Advances in Radiation Oncology (2021) 7, 100880

advances in radiation oncology

www.advancesradonc.org

Research Letter

Dosimetric Modeling of Lymphopenia in Patients With Metastatic Cancer Receiving Palliative Radiation and PD-1 Immune Checkpoint Inhibitors

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Received July 19, 2021; accepted December 9, 2021

Abstract

Purpose: Radiation therapy (RT)—associated lymphopenia may adversely affect treatment outcomes, particularly in the era of immunotherapy. We sought to determine dosimetric factors correlated with lymphopenia after palliative RT in a cohort of patients with advanced cancer treated with anti-PD-1 immune checkpoint inhibitors.

Methods and Materials: We included patients with metastatic lung cancer, melanoma, or renal cell carcinoma who were treated with either pembrolizumab or nivolumab and received palliative RT to an extracranial site. Baseline and nadir absolute lymphocyte counts (ALCs) within 6 weeks of RT were recorded. Dosimetric factors were extracted from the corresponding dose-volume histograms and also used to model the dose to circulating lymphocytes via a whole-body blood flow model that simulates the spatiotemporal distribution of blood particles in major organs during RT.

Results: We analyzed 55 patients who underwent 80 total courses of palliative RT; most (94%) were treated with 3-dimensional conformal RT. Doses to the whole body, bone, and large blood vessels (LBVs) were negatively correlated with the ALC nadir, with the strongest correlations seen at V15 (r_s, −0.38, −0.43, and −0.37, and P = .0004, .0001, and .0008, respectively). Doses to other organs were not significantly correlated with the ALC nadir. The modeled dose to circulating lymphocytes was also negatively correlated with the ALC nadir and percent ALC change (for D2%, r_s, −0.31 and −0.44, and P = .005 and .0001, respectively). Grade ≥3 lymphopenia was associated with LBV V15 (odds ratio [OR], 1.16; 95% CI, 1.07-1.26; P < .001), bone V15 (OR, 1.04; 95% CI, 1.01-1.08; P = .03), body V15 (OR, 1.003; 95% CI, 1.001-1.006; P = .008), and modeled lymphocyte dose (OR, 1.45; 95% CI, 1.16-1.82; P < .001).

Sources of support: This work was supported by the National Institutes of Health (T32GM007753 [to E.A.G.] and R21 CA248118 / R01 CA248901 [to C.G.]).

Disclosures: Dr Schoenfeld reports research support paid to his institution from Merck, Bristol Myers Squibb, Regeneron, Debiopharm, Adenoid Cystic Carcinoma Research Foundation, and Gateway for Cancer Research; receiving consulting, scientific advisory board, and travel fees from Genentech, Immunitas, Debiopharm, Bristol Myers Squibb, Nanobiotix, Tilos, AstraZeneca, LEK, Catenion, ACI Clinical, Astellas, and Stimit; and receiving expert witness fees and stock options from Immunitas. Dr Bang reports receiving honoraria from AstraZeneca. Dr Pike reports receiving consulting fees from Blackstone Investments/Clarus Ventures, Third Rock Ventures, Galera Therapeutics, Dynamo Therapeutics, Myst Therapeutics, Monte Rosa Therapeutics, and Best Doctors/Teledoc Inc and stock ownership in Schrödinger, Novavax, and Clovis Oncology. All other authors have no disclosures to declare.

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https://doi.org/10.1016/j.adro.2021.100880

Conclusions: The RT dose to the whole body, bone, and LBVs and the modeled dose to circulating lymphocytes were correlated with lymphopenia in patients treated with palliative RT and anti-PD-1 immune checkpoint inhibitors. These findings may inform future radiation planning in this setting.

Introduction

Radiation therapy (RT) has multiple effects on the immune system and its anticancer effects. Radiation therapy can cause lymphopenia, and both hematopoietic stem cells[1] and circulating lymphocytes[2-4] are sensitive to RT, suggesting that RT-induced lymphopenia is attributable to both disruption of lymphocyte production and direct cytotoxicity. Lymphopenia after chemoradiation has been associated with poorer survival in multiple cancer types.[5] Additionally, RT-induced lymphopenia before initiation of immune checkpoint inhibitor (ICI) therapy is associated with poorer outcomes in metastatic non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC).[6] Given the prognostic importance of RT-induced lymphopenia, clarifying dosimetric parameters associated with lymphopenia may inform RT planning and guide patient selection for radiation and immunotherapy approaches.

Conceptualizing the immune system as an organ-at-risk (OAR) in RT planning is challenging. Unlike traditional OARs, the immune system cannot be localized to any single anatomic region, and immune cells may circulate in and out of the radiation field during treatment. Whereas some studies have shown that doses to organs such as the lung, heart, spleen, and bone marrow are associated with lymphopenia,[7] these studies were restricted to single disease sites or anatomic regions, limiting their generalizability. Therefore, we examined dosimetric correlates of lymphopenia in a real-world population of patients with metastatic NSCLC, melanoma, or RCC who received ICIs and underwent palliative radiation to various extracranial sites. We also tested a recently developed dynamic mathematical model of RT dose to circulating lymphocytes[8] using this real-world data.

Methods

Study design

From a multi-institutional database of patients who received treatment with palliative radiation and a PD-1 inhibitor,[6] we identified patients who underwent at least 1 course of extracranial radiation. Patients had at least 1 blood draw within 6 weeks before and after completing radiation; none received cytotoxic chemotherapy concurrently. Baseline and nadir absolute lymphocyte counts (ALCs) were calculated for each radiation course. Dose-volume histograms from each RT plan were extracted for the heart, lungs, liver, kidneys, spleen, bone, and large blood vessels (LBVs) (aorta, inferior vena cava, and primary branches thereof) near the radiation field after manual contouring. Based on prior work,[6] Common Terminology Criteria for Adverse Events, version 5.0, grade $\geq$3 lymphopenia (ALC <500 cells/mL) was used as a cutoff.

We calculated the dose to circulating lymphocytes using a time-dependent whole-body blood flow network.[8] The spatiotemporal distribution of blood was simulated within 28 organs based on blood volumes and flow rates from International Commission on Radiological Protection Publication (ICRP) 89.[9] Physical dose distribution received by contoured organs was calculated from RT plans and used directly in modeling, whereas the dose to noncontoured areas was distributed among other compartments (muscle, skin, fat, and vasculature) based on treatment site. Various dose parameters were calculated, including V0.5 and V1 (fraction of lymphocyte volume receiving a low dose of 0.5 Gy and 1 Gy, respectively) and D2% (dose to the hottest 2% of lymphocyte volume).

Statistical analyses

Analyses were performed using Stata, version 13.0. Continuous and categorical data were compared between groups using Wilcoxon rank sum and Fisher exact tests, respectively. As done in other work,[10] we used Spearman correlation coefficients to examine associations between dosimetric parameters and ALC nadirs; parameters with the most negative correlation were used in further analyses. Logistic regression was used to examine factors associated with development of grade $\geq$3 lymphopenia. To account for intrapatient correlation (given that some patients underwent multiple RT courses), a sandwich estimator was used to adjust standard errors. Owing to significant collinearity, dosimetric factors were analyzed individually and in combination only with other potentially confounding nondosimetric factors including age, Eastern Cooperative Oncology Group (ECOG) performance status, baseline ALC, serum albumin, and receipt of prior RT. All P values were 2-sided, and significance was set at $P < .05$.

Table 1 Clinical and radiation details per treatment course.

Characteristic	Lymphopenia grade ≤2 (N = 49)	Lymphopenia grade ≥3 (N = 31)	*P* value
ECOG performance status, n (%)			
0-1	38 (78)	21 (68)	.44
2-4	11 (22)	10 (32)	
Anatomic site, n (%)			
Spine	17 (35)	11 (35)	.21
Thoracic	10 (20)	11 (35)	
Abdominal/pelvic	9 (18)	4 (13)	
Neck	6 (12)	0 (0)	
Extremity	7 (14)	5 (16)	
Modality, n (%)			
3D	44 (90)	31 (100)	.15
SBRT	5 (10)	0 (0)	
Number of fractions, n (%)			
≤5	26 (53)	13 (42)	.37
≥6	23 (47)	18 (58)	
Dose, median (IQR), Gy	27 (20-30)	24 (20-30)	.82
Any previous radiation, n (%)			
Yes	26 (53)	17 (55)	.99
No	23 (47)	14 (45)	
ALC at baseline, median (IQR), 10^9/L	1.18 (0.76-1.47)	0.77 (0.47-0.92)	.0003
Albumin at baseline, median (IQR), g/dL	3.5 (3.4-4)	3.5 (3-3.9)	.35
Time to nadir ALC measurement, median (IQR), d	16 (5-28)	9 (4-27)	.36

Abbreviations: 3D = 3-dimensional; ALC = absolute lymphocyte count; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; SBRT = stereotactic body radiation therapy.

Results

We included 55 patients who underwent 80 radiation courses in total. The median age at metastatic diagnosis was 64 years (interquartile range, 54-70 years), and 65% of the patients were male; 67% had NSCLC, 20% had melanoma, and 13% had RCC. Most patients (62%) underwent 1 palliative RT course; the remainder underwent 2 to 4 courses. Details per RT course, grouped by development of grade ≥3 lymphopenia, are summarized in Table 1.

Various dosimetric parameters were moderately correlated with the ALC nadir after RT. The most negative correlations were observed at the volume receiving 15 Gy (V15) for LBVs (r_s, −0.37; P = .0008), bone (r_s, −0.43; P <.0001), and the whole body (r_s, −0.38; P = .0004) (Fig. 1). The dose to other organs did not correlate with ALC nadirs, except for the kidney V5 (r_s, −0.32; P = .004). To confirm these findings, we examined correlations between these dosimetric parameters and the percentage change in the ALC from baseline. The V15 for LBVs (r_s, −0.44; P < .0001), bone (r_s, −0.40; P = .0004), and the whole body (r_s, −0.40; P = .0004) remained significantly correlated; the kidney V5 did not (r_s, −0.19; P = .10).

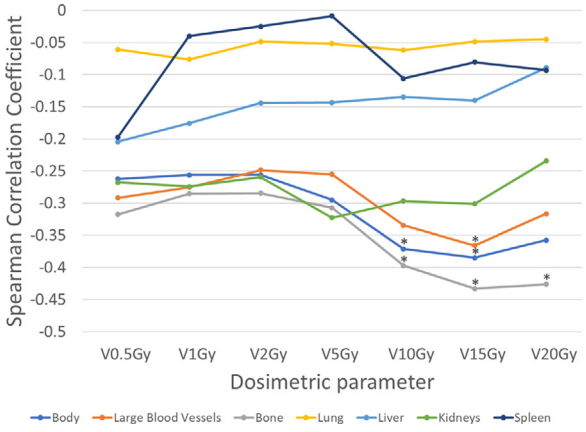

Fig. 1 Spearman correlation coefficients between dosimetric parameters and lymphocyte nadir. *P < .001.

Subsequently, we analyzed the modeled lymphocyte dose. Notably, the modeled V0.5 and V1 were heavily skewed toward high coverage, with 71% of cases having V0.5 > 90% and 51% of cases having V1 > 90% (Fig. E1). Nevertheless, the V0.5, V1, and D2% were all correlated with both the ALC nadir (r_s, −0.27; P = .02; r_s, −0.25; P = .02; and r_s, −0.31; P = .005, respectively) and the percentage ALC change from baseline (r_s, −0.42; P = .0002; r_s, −0.44; P < .0001; and r_s, −0.44; P < .0001, respectively).

To adjust for potential nondosimetric confounders, each dosimetric parameter was examined for association with grade ≥3 lymphopenia using logistic regression (Table 2). The strongest associations in the adjusted models were seen with the LBV V15 (per 10-cm^3 increase, adjusted odds ratio [OR], 1.16; 95% CI, 1.07-1.26; P < .001) and lymphocyte D2% (per 1-Gy increase, adjusted OR, 1.45; 95% CI, 1.16-1.82; P < .001); the planning target volume was not significantly associated after adjustment. Given the heterogeneous nature of our patient cohort, we ran additional sensitivity analyses on various subsets, excluding patients who received a prescription dose of 8 Gy or less, had a baseline ALC <500 cells/mL, or received any prior radiation in the preceding 6 months. In each case, results were consistent with those from the overall cohort (Table E1).

Discussion

In this study, we identified dosimetric correlates of lymphopenia in a cohort of patients with metastatic NSCLC, melanoma, or RCC who received ICIs and palliative radiation therapy. We found that the RT dose to LBVs, bone, and the whole body were moderately correlated with lymphopenia and that the dose to circulating lymphocytes, estimated using a novel compartment model, was also correlated with lymphopenia. These analyses extend our previous work, demonstrating an association between lymphopenia and extracranial RT or >5 fraction RT in this population.[6]

These findings build on previous studies that identified correlates of RT-induced lymphopenia in specific indications using primarily single-organ dose-volume histogram parameters. In a prospective phase 2 study combining focal liver radiation with a combined PD-L1/CTLA-4 blockade, increased radiation dose was correlated with greater declines in circulating lymphocytes and activated CD4 and CD8 subsets.[11] The volume of irradiated bone marrow is correlated with hematologic toxic effects in cervical, anal, and prostate cancer.[12-14] Lymphopenia is associated with long-course fractionation in pancreatic cancer,[15] body dose in lung cancer,[16] and gross tumor volume and lung V5 in NSCLC.[17,18] The current findings add to these

Table 2 Logistic regression results for dosimetric parameters associated with grade ≥3 lymphopenia.

Characteristic	Lymphopenia grade ≤2 (n = 49)	Lymphopenia grade ≥3 (n = 31)	Univariable OR* (95% CI, *P* value)	Adjusted OR*,† (95% CI, *P* value)
Large blood vessel V15, median (IQR), cm^3	46 (9-93)	94 (53-194)	1.10 (1.04-1.16, P = .002)	1.16 (1.07-1.26, P < .001)
Bone V15, median (IQR), cm^3	180 (69-304)	373 (231-563)	1.04 (1.01-1.07, P = .004)	1.04 (1.01-1.08, P = .03)
Body V15, median (IQR), cm^3	1522 (694-2772)	3086 (1630 -5310)	1.003 (1.001-1.005, P = .002)	1.003 (1.001-1.006, P = .008)
PTV, median (IQR), cm^3	620 (347-1228)	1620 (880-2490)	1.005 (1.001-1.008, P = .009)	1.004 (0.999-1.009, P = .08)
Modeled lymphocyte dose D2%, median (IQR), Gy	2.9 (1.3-4.2)	4.0 (2.3-6.9)	1.30 (1.08-1.56, P = .006)	1.45 (1.16-1.82, P < .001)

Abbreviations: CI = confidence interval; D2% = dose to hottest 2% of volume; IQR = interquartile range; OR = odds ratio; PTV = planning target volume; V15 = absolute volume receiving 15 Gy or greater.
* For volume parameters, ORs are given as per 10-cm^3 increase.
† Adjusted for age, baseline absolute lymphocyte count, serum albumin, Eastern Cooperative Oncology Group performance status, and receipt of any prior radiation.

prior studies by examining the entire estimated dose distribution to circulating lymphocytes in a real-world patient cohort encompassing multiple cancer types and irradiated sites and in the context of combination immunotherapy and RT. Notably, our results showed that the correlation between dosimetric parameters and lymphopenia held independently of tumor location and other clinical factors.

We also investigated a recently developed dynamic model of RT dose to circulating lymphocytes[8] to help conceptualize the immune system as an OAR and showed its applicability to multiple cancer types and RT sites. Dynamic blood flow simulations provided the entire dose distribution to circulating lymphocytes, not just an average dose, which showed that a high dose to circulating lymphocytes (D2%) exhibited stronger correlations with lymphocyte depletion than the low-dose bath (V0.5 or V1). This goes beyond correlation to single dosimetric parameters or static concepts such as the effective dose to immune cells,[19] which give a single dose value that is closely tied to integral dose and does not factor in the dynamic nature of radiation delivery. Our model simulations showed that even for palliative regimens, >90% of circulating lymphocytes received doses >1Gy in most patients. Ultimately, this model could help predict lymphopenia risk across disease types and irradiation sites, which is known to hinder the efficacy of ICIs.[6]

There are several limitations to our analyses. The retrospective nature and heterogeneity of this cohort emphasize the need for additional confirmatory studies. When calculating dosimetric volumes and estimating perfusion, organs were treated as uniform tissues, thereby discounting intraorgan heterogeneity (eg, variable bone marrow activity). Although some body parts likely contribute more to an immune OAR than others, given the predominant use of 3-dimensional conformal radiotherapy and the high degree of collinearity here among individual dosimetric parameters, we cannot conclude that diverting the dose from 1 organ to another would necessarily decrease lymphopenia risk. Finally, RT effects on the tumor microenvironment and on specific subpopulations of potentially radioresistant lymphocytes,[20] as well as the role of RT-induced lymphocyte extravasation from circulation into the tumor microenvironment and peripheral tissues, remain open questions.

These findings provide real-world identification of dosimetric correlates of lymphopenia in a diverse patient cohort. Although still hypothesis-generating, the dosimetric factors examined in this study may help guide RT planning to minimize lymphopenia risk. Additional prospective investigation is necessary to test the effects of modified RT planning on lymphopenia risk and ultimately on patient outcomes.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2021.100880.

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