Oral Oncology 85 (2018) 29–34

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Radiologic predictors of immune checkpoint inhibitor response in advanced head and neck squamous cell carcinoma

Vishwajith Sridharan[a,c], Rifaquat M. Rahman[a], Raymond Y. Huang[e], Nicole G. Chau[b], Jochen H. Lorch[b], Ravindra Uppaluri[d], Robert I. Haddad[b], Glenn J. Hanna[b,*], Jonathan D. Schoenfeld[a,*]

[a] Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA 703-389-1895, United States
[b] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States
[c] Harvard-MIT Health Sciences and Technology, Harvard Medical School, Boston, MA, United States
[d] Department of Surgery/Otolaryngology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, United States
[e] Department of Radiology, Brigham and Women's Hospital, Boston, MA, United States

ARTICLE INFO

Keywords:
Head and neck cancer
PD-1
Immune checkpoint blockade

ABSTRACT

Radiologic predictors of response to immune checkpoint blockade (ICPi) in advanced head and neck squamous cell carcinoma (HNSCC) patients could help guide patient selection and management. We analyzed a large institutional cohort of 100 consecutive HNSCC patients treated with ICPi to investigate associations between molecular and radiologic phenotype and assess radiologic predictors of response and survival. Of particular interest was the impact of increased total tumor burden (TB), calculated as the sum of the largest diameter of all measurable lesions according to RECIST 1.1, and early radiologic indicators of response versus progression.

Within our cohort, 42% of patients had HPV+ associated disease, 64% had persistent/recurrent head and neck lesions, and 77% had distant metastases. Median TB was 5.4 cm. HPV+ disease and increased total mutational burden were associated with distant disease in the absence of locoregional disease ($p < 0.01$ and $p = 0.03$, respectively).

Forty patients (40%) demonstrated clinical benefit to ICPi, and the median overall survival (OS) on PD-1 therapy was 4.5 months. A lower tumor burden at baseline was associated with clinical benefit ($p = 0.03$) and improved OS ($p < 0.01$, HR 2.33). There was only one instance of pseudoprogression; indeed any increase in TB on first interval scan was associated with poor OS ($p = 0.02$, HR 2.39). These data suggest that HNSCC patients who benefit from ICPi are more likely to have lower tumor burden at the onset of treatment and minimal increase in tumor burden while on treatment.

Introduction

Immune checkpoint inhibitors (ICPi) that inhibit the PD-1 receptor have demonstrated activity and survival benefit in advanced head and neck squamous cell carcinomas (HNSCC) [1–4]. However, given the potential morbidity of immune-related toxicities, and response rates of 10–20%, there is a need to identify biomarkers to guide patient selection [5]. Genomic elements, such as increased tumor mutational burden (TMB) and the presence of somatic frameshift events, have been implicated as predictors of response, likely because these genetic factors signify enhanced probability a tumor possesses neoantigens that can be recognized by the immune system. The presence of immune infiltrates and associated markers within the tumor microenvironment (e.g. PD-L1 expression) have also been shown to correlate with PD-1 response [6–9]. In HNSCC specifically, studies have suggested that human papillomavirus (HPV) positivity, detectable PD-L1 expression, and the above mentioned molecular factors are of potential significance when predicting response to PD-1 blockade; however, none of these factors has yet proven adequate for clinical decision making [10,11].

Patterns of response to ICPi are unique when compared to cytotoxic chemotherapy. For example, some patients undergoing PD-1 blockade exhibit pseudoprogression, where new or enlarging radiographic

* Corresponding authors at: Dana-Farber/Brigham and Women's Cancer Center, Department of Radiation Oncology, 450 Brookline Ave, DA L2-57, Boston, MA 02114, United States (J.D. Schoenfeld). Dana-Farber Cancer Institute, Department of Medical Oncology, 450 Brookline Ave, DA 2-140, Boston, MA 02215, United States (G.J. Hanna).

E-mail addresses: vsridharan@partners.org (V. Sridharan), glenn_hanna@dfci.harvard.edu (G.J. Hanna), jdschoenfeld@partners.org (J.D. Schoenfeld).

https://doi.org/10.1016/j.oraloncology.2018.08.005
Received 17 June 2018; Accepted 7 August 2018
1368-8375/ © 2018 Elsevier Ltd. All rights reserved.

lesions appear after ICPi initiation but subsequent imaging reveals an overall decrease in total tumor burden [12]. This phenomenon has been documented in melanoma, but may not be as common in other solid tumors, including HNSCC [4,13]. Given the central role that serial imaging currently serves in cancer management, characterizing imaging parameters that predict long-term clinical benefit in patients treated with immune checkpoint blockade is critical. Additionally, evolving guidelines have been implemented to track tumor response in immunotherapy patients, but there is no pattern of response data specific to immunotherapy used in head and neck malignancies [14,15]. Recent studies have also demonstrated that imaging parameters may offer insights into tumor biology; as changes in radiologic features have been associated with underlying gene-expression levels in several tumor types [16–19].

Here, we present one of the largest institutional HNSCC patient cohorts receiving ICPi with molecular characterization of PD-L1 and TMB alongside detailed imaging analyses and clinical outcomes to identify predictive radiologic biomarkers and describe patterns of response.

Methods

Patient population and study design

We retrospectively identified 100 consecutive HNSCC patients treated with single-agent ICPi using a PD-1 inhibitor at our institution between 2014 and 2017. We obtained patient demographic and treatment data from the electronic medical record, including sex, age, race, smoking, previous treatment (surgery, radiation and/or chemotherapy), date of immunotherapy initiation, and treatment associated toxicity including immune-related adverse events (irAEs). For oropharyngeal cancer or carcinoma of unknown primary patients, HPV status was determined using p16 immunohistochemistry (IHC) followed by confirmation with either in situ hybridization or polymerase chain reaction. Tumor stage at diagnosis was determined according to the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition. We also collected outcomes data including best objective clinical response as determined by RECIST v1.1 and overall survival (time from diagnosis to death or censored at last follow-up). Criteria for complete response (CR) was defined as > 99% reduction in the target lesions, partial response (PR) as ≥30% reduction in target lesions, progressive disease (PD) as at least a 20% increase in the sum of diameters of target lesions, and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Radiologic data collection

Patients were generally imaged immediately prior to starting PD-1 inhibitor therapy (median days between baseline scan and PD-1 initiation was 13 days) and then again approximately 8 weeks later. Our standard practice is to perform positron emission tomography (PET) – computed tomography (CT) of the chest, abdomen and pelvis following the administration of intravenous contrast according to standard institutional protocols in patients in whom this is not contraindicated. Magnetic resonance imaging (MRI) with or without gadolinium administration was also performed as clinically indicated.

We reviewed data from the scans performed immediately prior to immunotherapy initiation and then the first scan performed on treatment when available. Data was collected on the largest diameter of all measurable lesions using RECIST v1.1 criteria, as well as the presence of metastatic lesions in the lung, liver, and bone. The largest lesions (measuring at least 1-cm or greater in any axis, up to 2 per organ, and up to 5 total) for each patient were included for analysis. Lymph nodes with a short axis ≥1.0 cm were considered measurable and assessable as target lesions. Clinical and radiologic data were used to determine whether there was recurrent or progressive disease in the head and neck, defined as any patient that had clear progression or recurrence of disease following, or in the absence of, locoregional therapy. Tumor burden (TB) was calculated as the sum of the largest diameter of all measurable lesions by RECIST 1.1 as described above and as has been previously described [20]. Investigators were blinded to clinical outcomes when radiologic data were collected.

Biologic data collection

Targeted massively parallel sequencing using our institutional platform (Oncopanel) was performed using patient tumor samples. Oncopanel is a custom biotinylated RNA bait set (Agilent SureSelect) targeting the full coding regions of 300+ genes as well as intronic regions of additional genes and key structural rearrangements to capture and amplify libraries of tumor DNA [10]. Sequencing was performed to an attempted coverage of 300× per sample. Total mutational burden (TMB) was calculated using the total number of non-synonymous mutations per megabase of exon sequences, as previously described [10]. A non-fixed cell suspension from fresh tumor samples was also prepared for fluorescent immune labeling using anti-PD-L1 monoclonal antibodies and coupled with mouse anti-human surface antibodies to characterize PD-L1 status [10].

Statistical methods

We evaluated associations between socio-demographic, tumor, and treatment parameters using the Pearson's χ^2 test. We generated survival curves via the Kaplan-Meier method, and analyzed univariate predictors of overall survival (OS) using log-rank regression. Two-sided p-values < 0.05 were considered statistically significant. All statistical analyses were computed using JMP Pro13 (SAS Institute Inc, Cary, NC) or GraphPad Prism (GraphPad Software Inc, La Jolla, CA).

Results

Clinical and molecular characteristics

We retrospectively identified 100 patients diagnosed with advanced HNSCC treated with immunotherapy between 2014 and 2017. Baseline patient characteristics are displayed in Table 1. The median patient age at diagnosis was 57 (range 20–89). The majority of patients were male (82%), with nearly half (49%) being former or current smokers (defined as ≥10 pack-years). Among 51 oropharyngeal cancer patients, 42 cases (82%) were causally related to HPV. Most patients were initially diagnosed with locoregionally advanced disease (88%) as evidenced by 82% with cervical nodal involvement. At the time of PD-1 inhibitor initiation, most patients had previously received chemotherapy or concurrent chemoradiation (n = 81). The average prior lines of therapy was 1.6. In our cohort, recurrent or persistent locoregional disease was observed in 64% of patients (Table 2). The majority (77%) of patients had distant disease (67% lung, 17% bone, 13% liver). Forty-two percent of patients had metastatic involvement across multiple organ systems. Patients with HPV associated disease were more likely to have distant disease in the absence of active locoregional disease ($p < 0.01$, Fig. 1) as compared to patients with HPV negative or non-oropharyngeal primaries. HPV-associated cancers were also inversely correlated with the presence of lung metastases as compared with HPV-negative cancers, but specific associations with liver or bone metastases were not significant (Supplemental Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2018.08.005.

Of the 31 tumors tested, 19% were PD-L1 negative, 55% showed at least 1% PD-L1 expression, and 26% showed > 50% PD-L1 expression. There was no correlation between HPV status and PD-L1 expression patterns (Supplemental Table 1). The median TMB was 7.6 (IQR

Download English Version:

https://daneshyari.com/en/article/8707092

Download Persian Version:

https://daneshyari.com/article/8707092

Daneshyari.com