Concurrent immunotherapy and re-irradiation utilizing stereotactic body radiotherapy for recurrent high-grade gliomas

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Abstract

Background: Clinical trials evaluating immune checkpoint inhibition (ICI) in recurrent high-grade gliomas (rHGG) report 7-20% 6-month progression-free survival (PFS), while re-irradiation demonstrates 28%-39% 6-month PFS. Aims: We evaluate outcomes of patients treated with ICI and concurrent re-irradiation utilizing stereotactic body radiotherapy / fractionated stereotactic radiosurgery (SBRT) compared to ICI monotherapy. Methods and Results: Patients >18-years-old with rHGG (WHO grade III and IV) receiving ICI+SBRT or ICI monotherapy between 1/1/16-1/1/19 were included. Adverse events, 6-month PFS and overall survival (OS) were assessed. Log-rank tests were used to evaluate PFS and OS. Histogram analyses of apparent diffusion coefficient maps and dynamic contrast-enhanced magnetic resonance perfusion metrics were performed. Twenty-one patients with rHGG (ICI+SBRT: 16; ICI: 5) were included. The ICI+SBRT and ICI groups received a mean 7.25 and 6.2 ICI cycles, respectively. There were five grade 1, one grade 2 and no grade 3-5 AEs in the ICI+SBRT group, and four grade 1 and no grade 2-5 AEs in the ICI group. Median PFS was 2.85 and 1 month for the ICI+SBRT and ICI groups; median OS was 7 and 6 months among ICI+SBRT and ICI groups, respectively. There were significant differences in pre- and post-treatment tumor volume in the cohort (12.35 vs. 20.51; p=0.03), but not between treatment groups. Conclusions: In this heavily pretreated cohort, ICI with re-irradiation utilizing SBRT was well tolerated. Prospective studies are warranted to evaluate potential therapeutic benefits to re-irradiation with ICI+SBRT in rHGG.

Introduction

High-grade gliomas (HGG), including glioblastoma (GBM) and anaplastic astrocytomas, are associated with a poor prognosis and quality of life (1-5). The majority of HGGs recur, at which point treatment options include re-resection, re-irradiation, bevacizumab, 'off-label' chemotherapy, tumor-treating fields, or clinical trial enrollment (6-8). Unfortunately, recurrent high-grade glioma (rHGG) trials historically produce high failure rates (9-11), necessitating the development of new therapeutic approaches.

Immune checkpoint inhibitors (ICIs) provided impressive results in melanoma, non-small cell lung cancer (12), and in untreated brain metastases secondary to these malignancies (13). While several clinical trials evaluating ICI in HGGs are ongoing, results are disappointing to date. Prior studies evaluating salvage re-irradiation report 6-month progression-free survival (PFS) rates of 28% to 39%, and a median 1-year overall survival (OS) of 26% (11, 14-18). Radiotherapy (RT) may improve ICI efficacy through several mechanisms, including altering tumor cell surface proteins, and enhancing the quantity and diversity of intracellular peptide pools. These effects, in conjunction with inducing MHC class I expression, provides a larger repertoire of antigenic targets to elicit an immune response. RT induces major histocompatibility complex (MHC) class I expression via upregulation of interferon-γ, which may play a role in T cell recruitment (19), conferring

increased survival compared with either modality alone in mouse models (20, 21). Additionally, stereotactic body radiotherapy / fractionated stereotactic radiosurgery (SBRT), entailing conformally delivering higher RT doses in fewer treatments, may be preferable over conventional RT delivered over several weeks with regard to augmenting immune responses (22), while minimizing the impact on circulating lymphocytes.

There is a clear rationale for combining ICI with RT to increase the therapeutic ratio in rHGG, however, there is a paucity of data evaluating safety and efficacy of concurrent re-irradiation with ICI+SBRT. We report treatment-related adverse events (AE) in patients with rHGG treated with concurrent ICI + SBRT at our institution. PFS, OS and changes in tumor volume and perfusion characteristics after treatment were also evaluated.

Methods

Patient selection

Patients age $>$ 18 at the time of rHGG diagnosis (WHO grade IV GBM or WHO grade III anaplastic astrocytoma) treated with concurrent ICI+SBRT or ICI monotherapy at New York-Presbyterian Hospital between 1/1/16 to 1/1/19 were included for analysis. This study was approved by the Weill Cornell Medicine Institutional Review Board. Demographic data, tumor pathological characteristics and profiling from available Foundation studies, radiology variables (tumor size, perfusion/diffusion metrics, and RT necrosis), prior treatments, AE's attributable to treatment, PFS and OS following concurrent ICI + SBRT were collected. Survival data was obtained from available medical records.

Treatment

Patients treated with nivolumab received intravenous infusions at a dose of 3 mg/kg once every two weeks. A cycle of therapy was operationally defined as 28 days, during which nivolumab was administered on day 1 and day 14. Patients treated with pembrolizumab received intravenous infusions at a dose of 2 mg/kg once every three weeks. A cycle of therapy was operationally defined as 21 days, during which pembrolizumab was administered on day 1 and day 21. Treatment was repeated every 14 days for nivolumab, and every 21 days for pembrolizumab, provided all hematologic toxicity from the previous cycle had resolved to grade 2 or less, and all non-hematologic toxicities recovered to either grade 1 or less. When indicated, the subsequent ICI cycle was delayed until these criteria were met.

Radiotherapy planning volumes were contoured by a radiation oncologist and a neurosurgeon. Dose and fractionation were determined on the basis of lesion size, prior radiotherapy, and meeting dose constraints for adjacent organs at risk. For treatment planning, high-resolution thin-slice magnetic resonance T1 sequences with contrast were rigidly fused to CT simulation scans. All patients were treated using non-coplanar volumetric modulated arc therapy (VMAT) using 3-4 arcs and either 6X or 10X flattening filter-free beams that maintained a minimum coverage of 95% of the planning target volume receiving 100% of the prescription dose. The treatment plans were generated using Eclipse v15.6 (Varian Medical Systems, Palo Alto, CA) with either AAA or AcurosXB calculation algorithms. All dose constraints for SBRT plans were evaluated using TG101 guidelines. Patients were treated on a Novalis (BrainLab, Munich, Germany) Truebeam STX linac (Varian Medical Systems, Palo Alto, CA), with multileaf collimator leaf width of 2.5 mm.

Imaging

All patients underwent MRI of the brain on 1.5 or 3 Tesla systems (Skyra, Aera, Biograph mMR, Siemens Healthcare; Discovery 750w, Signa HDxt, GE Healthcare, Milwaukee, WI), pre- and post-treatment. MRI sequences included axial T1-weighted (repetition time/echo time [TR/TE]: 550-700 milliseconds/7-10 milliseconds, 3-5 mm slice thickness) or 3-dimensional T1 SPACE (TR/TE: 600-700 milliseconds/11-19 milliseconds, 120 degree flip, 1 mm slice thickness), axial T2 (TR/TE: 3,200-4,000 milliseconds/93-98 milliseconds, 5 mm slice thickness), and axial T2 fluid attenuation inversion recovery (FLAIR) or 3- dimensional T2 FLAIR (TR/TE: 6,300-8,500 milliseconds/394- 446 milliseconds, 120 degree flip, 1 mm slice thickness). Axial diffusion-weighted sequences were obtained (TR/TE: 6,280-9,000 milliseconds/78-103 milliseconds, 90- or 180- degree flip, 5 mm slice thickness) with ADC maps. Additionally, T1-weighted DCE perfusion MRI was

performed (TR = 4 milliseconds, TE = 1-2 milliseconds, flip angle: 13 degrees, slice thickness: 3 mm, 44 slices to cover the entire lesion volume, 24 phases with 4 phases before and 20 phases after intravenous bolus administration of 0.1 mL/kg gadopentetate).

Olea Medical 3.0 software (La Ciotat, France) was used for DCE perfusion MRI processing and histogram analysis. Histogram analysis was performed on volumes-of-interest that included the entire enhancing tumor volume, encompassing all voxels with enhancing tumor, pre- and post- treatment. Blood-brain barrier permeability metrics, including median, mean, and 90th percentile of the plasma volume (Vp) and volume transfer constant (Ktrans) were derived from the histogram analysis from the volumes-of-interest. Diffusion metrics, including median, mean, and 10th percentile of the ADC were derived from the histogram analysis from the volume-of-interest. All values were normalized utilizing the contralateral normal white matter.

Evaluation

Laboratory tests (complete blood counts and basic metabolic panel) were obtained weekly, a physical examination was performed at every clinical visit with the medical oncologist, and contrast-enhanced brain MRI was performed every 4 weeks.

Neuroradiologic response following treatment was determined by response assessment in neuro-oncology (RANO) criteria (23). Complete response (CR) was defined as the disappearance of all contrast-enhancing tumor or non-enhancing tumor, as defined on MRI FLAIR sequence, on consecutive MRIs at least 1 month apart, with the patient off corticosteroids. Partial response (PR) was defined as a >50% reduction in the size of tumor derived by the sum of cross-sectional radii measured by the contrast enhanced MRI and the MRI FLAIR sequence on consecutive MRI scans at least 1 month apart, with a stable or decreased corticosteroid dose. Progressive disease (PD) was defined as a greater than 25% increase in the size of tumor on either the contrast enhanced MR or FLAIR tumor, or presence of new lesions. Stable disease (SD) was defined as all other situations and required a confirmation MRI one month after documenting best response. Patients were continued on ICI until documentation of PD or unacceptable adverse effects (AE) at which time patients either discontinued ICI, had bevacizumab added to their regimen, or were offered alternative therapy.

PFS and OS were defined as the time from the first day of treatment with ICI until progression of disease or death, or at date of last follow-up. AE were retrospectively determined for all patients and tabulated using Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

Descriptive statistics (including mean, standard deviation, median, interquartile range, frequency, and percent) was calculated to characterize the study sample (i.e., demographics, tumor profiling, clinical outcomes, adverse effects, and radiographic factors). Kaplan-Meier survival analysis was used to descriptively assess PFS and OS. With a sample size of 21 patients in the study, two-sided 95% confidence intervals for PFS/OS at defined time points of interest (i.e., six-months, etc.) were constructed to be within ± 22.8% of the observed survival proportion estimates. This calculation assumes PFS/OS proportion estimates of 50% to conservatively maximize the width of the obtained confidence intervals. Due to the small number of patients with rHGGs who have completed concurrent ICI+ SBRT, multivariable modeling was not performed. All p -values were two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for median PFS/OS survival time and six-month PFS were calculated to assess the precision of the obtained estimates. Mann-Whitney U tests were used to identify significant differences between diffusion and permeability histogram values. All analyses were performed in R Version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

In total, 356 patients with rHGG were evaluated from January 2016 to January 2019 (Supplementary Figure 1). Patients were excluded if they did not receive ICI monotherapy, ICI concurrently with SBRT (n=333), or

if they had outside imaging during treatment that was not available for analysis (n=2), leaving 21 patients for analysis. Patient demographics are displayed in Table 1. Sixteen patients with rHGG were treated with ICI+ SBRT, of which 10 were WHO grade IV and 6 were WHO grade III. MGMT methylation, IDH1 and TERT mutations were present in 4 (25%), 3 (19%) and 10 (63%) patients, respectively. Twelve patients received concurrent chemoradiation following their initial resection, and underwent an average of 4.5 lines of therapy. Five patients received ICI monotherapy, of which 2 were WHO grade IV and 3 were WHO grade III. MGMT methylation and TERT mutations were present in 1 and 2 patients, respectively, with no patients in this cohort possessing IDH mutations. Four patients underwent concurrent chemoradiation following their initial resection and received an average of 4.5 lines of therapy.

On average, patients received 3 lines of therapy before they were offered ICI+SBRT (Table 2). SBRT doses ranged from 18 Gy in 1-3 fractions to 35 Gy in 5 fractions. A mean of 7.25 ICI cycles were given. Twelve patients received dexamethasone during their treatment, and 6 received bevacizumab during their treatment. Patients in the ICI monotherapy received an average of three prior lines of treatment. A mean of 6.2 ICI cycles were given. Three patients received dexamethasone and one was treated with bevacizumab.

Adverse Events

Among the ICI+SBRT cohort, there were 4 instances of grade 1 fatigue and 1 instance of grade 1 thrombocytopenia (Table 3). One patient experienced grade 2 fatigue. Two patients experienced grade 1 fatigue and 2 experienced grade 1 constipation among the ICI monotherapy cohort. There were no grade 3-5 AE, radiographic findings consistent with radiation necrosis on follow-up imaging, or treatment-related deaths in either cohort. No patients discontinued ICI due to toxicity.

Response

Among the ICI+SBRT cohort, there were no CR, 2 PR, 8 SD and 6 PD at one month (Figure 1). Thirteen patients progressed at 6 months. The ICI monotherapy cohort had no CR or PR, 2 SD and 3 PD at one month, with 4 patients progressing by 6 months. There were no significant differences in PFS ($p = 0.4$), OS ($p = 0.3$) or in median PFS time for patients receiving ICI+SBRT (2.85 months; 95% CI: 1.7, 7.5) or ICI (1 month; 95% CI: 1 to unknown). Estimated six-month PFS probability was 0.19 (95% CI: 0.07 to 0.52) for patients receiving ICI+ SBRT and 0.2 (95% CI: 0.035 to 1) for patients receiving ICI. The median OS was 7 months (95% CI: 6 to 10) for patients receiving ICI+SBRT and 6 months (95% CI: 4 to unknown) for patients receiving ICI. Estimated six-month OS probability was 0.625 (95% CI: 0.43 to 0.91) for patients receiving ICI+SBRT and 0.4 (95% CI: 0.14 to 1) for patients receiving ICI. Kaplan-Meier plots for PFS and OS are shown in Figure 2.

Radiologic Analyses

DCE perfusion data was available in 15 of 16 ICI+SBRT patients pre-treatment, 16 of 16 ICI+ SBRT patients post-treatment, and 5 of 5 ICI monotherapy patients pre- and post-treatment. ADC maps were available in all 21 patients pre- and post-treatment. There was a significant difference in tumor volumes pre- and post-treatment (12.35 vs. 20.51; *p=0.03*). However, no statistically significant difference was found in the other imaging metrics (reported pre- vs. post-treatment): mean ADC (1.73 vs. 1.69; *p=0.58*), mean Vp (6.63 vs. 5.78; *p=0.43)* ; mean Ktrans (19.19 vs. 23.25; *p=0.63*). A post-hoc analysis comparing perfusion and diffusion imaging metrics between the ICI+SBRT and ICI monotherapy groups pre- and post-treatment demonstrated no statistically significant difference in imaging metrics after drug initiation (reported pre-treatment ICI+SBRT to post-treatment ICI+SBRT versus pre-treatment ICI to post-treatment ICI): mean ADC (1.73 to 1.74 vs. 1.73 to 1.51; p =0.18), mean Vp (7.39 to 6.04 vs. 4.35 to 4.98; p =0.80), mean Ktrans (20.64 to 25.85 vs. 14.85 to 14.93;p =0.46), tumor volume (13.25 vs. 22.33 vs. 8.74 to 13.20;p =0.61).

Discussion

There is a paucity of therapeutic options and no validated standard of care for rHGG. This retrospective series demonstrated ICI with concurrent re-irradiation using SBRT can be safely delivered in rHGG. Preclinical data provides a rationale for evaluating ICI in this clinical setting (21, 24). The statistically significant

increase in post-treatment tumor volumes identified within our cohort may in part have reflected a component of pseudoprogression related to ICI. Prior studies associate ICI treatment response with a preceding increase in tumor volume related to intratumoral immune cell infiltration, resulting in a transient inflammatory reaction (25).

Understanding ICI response requires further elucidation of the intratumoral milieu and systemic immune response (26-31). Several studies support preoperative ICI enhance expression of chemokine transcripts including interferon-γ, increase immune cell infiltration, and augment T cell receptor clonal diversity, but with conflicting clinical results (32, 33). One putative explanation for suboptimal immune response is the high rate of lymphopenia observed in HGG patients, with one group reporting that T cells are available in this population but are sequestered in the bone marrow (34).

The aforementioned studies provide a rationale for optimizing immunotherapeutic efficacy through its implementation in an immunologically favorable setting, such as priming the immune system to tumor-specific antigens. RT may improve ICI effects by increasing the quantity and diversity of intracellular peptides, increasing MHC class I expression, and promoting T cell recruitment and infiltration (20-22, 35-38). Technological advancements in the delivery of SBRT allow for highly conformal treatments that significantly reduce the toxicity associated with re-irradiation in other disease sites (16). Several studies show an improvement in functional status and discontinuation of corticosteroid usage following SBRT monotherapy with a low risk of late central nervous system toxicity (14, 15, 17, 18, 39). Additionally, SBRT dose-fractionation schemes may be more effective than conventionally fractionated RT with regard to augmenting immune responses (22, 40). This option also allows RT completion within one to five treatments, which is convenient for patients.

A closer look at this cohort notes several limitations that could be considered in future studies geared towards optimizing a response. Most patients had multiple recurrences and subsequently received various systemic treatments either on or off clinical trials. There was a mean of 4.5 lines of treatment administered with ICI+SBRT therapy given as the last line in 8 of these patients. There is a possibility that these prior treatments negatively impacted the ability to prime the immune system, and a more robust response may be seen if treated with ICI + SBRT at first recurrence. Patients were treated without knowing PD-L1 expression status. A few reports show higher response rates with increased expression in other malignancies (41), however the prognostic value of PD-L1 for HGG is still under investigation. While foundational analyses were available, advanced correlation studies were limited by the cohort size. Two-thirds of the patients in this cohort were on dexamethasone while receiving ICI which may interfere with the ICI efficacy.

The optimal treatment approach for patients with rHGG continues to be an area of ongoing investigation. This small retrospective study suggests ICI can be safely given concurrently with re-irradiation using SBRT for patients with rHGG. These initial findings support evaluating whether optimizing conditions for combinatory ICI + SBRT approaches may lead to favorable clinical responses, or whether attention should be turned to other therapeutic avenues to address this unmet need in neuro-oncology.

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Table 1: Demographic and Clinical Characteristics

Patient Characteristics
Gender (n)
Race (n)
Age (years)
KPS (n)
Initial Resection Extent (n)
WHO Tumor grade (n)
MGMT methylation status (n)
IDH mutation status (n)
TERT promotor mutation (n)
Adjuvant TMZ + radiation (n)
Lines of therapy (including TMZ + radiation)

Abbreviations: KPS: Karnofsky Performance Status; WHO: World Health Organization; MGMT: O6-Methylguanine-DNA M

Table 2: Treatment Data

Parameter
ICI / ICI and SBRT given as what line of therapy (n)
Cycles ICI given
SBRT Dose (n)

Average PFS from 2nd line treatment onward
Average PFS on intervention
Best one-month response (RANO)

6-month PFS (n)

OS after intervention (months)
Adverse Events (CTCAE)

Steroids (n)

Bevacizumab (n)

Abbreviations: ICI: immune checkpoint inhibition; Gy: Gray; SBRT: stereotactic body radiation therapy; PFS: progression-

Table 3: ICI monotherapy and ICI + SBRT toxicity in recurrent high-grade gliomas

	ICI + SBRT	ICI + SBRT	ICI + SBRT	ICI + SBRT	ICI + SBRT	ICI monothera
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1
Anemia	0	0	0	0	0	0
Colitis	0	0	0	0	0	0
Constipation	0	0	0	0	0	2
Fatigue	4	1	0	0	5	2
Intracranial hemorrhage	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0
Infection without neutropenia	0	0	0	0	0	0
Lymphopenia	0	0	0	0	0	0
Nausea	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0
Thrombophlebitis	0	0	0	0	0	0
Thrombocytopenia	1	0	0	0	0	0
Wound Dehiscence	0	0	0	0	0	0
Totals	5	1	0	0	6	4

Abbreviations : ICI: immune checkpoint inhibition; SBRT: stereotactic body radiotherapy

Figure 1 : Partial Response in Patient Receiving ICI + SBRT. 83-year-old man with right temporal WHO grade IV glioblastoma status-post resection and adjuvant concurrent radiotherapy and temozolomide who received 30 Gy in 5 fractions concurrently with 15 cycles of ICI as his third line treatment. Radiotherapy isodose line key shown in (A). Representative (B) axial (C) sagittal and (D) coronal images of his RT plan. Pretreatment MRI (E) axial T1 and (F) axial T2 FLAIR showing 2 x 2.1 cm nodular enhancing mass along anterior/medial margin of the resection cavity. MRI 4 months post-SBRT (G) axial T1 and (H) axial T2 FLAIR showing overall decrease in size and nodular enhancing component of the lesion

Figure 2: Kaplan-Meier curves for (A) progression free survival and (B) overall survival time. Dashed lines are 95% confidence intervals

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