Research Article

Cancer Immunology Research

Improved Risk-Adjusted Survival for Melanoma Brain Metastases in the Era of Checkpoint Blockade Immunotherapies: Results from a National Cohort

J. Bryan Iorgulescu[1,2,3], Maya Harary[2,3], Cheryl K. Zogg[4,5], Keith L. Ligon[1,2,6], David A. Reardon[2,7], F. Stephen Hodi[2,8], Ayal A. Aizer[2,9], and Timothy R. Smith[2,3]

Abstract

The successes of checkpoint blockade immunotherapy (CBI) and $BRAF^{V600}$-targeted therapy trials have generated substantial promise for revolutionizing the management of patients with advanced melanoma. However, because early clinical trials of CBIs and $BRAF^{V600}$-targeted therapy either excluded or included disproportionately fewer cases of melanoma brain metastases (MBMs), the survival benefit of these novel therapies for MBM remains unknown. We, therefore, evaluated the characteristics, management, and overall survival (OS) of patients who presented with cutaneous MBMs during 2010 to 2015 using the National Cancer Database, which comprises 70% of all newly diagnosed U.S. cancers. OS was analyzed with risk-adjusted proportional hazards and compared by Kaplan–Meier techniques. We found that 2,753 (36%) of patients presenting with stage 4 melanoma had MBMs. Following the 2011 FDA approvals for CBI and $BRAF^{V600}$-targeted therapy, MBM patients demonstrated a 91% relative increase in 4-year OS to 14.1% from 7.4% preapproval ($P < 0.001$). Postapproval, the proportion of MBM patients who received CBI rose from 10.5% in 2011 to 34.0% in 2015 ($P < 0.001$). Initial CBI in MBM patients displayed an improved median and 4-year OS of 12.4 months (compared with 5.2 months; $P < 0.001$) and 28.1% (compared with 11.1%), respectively. These benefits were pronounced in MBM patients without extracranial metastases, in which CBI demonstrated improved median and 4-year OS of 56.4 months (compared with 7.7 months; $P < 0.001$) and 51.5% (compared with 16.9%), respectively. Using a large national cohort composed of a "real-life" MBM treatment population, we demonstrated the dramatic OS improvements associated with novel checkpoint blockade immunotherapies. *Cancer Immunol Res; 6(9); 1039–45. ©2018 AACR.*

Introduction

The incidence of melanoma continues to grow at a rate faster than any other solid tumor, with approximately 1 in 54 people projected to develop melanoma over their lifetime (1). The majority of melanomas are diagnosed at an early enough stage where excision is frequently curative. However, the management of advanced melanoma has traditionally been tempered by limited responses to conventional therapies, resulting in a median overall survival (OS) of less than 1 year. Of all primary cancers, melanoma has one of the highest predilections for metastasizing to the brain (MBM), representing the third most common source of brain metastases—a rate that continues to increase with improvements in surveillance, imaging techniques, and systemic therapies (2–4). There is evidence that MBMs confer a distinct disease course, as reflected by the new American Joint Commission on Cancer (8th ed.) M1d designation that poses particularly significant challenges to conventional therapies.

In 2011, however, the landscape of advanced melanoma treatment was revolutionized by the FDA approvals of two new therapeutic classes: checkpoint blockade immunotherapy (CBI), with the anticytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody ipilimumab, and $BRAF^{V600}$-targeted therapy, with the $BRAF^{V600}$-mutant inhibitor vemurafenib. In addition to ipilimumab and vemurafenib, antiprogrammed death-1 (PD-1; nivolumab and pembrolizumab, 2014) CBIs, BRAF inhibitors (dabrafenib, 2013), and MEK inhibitors (trametinib and cobimetinib, 2013) have since been approved, with $BRAF^{V600}$-targeted therapies approved for the approximately half of melanomas with mitogen-activation protein kinase (MAPK) pathway dysregulation.

Anti–CTLA-4 (e.g., ipilimumab) blocks T cells' CTLA-4 receptor's inhibitory binding of B7 ligands on antigen-presenting cells, thereby enabling the costimulatory B7 ligands to bind with T cells'

[1]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. [2]Harvard Medical School, Boston, Massachusetts. [3]Computational Neuroscience Outcomes Center, Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts. [4]Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, Massachusetts. [5]Yale School of Medicine, New Haven, Connecticut. [6]Department of Oncologic Pathology, Dana-Farber Cancer Center, Boston, Massachusetts. [7]Center for Neuro-Oncology, Department of Medical Oncology, Dana-Farber Cancer Center, Boston, Massachusetts. [8]Melanoma Center, Center for Immuno-Oncology, Department of Medical Oncology, Dana-Farber Cancer Center, Boston, Massachusetts. [9]Department of Radiation Oncology, Brigham and Women's Hospital, Dana-Farber Cancer Center, Boston, Massachusetts.

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Corresponding Author: J. Bryan Iorgulescu, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Phone: 617-732-7510; Fax: 617-277-9015; E-mail: jiorgulescu@bwh.harvard.edu

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CD28 receptor and provide the secondary activation signal necessary for persistent T-cell activation (5). Anti–PD-1 (e.g., nivolumab and pembrolizumab), on the other hand, thwarts the inhibitory binding of PD-L1 ligands to T cells' PD-1 and, thereby, prevents T-cell anergy and depletion (5). Through blockade of these immune checkpoint pathways in melanoma, a tumor type with a particularly high mutational burden, anti–CTLA-4, and anti–PD-1 immunotherapies help unleash a robust expansion of tumor-specific T cells that have displayed antitumoral and survival benefits.

The current National Cancer Comprehensive Network (NCCN; Melanoma v2.2018 and CNS cancers v1.2017) guidelines for treating MBMs are based on their symptomatology, number, volume, and resectability and recommend prompt resection in an attempt to prevent neurological dysfunction, hemorrhages, or seizures and that stereotactic radiosurgery (SRS) and/or whole brain radiotherapy (WBRT) be administered either in an adjuvant setting following resection or as a primary treatment to help improve local disease control (6, 7). Based on the promising outcomes and safety results of several early randomized clinical trials in advanced melanoma patients, systemic therapy with CBI, either as anti–PD-1 monotherapy or combination anti–PD-1/CTLA-4 therapy, and/or targeted therapy for patients with $BRAF^{V600}$-mutant melanoma, either as BRAF inhibitor monotherapy or combination BRAF/MEK inhibitor therapy, may be administered during or after the treatment of CNS metastases (1, 8–10). Due to the successes of CBI and $BRAF^{V600}$-targeted therapy in advanced melanoma, there no longer is a first-line role for conventional cytotoxic chemotherapies (e.g., dacarbazine, temozolomide, carboplatin/paclitaxel, and/or fotemustine) or biochemotherapies (e.g., high-dose IL2 and interferon alfa-2b).

The preliminary successes of these novel therapeutic classes have been exciting for melanoma patients and providers alike, and although their efficacy and safety have been robustly evaluated in multiple randomized clinical trials (RCTs) of advanced melanoma, patients with CNS metastases were disproportionately excluded (10). In order to fill these critical gaps, we examined the outcomes in a national cohort of stage 4 melanoma patients who presented with MBMs in the contemporary era of CBIs and $BRAF^{V600}$-targeted therapies.

Materials and Methods

Data source and study design

Developed by the American College of Surgeons and American Cancer Society, the National Cancer Database (NCDB) is a hospital-based nationwide database that comprises approximately 70% of newly diagnosed cancers in the United States (11). Patients newly diagnosed with cutaneous melanoma (i.e., World Health Organization ICD-O3 morphologic codes 8720–8723, 8726, 8730, 8740–8746, 8750, 8760–8761, 8770–8774, and 8780, with behavior codes 2–3, and skin topographical codes C44.0–44.9) from 2010 to 2015 were identified (12). Exclusion criteria include age less than 20 years, prior diagnosis of cancer (i.e., case sequence greater than 1), lacking data about brain metastasis, or patients with a diagnosis at an index institution but treated entirely elsewhere.

Variable design

Stage 4 (i.e., disseminated metastases) cases with and without brain involvement were identified by a composite of the American Joint Committee on Cancer (AJCC, 7th ed.) M staging and metastasis collaborative stage site-specific factors for cutaneous melanoma. The NCDB began encoding metastatic brain involvement in 2010. MBM-only involvement was defined as cases presenting with brain metastasis, without concurrent bone, lung, liver, subcutaneous, or distant lymph node metastases. Patient characteristics at presentation were summarized and compared, including age, sex, race, insurance status, Charlson–Deyo comorbidity index (CDCI), geographic location and type of treating hospital, year of diagnosis, lactate dehydrogenase (LDH) level, AJCC pT and pN classification, and the primary lesion's characteristics of site, histologic subtype, histological ulceration, and mitotic proliferation index.

Management characteristics were also summarized and compared, including surgery of primary lesion (i.e., no surgery, local excision, gross excision, or wide excision), resection of a metastatic lesion, radiotherapy (RT) of a metastatic lesion, chemotherapy, and immunotherapy. NCCN guidelines have relegated biochemotherapeutics (i.e., interferon alfa-2b and high-dose IL2) and cytotoxic chemotherapeutics to second-line therapy for stage 4 patients that fail initial CBI. The NCDB only encodes the initial first-line therapies for a patient, and, thus, the majority of immunotherapies and chemotherapies encoded in NCDB in 2011 and onward for melanoma patients should represent CBI and $BRAF^{V600}$-targeted chemotherapies, respectively. Brain-directed RT was defined by a brain target volume and stratified as single-fraction SRS (i.e., 15–24 Gy in 1 fraction), hypofractionated stereotactic RT (SRT; i.e., 18–30 Gy delivered in 2–5 fractions), WBRT (i.e., external beam RT used to deliver 30–40 Gy in 10–20 fractions), or other fractionation scheme. In the absence of detailed information (e.g., size, number, symptomology, exact location, etc.) about metastases in the NCDB, the type of brain-directed RT may, in part, reflect the disease burden of MBM in multivariable analyses. However, the NCDB does not directly encode BRAF mutational status. The receipt of targeted therapy served, in part, as a surrogate for BRAF-mutant status in multivariable analyses.

Statistical analyses

Clinicopathologic and treatment characteristics were compared by χ^2 test and t test between stage 4 melanoma patients who presented with and without brain involvement, and among the patients with brain involvement, between those who were treated with CBI versus those who were not. Risk-adjusted predictors of presenting with brain involvement or of receiving CBI were assessed by multivariable logistic regression. For survival analysis, OS was evaluated using multivariable Cox proportional hazards. Interaction effects for those variables significantly associated with receipt of CBI in multivariable logistic results were additionally included in the multivariable proportional hazards analyses. Unadjusted differences were additionally compared via Kaplan–Meier methods and log-rank tests. Due to limited follow-up, the NCDB does not include survival information for the most recent year, which for this release was 2015. The endpoint was designated as date of death, with patients censored at the date of last follow-up. Estimated OS was compared for MBM patients diagnosed before and after the start of FDA approvals (i.e., 2011) of CBI and $BRAF^{V600}$-targeted therapy. For patients diagnosed in the postapproval era, OS was further compared between those who received CBI versus those who did not. All multivariable analyses included those data elements missing <10% of data.

Patients were excluded from multivariable analyses if they were missing any of the data elements. Statistical analyses were performed with STATA (v. 14.2, StataCorp) and two-tailed $P < 0.05$ were designated as significant. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Partners HealthCare Institutional Review Board (approval #2015P002352).

Results

Characteristics of patients presenting with MBMs

A total of 220,439 patients diagnosed with cutaneous melanoma from 2010 to 2015 met inclusion criteria, of whom 3.5% ($n = 7,689$) initially presented with distant metastases (i.e., AJCC stage 4 or M1). The brain was involved in 35.8% ($n = 2,753$) of stage 4 melanoma patients. The characteristics of patients presenting with stage 1 to 3 disease, stage 4 disease without brain involvement, and stage 4 disease with MBM are reported in Supplementary Table S1, along with multivariable logistic results for stage 4 melanoma presenting with and without MBMs. Stage 4 patients with MBM were further stratified into MBM only ($n = 1,093$, 39.7%) and MBM with extracranial metastatic disease ($n = 1,660$, 60.3%), for which only younger age [reference, 60–69 years old; compared with 50–59 years old: odds ratio (OR), 1.28, 95% confidence interval (CI), 1.02–1.61, $P = 0.04$; 70–79 years old: OR, 0.86; 95% CI, 0.67–1.61, $P = 0.24$; and 80–89 years old: OR, 0.70; 95% CI, 0.51–0.96, $P = 0.03$] and geographic location were independent predictors of presenting with MBM-only disease (Supplementary Table S2). MBM patients with extracranial disease included involvement of lung (82.9%), liver (8.1%), bone (6.0%), and distant subcutaneous skin or lymph nodes (3%).

Improved OS of MBM patients following FDA approval of CBI and targeted therapies

Without treatment, MBM patients demonstrated a median OS of 1.8 months ($n = 299$; 95% CI, 1.5–2.3) and a 12.4% 1-year OS rate (95% CI, 8.9–16.6). Of MBM patients, 81.6% ($n = 2,247$) presented following FDA approval in 2011 of the CBI ipilimumab and BRAF inhibitor vemurafenib (i.e., 2011–2015, including the subsequent approvals of PD-1, MEK, and BRAF inhibitors). Following FDA approval, median OS among MBM patients increased to 6.2 months (95% CI, 5.8–6.7; $P < 0.001$) from 5.1 months (95% CI, 4.6–5.8) preapproval, and 4-year OS improved to 14.1% (95% CI, 12.2–16.1) from 7.4% (95% CI, 5.3–10.0, $P < 0.001$). Stratified by the extent of systemic disease, the median OS after FDA approval was 4.8 months (95% CI, 4.3–5.4) for MBM patients with extracranial disease, 9.0 months (95% CI, 8.0–10.5) for MBM-only patients, and 17.5 months (95% CI, 15.3–20.0) and 7.1 months (95% CI, 5.6–8.7) for stage 4 melanoma patients with lung-only and liver-only metastatic disease, respectively.

In order to examine the clinicopathologic characteristics that impacted the OS of MBM patients diagnosed in the postapproval era, Cox proportional hazards were risk adjusted for variables with less than 10% of data missing, for which 1,434 patients had complete data and 82.2% ($n = 1,179$) reached endpoint (Supplementary Table S3). For variables that were significantly associated with receipt of CBI, their interaction effects with CBI were included in a second multivariable Cox regression analysis, in which improved OS in MBM patients was significantly associated with female sex [hazard ratio (HR), 0.81; 95% CI, 0.70–0.93, $P = 0.002$], management at academic centers (vs. community cancer center: HR, 0.77; 95% CI, 0.60–0.98, $P = 0.03$), primary lesions of the face (upper limb as reference: HR, 0.53; 95% CI, 0.29–0.98, $P = 0.04$), scalp/neck (HR, 0.57; 95% CI, 0.35–0.96, $P = 0.03$), or trunk (HR, 0.70; 95% CI, 0.49–0.99, $P = 0.04$) and CBI (HR, 0.12; 95% CI, 0.03–0.49, $P = 0.003$); and in those patients who did not receive CBI: fewer comorbidities (CDCI of 1 vs. 0: HR, 1.48; 95% CI, 1.26–1.74, $P < 0.001$), private insurance (vs. no insurance: HR, 0.73; 95% CI, 0.56–0.96, $P = 0.02$), receipt of targeted therapy (HR, 0.59; 95% CI, 0.51–0.69, $P < 0.001$), MBM resection (HR, 0.52; 95% CI, 0.45–0.60, $P < 0.001$), and single-fraction SRS (vs. no RT: HR, 0.50; 95% CI, 0.41–0.62, $P < 0.001$; vs. hypofractionated SRT: HR, 0.53; 95% CI, 0.40–0.72, $P < 0.001$; and vs. WBRT: HR, 0.50; 95% CI, 0.40–0.61, $P < 0.001$). Race and geographic location had no association with OS. Although additional metastatic involvement of lungs (HR, 1.67; 95% CI, 1.45–1.93, $P < 0.001$) and bone (HR, 1.60; 95% CI, 1.09–2.34, $P = 0.02$) portended worse OS in patients who did not receive CBI; OS was independent of extracranial disease in MBM patients who received CBI. In MBM patients who received CBI, OS was also independent of age, insurance status, receipt of targeted therapy, and RT; however, MBM resection (HR, 1.81; 95% CI, 1.22–2.71, $P = 0.004$) and less recent diagnoses (2014 vs. 2011: HR, 0.57; 95% CI, 0.33–0.98, $P = 0.04$) were associated with worse OS.

CBI demonstrated improved OS in MBM patients

In the postapproval era, 20.5% of MBM patients received first-line CBI on average, rising from 10.5% in 2011 to 34.0% in 2015 ($P < 0.001$). Supplementary Table S4 reports the characteristics of MBM patients who received first-line CBI with corresponding multivariable logistic results, which revealed that MBM patients who were younger, more recently diagnosed (2015 vs. 2011: OR, 4.95; 95% CI, 3.16–7.77, $P < 0.001$), had fewer comorbidities (CDCI 1 vs. 0: OR, 0.65; 95% CI, 0.45–0.94, $P = 0.02$), insured privately (vs. uninsured: OR, 2.70; 95% CI, 1.31–5.58, $P = 0.007$) or through Medicare (vs. uninsured: OR, 3.05; 95% CI, 1.40–6.64, $P = 0.005$), diagnosed in New England, with brain-directed RT, or with other metastatic sites were more likely to receive CBI.

First-line CBI treatment was associated with a 1.4-fold improvement of the median OS to 12.4 months (95% CI, 10.4–15.8) from 5.2 months (95% CI, 4.7–5.9, $P < 0.001$), as well as a 1.5-fold improvement of the 4-year OS rate to 28.1% (95% CI, 22.1–34.4, $P < 0.001$) from 11.1% (95% CI, 9.3–13.1; Fig. 1). Because several clinicopathologic factors were significantly associated with receipt of CBI in MBM patients in multivariable logistic regression analyses (i.e., age, CDCI, insurance status, year of diagnosis, facility location, resection of metastasis, targeted therapy, brain-directed RT, and metastatic sites), the interaction effects between these clinicopathologic variables and CBI were included in the multivariable Cox proportional hazards analysis, which demonstrated persistently improved OS associated with CBI in MBM patients (HR, 0.12; 95% CI, 0.03–0.49, $P = 0.003$; Supplementary Table S3). The OS benefits associated with CBI were even more pronounced in MBM-only patients, in which the median OS improved to 56.4 months (95% CI, 25.0–not reached) from 7.7 months (95% CI, 6.7–8.7; $P < 0.001$), and the 4-year OS rate improved to 51.5% (95% CI, 38.9–62.8) from 16.9% (95% CI, 13.5–20.6; Fig. 2). In MBM patients with extracranial involvement, CBI also demonstrated improved median (9.6 months; 95% CI, 7.8–11.1; vs. 3.9 months; 95% CI, 3.5–4.3, $P < 0.001$) and 4-year OS (17.9%; 95% CI, 11.8–24.9; vs. 7.0%; 95% CI, 5.2–9.3, $P < 0.001$). In MBM patients who received targeted therapy

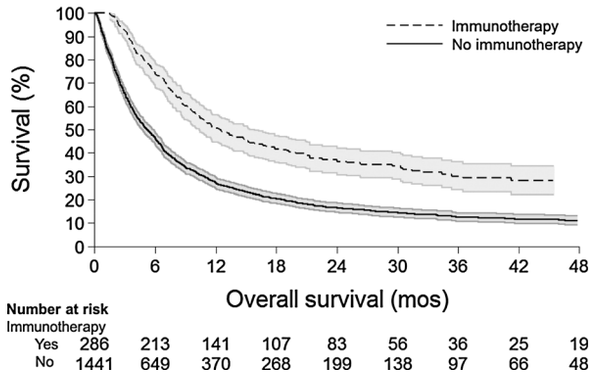

Figure 1.

Kaplan–Meier OS curves for MBM patients stratified by CBI. Survival curves of patients treated with (dashed line; $n = 286$) and without (solid line; $n = 1{,}443$) CBI, with number at risk table. $P < 0.001$ by log-rank test (95% CI, gray shading).

($n = 603$, 27.9%) and, therefore, likely represented $BRAF^{V600}$-mutant MBMs, only 9.8% ($n = 59$) additionally received CBI, which demonstrated a trend in improved median OS (10.5 months; 95% CI, 8.1–21.3; vs. 7.8 months; 95% CI, 7.0–8.9, $P = 0.05$) in this small subset.

Risk-adjusted OS results in MBM-only patients

To better understand the OS benefits associated with the management of MBM patients in the postapproval era, OS proportional hazards were risk adjusted and examined for melanoma patients who presented with brain-only metastatic involvement. The baseline median and 1-year OS for untreated MBM-only disease ($n = 115$) were 2.3 months (95% CI, 1.2–3.0) and 18.2% (95% CI, 11.7–25.9), respectively. Improved OS was associated with younger age (reference 60–69 years old; compared with 40–49 years old: OR, 0.52; 95% CI, 0.35–0.76, $P = 0.001$; 50–59 years old: OR 0.67; 95% CI, 0.51–0.89, $P = 0.005$; and 70–79 years old: OR 1.24; 95% CI, 0.90–1.71, $P = 0.19$), fewer comorbidities (CDCI 1 vs. 0: HR, 1.40; 95% CI, 1.09–1.81, $P = 0.01$), management at an academic hospital (vs. community cancer center: HR, 0.66; 95% CI, 0.44–0.99, $P = 0.04$), resection of the MBM (HR, 0.49; 95% CI, 0.39–0.61, $P < 0.001$), CBI (HR, 0.42; 95% CI, 0.29–0.63, $P < 0.001$), and single-fraction SRS of the MBM (vs. no brain-directed RT: HR, 0.53; 95% CI, 0.39–0.73, $P < 0.001$; Supplementary Table S5). In the fraction of MBM-only patients who underwent MBM resection ($n = 459$), the median OS was 12.6 months (95% CI, 10.3–15.4), and CBI showed an improved 4-year OS of 57.6% (95% CI, 41.3–70.8) from 23.2% (95% CI, 18.0–28.7, $P < 0.001$; Fig. 3). In the resected MBM-only cases, adjuvant treatment with single-fraction SRS (20.1% of cases) or hypofractionated SRT (14.6% of cases) was associated with a better 4-year OS (32.8%; 95% CI, 13.3–53.9; and 33.1%; 95% CI, 15.1–52.3, respectively) than no adjuvant RT (35.7% of cases; 4-year OS: 25.5%; 95% CI, 17.2–34.8) or adjuvant WBRT (29.0% of cases; 4-year OS, 12.6%; 95% CI, 5.4–22.9, $P < 0.001$). For the subset of MBM-only patients who were not amenable to resection ($n = 427$), the median OS was 6.1 months (95% CI, 4.7–6.9), and CBI demonstrated an improved 4-year OS of 38.3% (95% CI, 18.5–58.0) from 9.6% (95% CI, 5.8–14.5, $P < 0.001$).

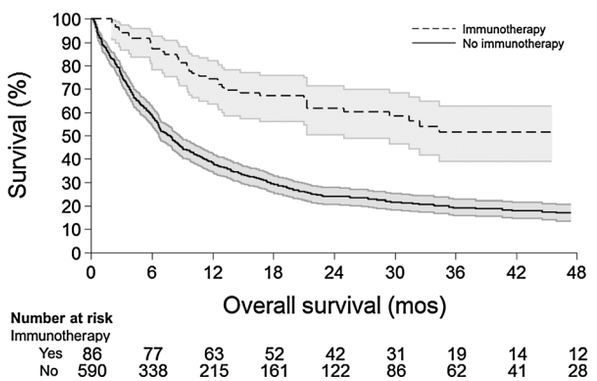

Figure 2.

Kaplan–Meier OS curves for MBM-only patients stratified by CBI. Survival curves of patients treated with (dashed line; $n = 86$) and without (solid line; $n = 591$) CBI, with number at risk table. $P < 0.001$ by log-rank test (95% CI, gray shading).

Discussion

Melanoma outcomes have steadily improved through more aggressive screening, standardized surgical protocols, sentinel lymph node dissections, discovery of targetable driver mutations, and development of CBIs (1). Brain melanoma metastases, in particular, were challenging to manage effectively, with our findings demonstrating a dismal median OS in untreated MBMs of 1.8 months. Consistent with prior retrospective series, we found that the incidence rate of stage 4 melanoma patients presenting with MBM was 36%, which supports the NCCN recommendations for brain imaging in the initial staging of melanoma patients presenting with suspected advanced disease (6, 7). Following the promising results of several key RCTs for stage 3 unresectable/4 melanoma, the FDA began approving CBI and $BRAF^{V600}$-targeted therapies in 2011, which have now been adopted as first-line therapies for these patients. Because patients with active CNS metastases have largely been excluded from the initial phase III CBI trials, we investigated the survival outcomes for MBMs in a national cohort. Following FDA approval of ipilimumab and vemurafenib in 2011 for stage 3 unresectable/4 melanoma, and including the subsequent approvals of BRAF inhibitor dabrafenib (2013), MEK inhibitor trametinib (2013), and anti–PD-1 pembrolizumab and nivolumab (2014), we observed a 91% relative increase in the 4-year OS rate of MBM patients compared with those MBM patients who were diagnosed prior to 2011.

The improved survival of melanoma brain metastases with checkpoint blockade immunotherapies

Approximately 9% of KEYNOTE-001 (NCT01295827, pembrolizumab) and KEYNOTE-006 (NCT01866319, pembrolizumab vs. ipilimumab) and approximately 3% of CheckMate-066 (NCT01721772, nivolumab), -067 (NCT01844505, ipilimumab with vs. without nivolumab), and -069 (NCT01927419, ipilimumab with vs. without nivolumab) clinical trial patients had MBMs. However, although these trials demonstrated improved overall outcomes for stage 3 unresectable/4 patients, MBM-specific outcomes were not specifically reported (8, 9, 13–16). The CA184-042 (NCT00623766) phase II trial of ipilimumab displayed acceptable toxicities and modest 3-month objective

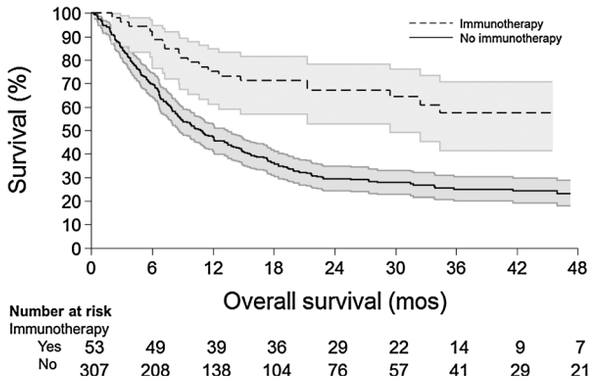

Figure 3.

Kaplan–Meier OS curves for resected MBM-only patients stratified by CBI. Survival curves of patients with (dashed line; $n = 53$) and without (solid line; $n = 307$) the addition of CBI to MBM resection, with number at risk table. $P < 0.001$ by log-rank test (95% CI, gray shading).

response rates of 16% and 5% in asymptomatic ($n = 48$) and symptomatic ($n = 19$) MBMs, with progression-free survival (PFS) of 1.5 and 1.2 months, respectively (17). Whereas in a phase II trial of pembrolizumab (NCT02085070) with 18 MBM patients, there was a response rate of 22%, and the median OS was not reached after a median follow-up of 12 months, with only two grade 3/4 adverse events (18). Preliminary results have been presented for the Checkmate-204 (NCT02320058) phase II trial of nivolumab with ipilimumab in 75 MBM patients, in which the objective response rate was 56% but with 48% of patients experiencing a grade 3/4 adverse event. A phase II trial of nivolumab with and without ipilimumab (NCT02374242) in 66 MBM patients demonstrated a 6-month OS of 44% to 76%, with 40% to 68% of patients experiencing a grade 3/4 adverse event (19, 20).

Taken together, these trial results suggest that the response rates and toxicities of CBIs are comparable between MBMs and extracranial metastatic disease, but also highlight the scarcity of MBM outcome data for CBI. In our analyses of a post-approval "real-life treatment" MBM population, CBI was associated with dramatically improved median OS of 12.4 and 56.4 months in MBM patients with and without extracranial metastasis, respectively. These survival benefits also persisted in multivariable risk-adjusted analyses. MBM patients who were younger, more recently diagnosed, had fewer comorbidities, insured privately or through Medicare, diagnosed in New England, had brain-directed RT, or had extracranial metastases were more likely to receive CBI.

Melanoma brain metastases with $BRAF^{V600}$-targeted therapies

$BRAF^{V600}$ mutations in the MAPK pathway are implicated in up to 43% of melanomas, and the development of $BRAF^{V600}$-specific inhibitors (e.g., vemurafenib and dabrafenib) has similarly revolutionized the treatment of $BRAF^{V600}$-mutant advanced melanoma (1, 21–24). Early $BRAF^{V600}$-targeted therapy clinical trials also largely excluded MBMs. However, the phase IV BRIM-3 trial (NCT01307397) of vemurafenib included 750 $BRAF^{V600}$-mutant MBM patients and found a 12.4-month median OS and 3.8-month median PFS (25). The BREAK-MB (NCT01266967) phase II trial of dabrafenib in 172 $BRAF^{V600}$-mutant MBM patients showed a 3.1- to 7.0-month median OS and 2.0- to 4.2-month median PFS, with 30% experiencing a serious adverse event (26). Although the NCDB lacks information on $BRAF^{V600}$-mutant status, the administration of targeted therapy was incorporated into our risk-adjusted multivariable analyses in part as a surrogate for $BRAF^{V600}$-mutant status. The subset of MBM patients who both received targeted therapy (i.e., thus representing $BRAF^{V600}$ mutants) and CBI was small but demonstrated a trend toward improved OS from CBI. Continued characterization of the efficacy of these agents in $BRAF^{V600}$-mutant MBM patients, particularly in conjunction with CBI, is necessary. Critically, comparative clinical trials are under way to investigate the benefits of combination and timing of first-line BRAF-targeted therapies with CBI.

Roles of resection and radiotherapy in melanoma brain metastases

For the initial treatment of MBMs, the NCCN guidelines recommend surgical resection for limited MBM (i.e., 1–3 metastases) in patients with stable systemic disease, to avert hemorrhages, seizures, or neurological dysfunction, promptly followed by adjuvant SRS and/or WBRT to help establish local disease control. For inoperable limited MBMs, primary treatment with SRS can also provide effective intracranial control (6, 7). SRS and hypofractionated SRT are preferred to WBRT due to their favorable toxicity profiles, whereas WBRT is often considered for MBMs with >3 lesions. In support of these guidelines, we found that MBMs amenable to surgical resection and/or SRS were associated with improved OS in multivariable analyses (24, 28–34). Patient selection for surgery and/or radiotherapy is influenced by overall disease burden, symptomatology, tumor location, size and number, systemic therapy, and patient performance status, features which are, unfortunately, not yet incorporated into registry-based data for metastases (27).

There has been concern that by modulating the local immune environment, concurrent use of CBI and RT may exacerbate perilesional inflammation and injury following RT, thereby leading to radionecrosis (35). Results from retrospective series of MBMs treated with concurrent CBI and RT have been variable with regard to the association between concurrent CBI and incidence of symptomatic radionecrosis (35–39). In the SRS and SRT settings for MBM, there appears to be an association between receipt of CBI and the development of symptomatic radionecrosis. Crucially, prospective studies are still needed to clarify the risks of radionecrosis following CBI and RT. At the same time, there remains uncertainty about any associated synergistic survival benefits, especially in instances of radionecrosis requiring steroid therapy that may dampen the local effects of CBI. The roles and timing of systemic therapy with MBM resection and/or RT will need to be further defined.

Limitations

The NCDB, although representing one of the largest cancer databases, has several key limitations (11). Notably, the NCDB only incorporates data from a patient's initial presentation, so our results may not apply to the majority of MBMs which develop after a melanoma patient's initial presentation. The NCDB also only incorporates OS data, without data on progression-free and recurrence-free survival and lacks detailed data about neurologic cause of death, symptomatology, number, size, intracranial location, and treatment specifics of metastases. Multivariable analyses were adjusted by type of brain-directed RT (i.e., single-fraction

SRS, hypofractionated SRT, and WBRT) to help adjust for the burden of intracranial disease.

The NCDB also lacks detailed information about chemotherapeutic and immunotherapeutic agents. Therefore, cytotoxic chemotherapeutics and biochemotherapeutics would also be encoded as chemotherapy and immunotherapy, respectively, but due to their limited efficacy and significant toxicities, have been relegated by NCCN guidelines to second-line therapy for stage 4 melanoma patients who fail initial CBI and/or $BRAF^{V600}$-targeted therapy. Because the NCDB only encodes the initial course of therapies, the majority of NCDB-encoded immunotherapy and chemotherapy since 2011 should represent CBI and $BRAF^{V600}$-targeted therapy, respectively. The NCDB lacks important data on systemic therapies as well, like dosages, schedules, adverse effects, and subsequent therapeutic courses, limiting analyses broadly to the initial course of therapy. A key limitation of the NCDB is its lack of molecular data, including BRAF mutational status for melanoma. Receipt of targeted therapy was included in multivariable analyses in part as a proxy for BRAF mutational status. Cancers are increasingly defined by their molecular drivers, which will be reflected by the WHO's future cancer classification and ICD-O encoding schema that will enable more comprehensive assessments of melanoma outcomes by mutational status.

Conclusions

Herein we demonstrated the dramatically improved OS following the incorporation of CBIs into the standard of care in a national-scale analysis of a "real-world" population of melanoma patients presenting with MBMs. Due to the high incidence of brain involvement, brain imaging should be considered as part of the initial staging of melanoma patients with suspected disseminated disease at presentation. Our findings help bridge the gaps in early clinical trials of CBIs that largely excluded stage 4 melanoma patients with MBMs, with checkpoint immunotherapy demonstrating a more than doubling of the median and 4-year OS of MBMs. In support of the NCCN guidelines, we additionally characterized the survival benefits associated with MBMs that were amenable to resection and single-fraction SRS. Taken together, our findings depict the exciting successes in the treatment of MBMs in the contemporary era of CBI and $BRAF^{V600}$-targeted therapy.

Disclosure of Potential Conflicts of Interest

D.A. Reardon has received honoraria from the speakers bureau of Abbvie, Agenus, Regeneron, Stemline, MerckKGaA, Bristol-Myers Squibb, Celldex, Genentech/Roche, Inovio, Merck, Novocure, Oncorus, and Oxigene, and is a consultant/advisory board member for Abbvie, Agenus, Montreros, Oxigene, Regeneron, Stemline, Bristol-Myers Squibb, Celldex, Genentech/Roche, Inovio, Merck, Merck KGaA, Novocure, and Oncorus. F.S. Hodi reports receiving a commercial research grant from Bristol-Myers Squibb and is a consultant/advisory board member for Merck, Bristol-Myers Squibb, EMD Serono, Sanofi, and Novartis. A.A. Aizer reports receiving a commercial research grant from Varian Medical Systems. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.B. Iorgulescu, C.K. Zogg, A.A. Aizer, T.R. Smith
Development of methodology: J.B. Iorgulescu, C.K. Zogg, A.A. Aizer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.B. Iorgulescu, F.S. Hodi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.B. Iorgulescu, M. Harary, C.K. Zogg, K.L. Ligon, F.S. Hodi, A.A. Aizer
Writing, review, and/or revision of the manuscript: J.B. Iorgulescu, M. Harary, C.K. Zogg, K.L. Ligon, D.A. Reardon, F.S. Hodi, A.A. Aizer, T.R. Smith
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.B. Iorgulescu, K.L. Ligon
Study supervision: J.B. Iorgulescu, T.R. Smith

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