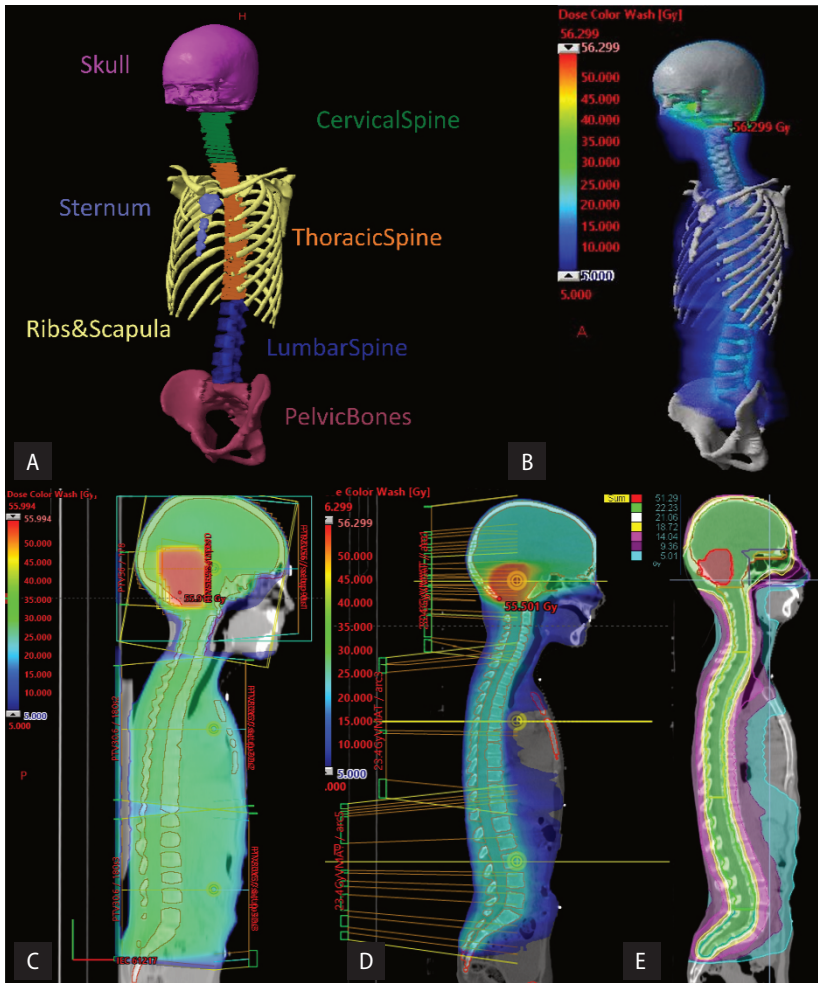

Figure 1A. Bone marrow segments contoured for each patient. **B.** Typical dose distribution overlayed on the bone marrow volume and Example cases of three different treatment plans of cranio-spinal irradiation and tumour bed boost within the posterior fossa: **C.** 3D conformal with three isocentres, two lateral opposed fields for the cranial segment and two posterior fields for the superior and the inferior spinal levels, respectively; **D.** Volumetric modulated arc therapy VMAT with three isocentres and three complete arcs; vertebral bodies were included in the prescribed craniospinal irradiation (CSI) dose **E.** Helical tomotherapy (HT) plan with continuous, helical dose distribution for a post-pubertal patient; vertebral bodies were not included in the prescribed dose (all patients received 23.4 Gy on the cranio-spinal axis with up to 54 Gy to the boost volume)

period, the majority for medulloblastomas (56%) and pancreatic neuroendocrine tumors (PNETs) (18%), with other treated pathologies being hematologic malignancies (6%), gliomas (6%), intracranial germ cell tumors (4%), ependymomas (4%) and pineal tumors (4%). Median age at radiotherapy was 10 years (range 4–18). Forty-six patients underwent surgery prior to radiotherapy, 43 received pre-radiotherapy chemotherapy and 16 also received concomitant chemotherapy. Three patients required anesthesia during CSI. Detailed patient characteristics are presented in Table 1.

Cranio-spinal irradiation

Sixty-three percent were treated with 3D conformal radiotherapy (3DCRT), 31% with intensity/volumetric modulated arc therapy (IMAT/VMAT) and 6% with helical tomotherapy (HT) (Fig. 1B). Eighty-four percent underwent CSI followed by a sequential boost and 16% only received CSI. CSI prescribed doses were 12–18 Gy in 9% of the patients, 23.4–27 Gy in 43%, 30– 30.6Gy in 31% and 36 Gy in 20% of the cases, with total doses of 41.4-54 Gy in four patients, 54 Gy in 33 patients and 54–64 Gy in six patients. There was a statistically significant difference between 3DCRT and VMAT/HT plans

Table 1. Detailed patient characteristics

Age	
Median, Range	10 (3–18)
Sex	
Male	33 (65%)
Female	18 (35%)
Diagnosis	
Medulloblastoma	29 (56%)
PNET	9 (18%)
Glioma	3 (6%)
Hematological malignancy	3 (6%)
Ependymoma	2 (4%)
Intracranial germ cell tumour	2 (4%)
Pineal tumor	2 (4%)
No pathological confirmation	1 (2%)
Type of radiotherapy	
CSI + Boost	43 (84%)
CSI only	8 (16%)
Radiotherapy technique	
3DCRT	32 (63%)
VMAT	16 (31%)
Helical tomotherapy	3 (6%)
RT dose — cranio-spinal [Gy]	
12–18	3 (6%)
23.4–27	22 (43%)
30–30.6	16 (31%)
36	10 (20%)
Total RT dose — including boost [Gy]	
41.4–54 Gy	4 (9%)
54 Gy	33 (77%)
54–64 Gy	6 (14%)
Chemotherapy	
Pre-radiotherapy	43 (84%)
Concomitant	16 (31%)
Surgery	46 (90%)
Anesthesia during RT	3 (6%)

PNET — pancreatic neuroendocrine tumors; CSI — craniospinal irradiation; 3DCRT — 3D conformal radiotherapy; VMAT — volumetric modulated arc therapy; RT — radiotherapy

in terms of V5, V20. V25, V30 and V35 for the entire BM, with higher values for 3DCRT, but no difference in Dmean, V10, V15 and V40 was observed between different techniques.

Median Dmean for the entire bone marrow was 17 Gy (range 6.3–28.4 Gy). For the spinal segments, median Dmean values were 27 Gy for the cervical spine (range 6.3–28.4 Gy), 28.5 Gy for the thoracic spine (range 7–4.2 Gy) and 26Gy for the lumbar spine (range 10–36.7 Gy). Median Dmean for pelvic bones was 5.7 Gy (range 9.4–36.6 Gy), for Sternum 16.7 Gy (range 0.5–20 Gy), for the Ribs and Scapula 2Gy (range 0.2-10.5 Gy) and 30.3 Gy for the Skull (range 12.3–60 Gy). Volumes receiving 5–40 Gy (V5–V40) for each structure are shown in Figure 2B.

Acute hematologic toxicities

Severe toxicities (Grade 3–4) were recorded as follows: 2% of the patients presented anemia, 8% thrombocytopenia, 25% leukopenia, 24% neutropenia. Ninety-eight percent of the patients presented lymphopenia (grade 1–4) at some point, 51% grade 2 and 43% grade 4. Twenty-nine percent required granulocyte-colony stimulating factor, 50% had a confirmed infection during irradiation, 55% received antibiotics (one prophylactic) and 8% required a blood transfusion during radiotherapy. Nadir was recorded in the third week for hemoglobin and thrombocytes, fourth week for lymphocytes and first week after completion of RT for white blood cells and neutrophils (Fig. 2A). By week four post-RT, 86%, 76%, 57% and 25.5% of the patients had fully recovered in terms of thrombocytes, hemoglobin, white blood cells and lymphocytes levels. Eight percent of patients had to temporarily interrupt treatment due to severe toxicity, but all patients completed treatment (maximum overall treatment time 63 days).

Predictors of toxicity

Dmean > 21.3 Gy for bone marrow, Dmean > 3.6 Gy for Pelvic Bones, Cervical Spine V10 Gy > 98.9% and pelvic bones V15 > 10.6% were associated with a higher risk of developing any ≥ G3 toxicities. Mean doses above 35 Gy delivered to the thoracic and lumbar spine and V30 Gy > 97% for the cervical and thoracic spine were associated with higher risk of ≥ G3 anemia. For ≥ G3 neutropenia the strongest predictors were Dmean for cervical spine > 30.4Gy and cervical spine volume receiving 10, 15 and 30 Gy being higher than 99.5%, 97.6% and 77%, respectively. Grade 3 and 4 thrombocytopenia was associated with the irradiation of the Thoracic spine with mean doses > 30.6 Gy and 99% of the segment receiving 25 Gy. Severe leukopenia was recorded for Dmean>3.4 Gy and V5 Gy > 20% for the Ribs and scapula and V5 Gy > 33.4% for the pelvic bones. G3–4 lymphopenia was associated with

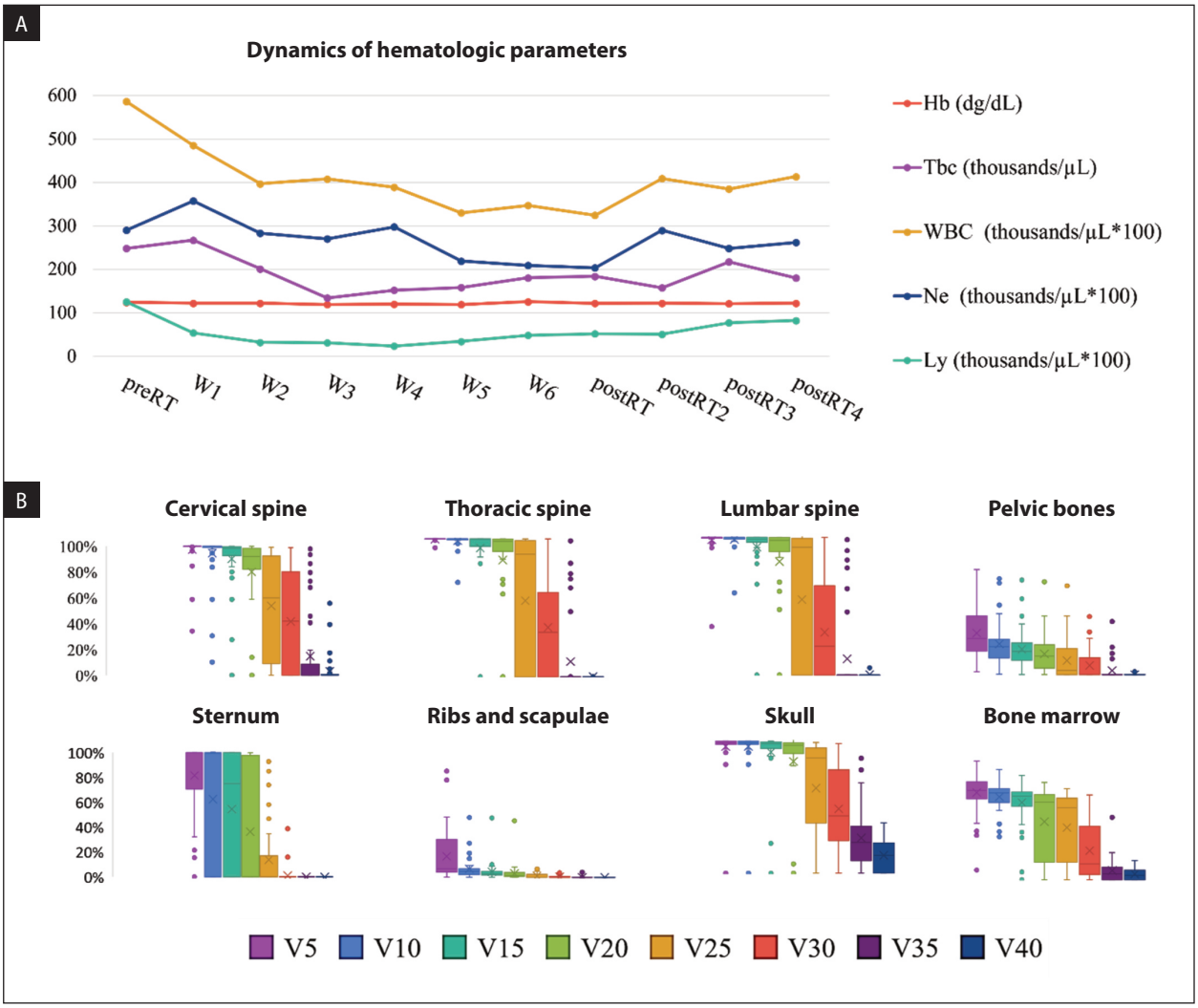

Figure 2A. Dynamics of blood counts at different timepoints. preRT — before the start of radiotherapy; W1-6 — first to sixth week of irradiation; postRT w1–4 — first to forth week after the end of radiotherapy; Ne — neutrophils; Hb — haemoglobin; TBC — thrombocytes; WBC — white blood cells; Ly — lymphocytes; **B.** Box plots showing V5–V40 Gy for each contoured structure. All values are expressed in percentage (%) from the total structure volume; V5 — volume (%) receiving 5 Gy; V10 — volume (%) receiving 10 Gy; V15 — volume (%) receiving 15 Gy; V20 — volume (%) receiving 20 Gy; V25 — volume (%) receiving 25 Gy; V30 — volume (%) receiving 30 Gy; V35 — volume (%) receiving 35 Gy; V40 — volume (%) receiving 40 Gy

Dmean > 3.6 Gy and V15 Gy >10.6% for the Pelvic bones. Detailed results, including sensibilities (Se) and specificities (Sp) for the calculated predictors are shown in Table 1.

Univariate logistic regression found that patients treated with VMAT or HT techniques were at higher risk of developing grade 4 lymphopenia than those treated with 3DCRT techniques [odds ratio (OR): 3.77, confidence interval (CI): 1.17–13.07, p = 0.03) also suggested by the multivariate analysis (OR: 4.62, CI: 1.15–23.03, p = 0.04). In univariate regression, the prescribed dose to the craniospinal axis and the use of concomitant chemotherapy was also found to be a significant predictor of grade 4 lymphopenia (OR: 1.12, CI: 1.01–1.26, p = 0.04/OR: 4, CI: 1.16–15.43, p = 0.03), but these were not confirmed in the multivariate analysis. The neutrophil levels before the start of radiotherapy were also found significant in predicting grade 3 neutropenia during and after CSI, with patients having prior neutropenia presenting a triple risk of developing this toxicity during RT, statistically significant in both univariate and multivariate regression models (OR: 2.86, CI: 1.39–7.34, p = 0.01/OR: 2.4, CI: 1.38–4.64, p = 0.04). No differences in toxicity profiles were found between different age groups, use of pre-radiation chemotherapy or prescribed CSI dose for grade 3 leukopenia and neutropenia or

Table 2. Dose/volume predictors of acute hematologic toxicity, selected according to highest area under the curve (AUC), highest sensibility (Se) and specificity (Sp)

Toxicity	Dose/Volume predictor	Cut-off	AUC (95% CI)	Sensibility (%)	Specificity (%)
Any ≥ Grade 3	Dmean pelvic bones	3.6 Gy	0.89 (0.77–0.97)	84.4	100
	V10 cervical spine	98.9%	0.86 (0.75–0.95)	84.4	100
	V15 pelvic bones	10.6%	0.84 (0.68–0.95)	77.7	100
≥ Grade 3 anaemia	Dmean thoracic spine	35.4 Gy	0.96 (0.13–0.37)	100	95.6
	Dmean lumbar spine	35.6 Gy	0.93 (0.15–0.38)	100	93.4
	V30 cervical spine	97.3%	0.98 (0.44–0.67)	100	97.8
	V30 thoracic spine	97.7%	0.98 (0.51–0.74)	100	97.8
≥ Grade 3 neutropenia	Dmean cervical spine	30.4 Gy	0.68 (0.48–0.87)	70	81.0
	V30 cervical spine	77.1%	0.71 (0.50–0.89)	70	78.3
	V10 cervical spine	99.5%	0.69 (0.52–0.83)	100	45.9
	V15 cervical spine	97.6%	0.69 (0.51–0.85)	90	51.3
≥ Grade 3 thrombocytopenia	Dmean thoracic spine	30.6 Gy	0.75 (0.50–0.94)	75	83.7
	V25 lumbar spine	99.2%	0.79 (0.52–0.97)	75	83.7
	V25 thoracic spine	99%	0.78 (0.54–0.95)	75	86.0
≥ Grade 3 leukopenia	Dmean ribs	3.4 Gy	0.70 (0.53–0.85)	61.5	82.3
	V5 ribs and scapula	20 %	0.73 (0.56–0.88)	61.5	85.2
	V5 pelvic bones	33.4%	0.69 (0.50–0.85)	69.2	73.5
≥ Grade 3 lymphopenia	Dmean pelvic bones	3.6 Gy	0.89 (0.75–0.97)	84.4	100
	V10 cervical spine	98.9%	0.86 (0.75–0.95)	84.4	100
	V15 pelvic bones	10.6%	0.84 (0.68–0.95)	77.7	100

CI — confidence interval

grade 4 lymphopenia. White blood cell and lymphocyte levels before CSI did not influence grade 3 leukopenia or grade 4 lymphopenia during and after treatment. Other variables were not suitable for testing due to low number of observations and small patient cohort.

Discussion

Hematologic toxicity is a frequently occurring acute toxicity during craniospinal irradiation, with almost all patients experiencing lymphopenia, but with small variations in the hemoglobin levels. However, mitigation of the side effects was successfully done with supportive and symptomatic treatment, grade 4 toxicity was limited to lymphopenia and no significant severe, life-threatening complications occurred during treatment. Treatment interruptions, when required, were short-term and no patient abandoned treatment, thus indicating that photon CSI is safe and usually well tolerated. Our results are in line with other reports from the literature, with other authors reporting similar findings, including the predominance of lymphopenia and thrombopenia and stable values of hemoglobin during treatment, with nadir levels occurring usually around the second-third week of treatment, after the completion of the cranio-spinal phase of the treatment [6, 7, 31–36]. Similar to other reports, no difference was observed between age groups or use of chemotherapy in our patient population, except for the concomitant chemotherapy potentially increasing the risk for severe lymphopenia. However, other authors demonstrated that age and chemotherapy could increase the risk of hematologic toxicity during CSI, with this aspect remaining controversial and subject to further research [6, 13, 14, 31, 37]. Moreover, pre-radiation neutropenia might increase the risk of subsequent neutropenia during treatment, with a higher prescribed dose being a risk factor for more severe toxicity. These findings underline the need for careful patient follow-up during radiotherapy, especially in the first three weeks of treatment. Patients with higher prescribed doses and previous hematologic toxicities require careful monitoring with

weekly complete blood count checks and prompt therapeutic interventions, when needed.

Despite numerous studies reporting on the incidence and severity of hematologic toxicity during RT, the literature is still scarce in terms of dose-volume constraints for bone marrow and sub-structures, with little to no data referring particularly to the pediatric population or cranio-spinal irradiation. In our study, the strongest correlation for any grade 3–4 toxicity was found for mean doses and volumes of spinal segments and pelvic bones, given the fact that these segments also have the highest relative contribution in hematopoiesis.

In terms of photon radiotherapy techniques, we observed higher overall doses received by the BM with 3DCRT techniques than with VMAT/HT. However, the low-dose volumes, the so-called "low dose bath", are usually larger with intensity-modulated techniques. Another fact that should be considered is that there are other organs with a role in hematopoiesis or containing large amount of blood or blood cells, such as the spleen, the liver, the lungs, the circulating blood or lymphatic tissues, with 85% of the lymphocytes existing outside the BM and being exposed to various levels of radiation across the body. Therefore, we cannot attribute the entire hematologic response to radiation solely to the bone marrow. This aspect, along with the high radiosensitivity of lymphocytes, could also explain the presence of lymphopenia in the majority of the patients, as well as the paradox of VMAT/HT patients presenting a higher risk of G4 lymphopenia compared to 3DCRT [38, 39].

There are different approaches to reduce toxicities during CSI, such as proton beam therapy and vertebral-sparing techniques. Several studies showed that proton beam therapy is equally efficient in terms of local tumor control, offering the benefit of lower toxicity rates, including hematologic ones [4, 14, 28, 35, 40]. Also, excluding the vertebral bodies from the prescribed dose volume in post-pubertal patients could further reduce the risk of cytopenia, with the spine being an important source of new blood cells. More, strategies to prevent neutropenia were tested, by using prophylactic granulocyte-colony stimulating factor (G-CSF), with inconclusive results and modest benefit [37].

We acknowledge several limitations of our study, with the retrospective and single institution study design, underlying that further validation on larger, independent cohorts is required. Also, patients with various tumor types were analyzed, including different chemotherapy and schedules and regimens. This brought the advantage of evaluating CSI toxicity in various clinical settings, but the heterogeneity in the study population could have interfered with the interpretation of the results.

Conclusion

Hematologic toxicity is a frequent acute side effect of CSI, with severity increasing with higher mean doses delivered to the hematogenous BM and larger volumes of BM receiving 30 or 35Gy. However, toxicities didn't lead to treatment abandonment or life-threatening complications in our cohort. Further validation of our findings is required in bigger, independent cohorts.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by A.T., B.H., C.G., C.B., R.C., O.D., Z.F., E.M., D.O., P.P., A.Ti., A.T, D.C. Statistical analysis was performed by D.L. D.L. and P.A.-C. have overseen and coordinated the study. The first draft of the manuscript was written by A.T., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Oncology Institute Cluj-Napoca.

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