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Scientific Article

Multi-institutional report on toxicities of concurrent nivolumab and radiation therapy

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Abstract

Purpose: Radiation therapy (RT) and nivolumab are standard therapies for a wide range of advanced and metastatic cancers, yet little is known about the toxicity profile of their combined treatment. The rate of grade ≥3 toxicities from nivolumab monotherapy and radiation-only palliative treatments has been reported at 10% to 18% and 0% to 26%, respectively. We reviewed our experience to assess the acute toxicity profile of concurrent RT-nivolumab.

Methods and materials: A retrospective review of all consecutive patients from January 2015 to May 2017 who received concurrent RT-nivolumab was conducted at 4 separate centers. Concurrent RT-nivolumab was defined as RT completed between 3 days prior to initial nivolumab infusion and 28 days after the last nivolumab infusion.

Results: Of the 261 patients who received nivolumab, 46 (17.6%) had concurrent RT to 67 treatment sites. The median follow-up was 3.3 months (interquartile range, 1.7-6.1 months) and the 1-year overall survival rate was 22%. For the 11 of 46 patients (24%) who were alive at last analysis, the median follow-up was 12.8 months (interquartile range, 8.3-14.9 months). The most common histology, RT prescription, and treatment site were non-small cell lung cancer (23 of 46 patients; 50%), 30 Gy in 10 fractions (24 of 67 patients; 35.8%), and abdomen/pelvis (16 of 67 patients; 24%), respectively. Four patients with melanoma had concurrent ipilimumab and were removed from the final toxicity analysis of RT-nivolumab. Within 3 months of treatment with RT-nivolumab, 4 of 42 patients (9.5%) experienced grade 3 toxicity and 2 of these patients' toxicities were attributed specifically to the addition of RT: grade 3 hearing loss after whole brain RT and grade 3 pancreatitis after stereotactic body RT to the left adrenal gland. One death from transaminitis was attributed to nivolumab alone because the RT field did not encompass the liver.

Conclusions: Concurrent RT-nivolumab did not appear to increase the toxicity profile from the previously reported toxicity rates from nivolumab or radiation alone.

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Introduction

Nivolumab is a monoclonal antibody against programmed death-1 (PD-1) that has resulted in improved outcomes in patients with a wide range of advanced or metastatic cancers, including melanoma, non-small cell lung, head and neck, lymphoma, renal, urothelial, colorectal, and hepatocellular cancers.[1-8] Radiation therapy (RT) is also commonly used in this patient population, most often at lower doses to palliate symptoms but also at higher doses using stereotactic body radiation therapy (SBRT) to ablate oligometastatic sites of disease. Furthermore, a growing amount of preclinical and clinical data describe the synergy between checkpoint inhibitor immunotherapy and RT across a wide range of RT doses.[9-12] This potential synergy may also increase the risk of toxicity, but this has not been well defined in the limited number of retrospective studies and case reports that have previously sought to address this issue.[13-15]

Nivolumab monotherapy results in a 10% to 18% risk of grades 3 to 4 immune-related adverse events (ir-AEs) such as diarrhea, nephritis, pneumonitis, hypophysitis, and hepatitis.[8,16,17] Grade 5 fatalities due to nivolumab, which may include but are not limited to encephalitis, neutropenia, pneumonitis, acute renal failure, or heart failure, are uncommon and account for <1% of treated patients.[1,8,17,18] Palliative radiation may be associated with a range of toxicities depending on the part of the body treated, but typically the rate of grade ≥3 toxicity is often negligible or up to 26%.[19-23]

The goal of this retrospective study is to better characterize the toxicities experienced by patients receiving concurrent RT and nivolumab to determine if or when greater caution may be appropriate when considering the use of this relatively new combined modality therapy in patients.

Methods and materials

A retrospective review of all patients from January 2015 to May 2017 who received concurrent RT-nivolumab was conducted at 4 separate centers at 2 separate institutions. For the purpose of this study, concurrent RT-nivolumab was defined as RT administered from 3 days prior to initial nivolumab infusion through 28 days after the final nivolumab infusion. This starting point was selected because preclinical studies have shown that RT-induced changes in the tumor microenvironment peak 3 days after the last dose of RT.[11] The 28-day ending point was selected because nivolumab's half-life of 26.7 days would result in approximately 50% of the drug remaining in the body 28 days after infusion.

Descriptive statistics were used to summarize patient demographics, treatment details, response to therapy, and toxicity. Most patients were seen weekly during their RT and at 1 month follow-up. We also utilized the medical oncology notes because the patients were seen prior to each nivolumab cycle. Duration of follow up was calculated from completion date of RT to last follow-up or date of death.

Toxicities during and after RT were assessed using the Common Terminology Criteria for Adverse Events version 4.0. Any symptoms that were present prior to RT or initial nivolumab administration were not classified as a toxicity from either treatment. Most patients had baseline fatigue, so this was not isolated as a side effect for further analysis. Grades 1 and 2 toxicities were also not reported because this study focused on more pronounced side effects that would more significantly affect a patient's quality of life. RT treatment plans were further evaluated in patients with grades 3 to 5 toxicities to determine whether the toxicities could be attributed to the addition of RT. If a given toxicity could be attributed to an organ within the RT field and the timing of the toxicity was either during RT or within 3 months of completing RT, the toxicity was attributed to RT; otherwise, it was considered to be from nivolumab alone.

Results

A total of 261 patients received nivolumab in the evaluated timeframe, of whom 127 (48.7%) also received RT, which was given concurrently with nivolumab in 46 patients (17.6%). Some of these patients received more than one 1 course of RT with nivolumab for a total of 67 different irradiated sites. Four patients with melanoma also received concurrent ipilimumab and were removed from the toxicity evaluation for RT-nivolumab alone. In all cases, nivolumab was initiated after previous progression of disease on other types of systemic therapy. Table 1 describes additional patient and treatment characteristics.

The median follow-up was 3.3 months (interquartile range, 1.7-6.1 months) and the 1-year overall survival rate was 22%. The majority of patients received palliative radiation and died due to progression of systemic disease. For the 11 of 46 patients (24%) who were alive at last analysis, the median follow-up was 12.8 months (interquartile range, 8.3-14.9 months).

Table 2 describes the RT characteristics including timing of RT-nivolumab, location of treatment, RT prescription, and technique. In addition to external beam radiation, 4 patients also received spatially fractionated grid radiation therapy, hyperthermia, or a combination of both.

Overall, 4 patients (9.5%) experienced grade 3 toxicity. There were no grade 4 toxicities and one grade 5 toxicity due to nivolumab-induced hepatitis. Two of the grade 3 toxicities (4.8%) were attributed to the use of RT. The treatment and toxicity details of these patients are described in Table 3. None of the other treatment site locations, including extremities, chest wall/axilla, or head and neck, had any unexpected or severe side effects. Also, none of the patients developed a severe or unexpected rash in the treatment field, a commonly reported generalized side effect of immunotherapy alone. Details of the 2 unexpected side effects

Table 1 Patient and treatment characteristics of concurrent nivolumab and radiation

	n = 46	%
Age, years		
Range (Median)	43-82 (62)	
Sex		
Male	27	58.7
Female	19	41.3
Primary cancer		
Lung	23	50.0
Renal	8	17.4
Gastrointestinal	3	6.5
Head and neck	3	6.5
Melanoma	9	19.6
Number of radiation therapy sites/patient		
1	30	65.2
2	13	28.3
3	1	2.2
4	2	4.3
Total cycles of nivolumab		
Mean	10	
Median	6	
Range	1-44	
Interquartile range	3-10	
Cycles of nivolumab prior to radiation therapy		
Mean	5	
Median	3	
Range	0-34[a]	
Interquartile range	2-6	

[a] Zero indicates nivolumab was started either during radiation or within 3 days of completing radiation therapy.

Table 2 Concurrent radiation therapy characteristics per site

	n = 67	%
Timing of concurrent RT and nivolumab		
RT completed ≤3 days prior to initial nivolumab	4	6.0
RT completed by final nivolumab	41	61.2
RT completed <14 days post-final nivolumab	6	9.0
RT completed >14-28 days post-final nivolumab	16	23.9
Location of treatment		
Abdomen/pelvis (including spine)	16	23.9
Brain	12	17.9
Extremity	12	17.9
Chest wall/axilla	11	16.4
Thorax (including spine)	10	14.9
Head/neck (including spine)	6	9.0
Technique		
3-dimensional conformal RT	54	80.6
SBRT	6	9.0
SRS	3	4.5
3-dimensional + SFGRT	2	3.0
3-dimensional + SFGRT + hyperthermia	1	1.5
3-dimensional + hyperthermia	1	1.5
Total dose/fraction (Dose/fraction)		
30 Gy/10 fractions (3 Gy)[a]	24	35.8
20 Gy/5 fractions (4 Gy)[b]	14	20.9
8 Gy/1 fractions (8 Gy)	11	16.4
20-50.4 Gy/10-28 fractions (1.8-2 Gy)	5	7.5
20-57.5 Gy/5-23 fractions ± 12-15 Gy SFGRT ± hyperthermia	4	6.0
21-39 Gy/3 fractions (7-13 Gy; SBRT)	4	6.0
15-22 Gy/1 fraction (Cranial SRS)	3	4.5
30-45 Gy/5 fractions (6-9 Gy; SBRT)	2	3.0

RT, radiation therapy; SBRT, stereotactic body radiation therapy; SFGRT, spatially fractionated grid radiation therapy; SRS, stereotactic radiation surgery.

[a] Includes 36 Gy/12 fractions and incomplete treatments: 5 treatments of 27 Gy/9 fractions; 1 treatment of 24 Gy/8 fractions, and 1 treatment of 9 Gy/3 fractions.

[b] Includes 1 incomplete treatment of 16 Gy/4 fractions.

from concurrent RT-nivolumab that developed in the RT field are described.

One patient developed grade 3 hearing loss after whole brain radiation therapy (WBRT). This patient had prior stereotactic radiation surgery (SRS) to 6 brain metastases that were treated at 20 to 22 Gy to the 50% isodose line, completed 4 months prior to WBRT (30 Gy in 10 fractions) and prior to his first dose of nivolumab. Subsequently, the patient had 4 cycles of nivolumab prior to WBRT. Although the patient had some hearing loss prior to WBRT, he reported significantly worsening hearing loss during the 2 months after completing WBRT. The patient was noted to have otitis media with effusion in both ears with resultant eustachian tube dysfunction, and an audiogram confirmed significant grade 3 hearing loss with hearing aids indicated. A brain magnetic resonance imaging scan did not reveal any other explanation for the hearing loss. None of the prior SRS treatments compromised the cochlea or internal auditory meatus. Although there was no prior audiogram available for comparison and chronic ear infections are known to lead to permanent hearing loss, WBRT was thought to be the cause of the rapid decline in hearing, which is an extremely rare side effect of WBRT alone.

Another patient unexpectedly developed grade 3 pancreatitis after 20 cycles of nivolumab and concurrent SBRT (33 Gy in 3 fractions) to a left adrenal mass.[24] Pancreatitis is a rare side effect of nivolumab and has never been reported after SBRT; therefore, the synergy of both treatments and toxicity profiles could have resulted in this toxicity. However, another patient in our analysis who had concurrent nivolumab-ipilimumab and SBRT (39 Gy in 3 fractions) to a left adrenal mass did not develop any signs of pancreatitis during follow up. The factors that led to the acute and unexpected side effect in one patient and not the other are not clear. None of the other patients who received SBRT experienced unexpected side effects.

Of note, among the 4 patients who received concurrent ipilimumab-nivolumab and RT, 3 (75%) experienced

Table 3 Details of Grade ≥3 toxicities from concurrent nivolumab and radiation

Toxicity grade	Toxicity description	RT target description	RT prescription	Reirradiation	Nivolumab cycles prior to toxicity	Probable cause of toxicity
5	Hepatitis	Duodenum	41 Gy/16 fx (2.5 Gy)	No	3	Nivolumab only; liver not in RT field
3	Pneumonitis; transaminitis	L4-Sacrum	30 Gy/10 fx (3 Gy)	No	2	Nivolumab only; neither lungs nor liver in RT field
3	Enterocolitis	T7-T9	30 Gy/10 fx (3 Gy)	No	4	Nivolumab only; bowels not in RT field
3	Sensorineural hearing loss	Whole brain	30 Gy/10 fx (3 Gy)	Yes, prior cranial SRS	8	Combined RT-nivolumab; extremely rare for hearing loss from WBRT or nivolumab alone
3	Pancreatitis	Left adrenal gland	33 Gy/3 fx (11 Gy)	No	20	Combined RT-nivolumab; extremely rare for pancreatitis from SBRT or nivolumab alone

fx, fraction; RT, radiation therapy; SBRT, stereotactic radiation therapy; SRS, stereotactic radiation surgery; WBRT, whole brain radiation therapy.

grade 3 or 4 toxicity, only 1 was also attributed to RT. One patient who received cranial SRS developed grade 4 hypophysitis resulting in hyponatremia (Na = 118), but the pituitary was far from the SRS volume and deemed to be unlikely to be radiation induced.

Another patient developed grade 3 acute interstitial nephritis 9 months after SBRT to the left adrenal gland, which also was not considered to be induced by RT given the very low kidney dose. However the third patient received 20 Gy in 5 fractions to a central lung tumor and developed grade 3 pneumonitis, likely exacerbated by the combination of RT-nivolumab-ipilimumab. These 4 patients were removed from the toxicity analysis of RT-nivolumab because combined checkpoint blockers are known to have a higher side effect profile than monotherapy.[25]

Discussion

Although cytotoxic chemotherapy is often held during palliative RT due to an increased rate of side effects without improvement in outcomes, it is impractical to hold nivolumab during palliative RT because nivolumab would take approximately 160 days (6 half-lives) to clear the patient's body.[19-21,23] Thus, it is inevitable that a patient on nivolumab who receives RT would receive concurrent therapy. Fortunately, our findings suggest that the addition of RT to nivolumab is generally safe and did not increase the rate of grade ≥3 toxicities previously reported for nivolumab monotherapy.

Prior studies using nivolumab monotherapy reported rates of grade 3 to 4 toxicities ranging from 10% to 18% and grade 5 as very rare. In a pooled analysis of 4 melanoma studies that included 576 patients, there were no grade 5 toxicities and a 10% rate of grade 3 to 4 treatment-related AEs.[16] A larger meta-analysis including 5353 patients from 9 randomized trials including either pembrolizumab or nivolumab reported the absolute risk of grade 3 to 4 AEs was 12.9%, and only 5 patients died in the nivolumab arms.[17] More recently, a report on the phase 2 trial of nivolumab in metastatic urothelial cancers (CheckMate 275) reported an 18% (48 of 270) rate of grade 3 to 4 treatment-related AEs, most commonly grade 3 fatigue and diarrhea. Three patients (1%) died from toxicities related to treatment (pneumonitis, acute respiratory failure, and cardiovascular failure, respectively).

Prior retrospective studies have tried to define the toxicity of combined RT-immunotherapy; however, all had small patient numbers, their definitions of concurrent therapy varied, and some evaluated several immunotherapy drugs that are known to have different toxicity profiles. Nevertheless, because there have not been many studies on nivolumab-RT specifically, it is valuable to discuss studies evaluating other checkpoint inhibitors and RT. At least 3 retrospective studies have assessed the safety of combined RT-ipilimumab, all with small cohorts ranging from 22 to 44 patients, and concluded that the combination of RT and ipilimumab was generally safe with no increased rates of local or systemic ir-AEs and only 14% to 15% rates of grade 3 to 4 toxicity.[26-28]

Another retrospective evaluation of 56 patients who had RT within 14 days of a checkpoint blockade (cytotoxic T-lymphocyte-associated protein 4 and/or PD-1) concluded that the ir-AEs did not appear to be associated with the particular site irradiated, and the authors specified that the toxicity rates of PD-1 inhibitors (pembrolizumab or nivolumab) were 4% for grade 3 to 4 and 0% for grade 5.[13] In another retrospective report on 26 patients with 73 melanoma brain metastases treated with intracranial radiosurgery within 6 months of receiving nivolumab, the authors con-

cluded that the radiosurgery was well tolerated with only 2 patients developing grade 3 edema in the setting of concurrent intracranial metastatic progression. There were no grade 4 or 5 toxicities reported.[15]

Lastly, there was another recent case report of concurrent nivolumab with 20 Gy in 4 fractions delivered to a large cervix tumor. The treatment was well tolerated without any significant toxicities and the patient had an excellent response both locally and at distant areas of disease.[14] All of these studies concluded that the combination of palliative RT and checkpoint inhibitors was well tolerated, with a 4% to 14% rate of grade 3 to 4 toxicity and no deaths.

There are limitations of our study that are inherent to its retrospective design. We did not have a control cohort or predefined list of toxicities to report on, so certain subclinical endocrinopathies or abnormal laboratory findings may not have been identified or reported. It is difficult to compare our toxicity rates to those from previous studies that had different criteria or levels of surveillance for toxicities.

We did not report on any corticosteroid use prior to or during RT in our cohort. The use of steroids could have altered the toxicity profile. Also, although our cohort of 42 patients who received RT-nivolumab is similar to the number of patients in prior retrospective studies evaluating toxicity of combination RT-immunotherapy, the small sample size limits the power of statistical analysis to evaluate potential risk factors for increased toxicity such as higher RT doses, more cycles of nivolumab prior to RT, or treatment site/lymphoid-rich tissues.

These limitations should be weighed against the strengths of our study. Most notably, this was a multi-institutional study and the largest study to describe toxicity among patients treated with concurrent nivolumab and RT. We also used a strict time interval to define concurrent treatment and had access to the RT plans to further evaluate the RT field in relation to the toxicity. These strengths helped us eliminate confounders of added toxicities from other immunotherapies and isolate and study patients who were in an ideal window for RT-nivolumab synergy.

Although the toxicity did not always correlate to organs within the RT field, local inflammatory response from RT could trigger an abscopal inflammatory response leading to toxicities in other organs of the body. Only a larger, prospective trial could shed light on this possibility of abscopal toxicity. Until these studies are complete, oncologists must closely monitor patients on RT-nivolumab as well as nivolumab monotherapy and have a low threshold to initiate corticosteroids that can alleviate some ir-AEs and permit patients to maximize the therapeutic benefit from immunotherapy.

Conclusions

This study did not detect an increase in grade ≥3 toxicity when RT was added to nivolumab compared with nivolumab monotherapy or historical standards for palliative RT. These data are encouraging, but caution and further understanding of combined RT and nivolumab, as well as RT combined with other immunotherapies, are still needed. Our experience adds to the emerging understanding of the complex interactions of nivolumab and RT and helps guide radiation oncologists when faced with a patient on nivolumab who may benefit from RT for local control or palliation.

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