Current Breast Cancer Reports (2019) 11:241–247
https://doi.org/10.1007/s12609-019-00335-1

IMMUNO-ONCOLOGY (S TOLANEY, SECTION EDITOR)

The Promise of Immunotherapy for Breast Cancer Brain Metastases

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Published online: 20 November 2019

Abstract

Purpose of Review The goal of our review is to describe the rationale for immunotherapy in the treatment of breast cancer brain metastases (BCBM), the current landscape of clinical trials for this disease process, and possible future directions based on anticipated results.

Recent Findings Immune checkpoint inhibition has shown efficacy in the treatment of several solid tumor brain metastases (i.e., melanoma and non-small cell lung cancer), but data specific to BCBM is relatively sparse. Preclinical studies in BCBM have illustrated a lower immune content in the brain microenvironment measured by tumor-infiltrating lymphocytes (TILs) in brain metastases compared to primary tumors. Yet, improved outcomes are associated with higher TIL content in the BCBM, and strategies to understand and alter the complex brain immune microenvironment are needed.

Summary of Findings Based on observations in the non-breast cancer setting and early results in advanced breast cancer, it is likely that novel, strategic combination immunotherapy strategies will be needed to yield meaningful outcomes for BCBM patients. Some exciting concepts underway include novel immunotherapy combinations, concurrent stereotactic radiosurgery, bi-specific antibody armed activated T cells, and HER2-chimeric antigen receptor T cells for leptomeningeal disease.

Keywords Breast cancer · Brain metastases · Central nervous system · Tumor-infiltrating lymphocytes · Immunotherapy

Introduction

Breast cancer to brain metastases (BCBM) are an increasing complication in all subtypes of advanced breast cancer and represent our patients in greatest need for improved outcomes. Nearly one-third to one-half of patients with advanced human epidermal growth factor 2 positive (HER2+) and triple negative breast cancer (TNBC) will develop brain metastases at some point in their metastatic disease course [1, 2]. Across subtypes, patients with BCBM from TNBC have relatively inferior outcomes with a median overall survival of 3–12 months [3–5]. This fact is largely due to the lack of anti-cancer agents capable of penetrating the central nervous system effectively, concurrent intracranial and extracranial disease progression, and the relative lack of "targets" such as the estrogen receptor and HER2. Patients with HER2+ BCBM have had improvements in overall survival to nearly 3 years [3], and their lifespan has improved over time due to the arsenal of blood brain barrier penetrable systemic treatment options such as ado-trastuzumab emtansine, lapatinib, and neratinib [6•]. Receipt of carefully selected systemic therapy after local treatment to BCBM improves outcomes and will be essential in the quest to further improve survival for all subtypes [7•]. Developing drugs that effectively treat or prevent solid tumor brain metastases has been fraught with challenges such as blood brain barrier penetrability, presence of efflux transporters expelling drugs, and dissociated intracranial/extracranial response to treatment. Immunotherapy is less reliant on blood brain barrier penetrability or efflux transporters of anti-cancer agents, but rather the patient's inherent anti-cancer immune response. As such, strategic integration of immunotherapy could hold promise in overcoming many of the historical barriers to advancing the treatment of BCBMs.

Immune checkpoint inhibition (ICI) targeting programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) have revolutionized the manner in which we treat diverse solid tumors with corresponding improvements in

This article is part of the Topical Collection on *Immuno-oncology*

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both progression-free and overall survival across many tumor types [8•, 9]. ICI has been studied in all breast cancer subtypes with disparate response rates [10]. Response rates appear superior with early integration, as opposed to later line, in the treatment course and in PD-L1 positive (PD-L1+) populations. The first immunotherapy combination, atezolizumab and nab-paclitaxel, was recently approved in advanced/metastatic TNBC whose tumor infiltrating lymphocytes (TILs) expressed ≥ 1% PD-L1. IMpassion130 was a landmark multicenter, randomized, phase III clinical trial in first-line metastatic/advanced TNBC comparing nab-paclitaxel plus placebo or atezolizumab [11]. Patients were stratified by PD-L1 positivity in the TILs via the Ventana SP142 assay (≧ 1%). The median PFS was 7.5 months versus 5.0 months in the PD-L1+ population (HR, 0.62; 95% CI, 0.49 to 0.78; $P < 0.001$). Among patients with PD-L1+ tumors, the median OS was 25.0 months versus 15.5 months (HR, 0.62; 95% CI, 0.45 to 0.86). Many interesting immunotherapeutic strategies are underway in breast cancer which will include combination agents that enhance immunogenicity and refinement of biomarkers that predict response.

The utility and efficacy of immunotherapy approaches to the treatment of BCBM remain unknown and lag behind other immunogenic solid tumors. There is a paucity of data surrounding intracranial response rates to ICI in breast cancer. IMpassion130 did include patients with stable and treated brain metastases at baseline. The outcomes of this subgroup in particular are of interest but have yet to be reported. This review will discuss what is known about the efficacy of immunotherapy in the treatment of solid tumor brain metastases, rationale for its use in breast cancer brain metastases, and intriguing strategies integrating the use of immunotherapy in treating BCBM in the clinic.

Prospective Clinical Trials Utilizing Immune Check Point Inhibitors in the Treatment of Solid Tumor Brain Metastases

Several prospective clinical trials in tumor types known to have potent systemic responses to ICI have evaluated intracranial efficacy and safety in the treatment of solid tumor brain metastases (Table 1).

CTLA-4 Inhibition

Single agent CTLA-4 inhibition in the treatment of melanoma brain metastases was first evaluated in the Italian NIBIT II trial of ipilimumab in combination with fotemustine, a nitrosourea analogue with activity in melanoma brain metastases [12]. The primary end point was the proportion of patients with immune-related disease control. Twenty asymptomatic brain metastases patients were included in the trial revealing a disease control rate of 50%. Five had reduced or stabilized brain disease, and five had brain metastases that became undetectable by scans. A follow-up phase II study of ipilimumab for patients with melanoma brain metastases was performed in 72 patients [13]. The trial comprised 51 asymptomatic patients with active brain metastases not requiring corticosteroids and 21 patients with symptomatic brain metastases requiring corticosteroids. An intracranial response rate of 16% was seen in the asymptomatic cohort versus 5% in the symptomatic cohort.

The only completed study, to our knowledge, utilizing ICI in the treatment of BCBM utilized standard-of-care brain radiation with tremelimumab-mediated CTLA-4 blockade to determine the extracranial abscopal effect [14••]. Twenty-six total patients with BCBM were treated with 23 patients receiving whole brain radiation and 3 receiving stereotactic radiosurgery. Patients were heavily pretreated. This study showed a non-CNS disease control rate (complete response, partial response, or stable disease at 12 weeks) of 10% (2/20) of women with HER2-negative disease. Tremelimumab with trastuzumab and brain radiation in HER2+ disease conferred non-CNS disease control in 33% (2/6); both of which were sustained at 6 months [14••]. Extracranial disease was not well-controlled with this regimen with 11/26 (42%) patients requiring discontinuation of the study due to rapid non-CNS progressive disease within 12 weeks of cranial radiation. The primary objective was to test the abscopal effect, and intracranial responses were ultimately not assessable due to the short time on protocol-directed therapy and the fact that the majority of patients had previously received WBRT.

PD-1 Inhibition in Solid Tumor Brain Metastases

In a non-randomized, open-label phase 2 clinical trial, patients with melanoma or PD-L1+ non-small cell lung cancer (NSCLC) and at least one untreated or progressive asymptomatic brain metastasis (5–20 mm) were treated with pembrolizumab every 2 weeks until progression [15••]. The primary endpoint was brain metastasis response (% patients with a complete or partial response per modified RECIST). A brain metastasis response was achieved in 22% of patients with melanoma and 33% of patients with PD-L1+ NSCLC.

A phase II trial assessed the activity and safety of nivolumab in patients with metastatic clear cell renal cell carcinoma (ccRCC) after vascular endothelial growth factor (VEGF)–directed therapies and included patients with asymptomatic brain metastases in two cohorts: untreated (A) or locally treated (B) [16••]. Intracranial response rate via modified RECIST was 12% in cohort A and limited to those with single brain lesions less than 1 cm. Median intracranial PFS was 2.7 months (95% CI, 2.3 to 4.6 months) in cohort A and 4.8 months (95% CI, 3.0 to 8.0) in cohort B.

Table 1 Prospective clinical trials studying immune check point inhibitors in patients with solid tumor brain metastases

Immunotherapy	Phase	Population	Brain metastases characteristics	Steroids (yes/no)	Outcome
Pembrolizumab (PD-1) [15••]	II	Melanoma and NSCLC (PDL-1+)	Untreated, 5–20 mm; asymptomatic	No	CNS response rate (modified RECIST): 22% (melanoma) 33% (PDL-1+ NSCLC)
Nivolumab (PD-1) [16••]	II	Renal cell carcinoma	Asymptomatic A: untreated, 5 mm or greater B: previous focal treatment	No	CNS response rate (modified RECIST): A, 12% Intracranial PFS: A, 2.7 m B, 4.8 m
Ipilimumab (CTLA-4) [13]	II	Melanoma	Untreated		CNS objective response rate (modified WHO criteria):
			A: asymptomatic	No	A, 16%
			B: symptomatic	Yes	B, 5%
Tremelimumab (CTLA-4) plus brain radiation (trastuzumab if HER2+) [14••]	Pilot	Breast cancer	Untreated	No	ORR 4% (non-CNS)
Nivolumab + ipilimumab [18••, 22]	II	Melanoma	Untreated, 5-30 mm		Intracranial response (modified RECIST):
			A: asymptomatic	No	A, CBR 58.4%; CR 29% PR 26%
			B: symptomatic	Yes	B, CBR 22.2% CR 11% PR 5.6%

Combination CTLA-4 and PD-1 Inhibition

Combining CTLA-4 inhibition (ipilimumab) with PD-1 inhibition (nivolumab) increases intracranial response rates compared to monotherapy in untreated melanoma brain metastases [17]. A phase II, single-arm study in patients with metastatic melanoma and at least one non-irradiated, asymptomatic brain metastasis (0.5 to 3 cm) evaluated nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) until progression or unacceptable toxicity. The rate of intracranial clinical benefit was 58.4% with a 29% complete response rate and 26% partial response rate [18••]. Intracranial response rates were much lower for patients with melanoma brain metastases presenting with neurologic symptoms with or without need for steroids. At a median follow-up of 5.2 months, intracranial objective response rate was 16.7% and the CBR was 22.2% (6.4–47.6) in this cohort [18••].

In conclusion, PD-1 inhibition has respectable intracranial activity in asymptomatic, untreated PD-L1+ NSCLC and melanoma brain metastases [15••]. Combination ICI is very effective for small, asymptomatic melanoma brain metastases, and local therapy can be used as salvage in those initiating therapy with ipilimumab and nivolumab. Patients with asymptomatic melanoma brain metastases not requiring steroids have superior responses to ICI than those with symptomatic lesions requiring steroids [18••]. Intracranial response to PD-1 inhibition appears limited in ccRCC and symptomatic melanoma brain metastases [16••]. Questions remain such as how to best sequence local therapy such as stereotactic radiosurgery or surgical resection for these patients and whether this should be done prior to ICI, concurrently, or as a salvage approach. Given the paucity of data informing ICI efficacy in BCBM, lessons learned in the non-breast cancer brain metastases space will certainly inform incorporation of immunotherapy approaches in the development of BCBM clinical trials and strategies.

Rationale for the Use of Immunotherapy in Breast Cancer to Brain Metastases

As discussed above, the development of immunotherapy in breast cancer lags behind development in other solid tumor types, such as melanoma and NSCLC. With the approval of atezolizumab in the treatment of PD-L1+ TNBC and a plethora of studies underway, we anticipate tremendous progress in the coming months to years. Given the concordant intracranial and extracranial response rates in melanoma and NSCLC, we are hopeful that similar observations are seen in PD-L1+ TNBC brain metastases. Preclinical studies in brain metastases have illustrated a lower immune content measured by TILs in brain metastases compared to primary tumors, particularly

in the TNBC subtype [19]. Yet, improved outcome is associated with higher TILs content in BCBM [20•]. Additional analysis evaluating immunohistochemical biomarkers in over 200 BCBM illustrated improved outcome for patients with increased TILs content, preferentially in HER2+ BCBM [21]. These findings are similar to findings in melanoma brain metastases where we have seen durable intracranial responses [22], thus providing additional rationale for continued clinical investigation of immunotherapy in the treatment of patients with BCBM across subtypes.

Novel Approaches Underway in Breast Cancer Brain Metastases

Currently, there are many clinical trials underway utilizing novel immunotherapy approaches specific to BCBM or leptomeningeal disease. Based on observations in the non-breast cancer setting and early results in advanced breast cancer, it is likely that novel, strategic combination immunotherapy strategies will be needed to yield meaningful outcomes. Some exciting concepts underway include novel ICI combinations, concurrent stereotactic radiosurgery and ICI, bi-specific antibody armed activated T cells, and HER2-chimeric antigen receptor T cells for leptomeningeal disease (Table 2).

The ability of radiation therapy to enhance immunogenicity has been studied for decades. Radiotherapy increases tumor PD-L1 expression, increases antigen presentation via increased surface expression of major histocompatibility complex class I molecules, and increases CD8+ T cells in the tumor microenvironment [23]. Preclinical data also suggest that acquired resistance to radiation can be overcome with concurrent PD-1/PD-L1 inhibition [24]. There is also interest in the ability of radiation therapy to induce distant tumor responses when combined with immunotherapy which is referred to as the "abscopal effect." This theory has been studied in metastatic TNBC with pembrolizumab and 5 fractions of radiation [25] yielding durable responses outside of the radiation field in 3/17 (18%) patients. Pembrolizumab has also been studied with palliative radiation therapy in hormone receptor positive metastatic breast cancer with a primary objective of response rate in a lesion outside the radiation field [26]. A total radiation dose of 20 Gray was delivered over 5 daily fractions and pembrolizumab 200 mg IV 2–7 days before day 1 of radiation, then every 3 weeks until disease progression. Eight women were enrolled into the first stage of the trial with no objective responses seen.

Several retrospective studies, to date, have suggested that adding stereotactic radiosurgery to concurrent immunotherapy in solid tumor brain metastases improves brain specific outcomes and that the combination is safe [27, 28]. There are several ongoing clinical trials combining ICI (nivolumab, atezolizumab, pembrolizumab, durvalumab/tremelimumab) with stereotactic radiosurgery in the treatment of BCBM (Table 2). Primary outcomes of each trial vary, though results of distant intracranial response and total intracranial brain control will be appealing.

Exciting preclinical evidence has shown that chimeric antigen receptor-engineered T cells (CAR T cells) targeting (HER2 CAR T cells) that contain a 4-1BB costimulatory domain reduce T-cell exhaustion and enhance proliferative capacity compared with HER2 CAR T cells containing the CD28 costimulatory domain. Local intracranial delivery of these HER2 CAR T cells showed potent in vivo antitumor activity and antitumor efficacy [29]. Based on this work, a phase 1

Table 2 Ongoing immunotherapy clinical trial strategies specific to breast cancer to brain metastases

Population	Phase	Intervention	Primary endpoint	Study identifier
BCBM	II	SRS + nivolumab	Safety	NCT03807765
BCBM	II	SRS + pembrolizumab	Tumor response for non-irradiated brain lesions; RECIST1.1	NCT03449238
BCBM, triple negative	II	SRS + atezolizumab	Progression free survival; RANO-BM	NCT03483012
BCBM	II	SRS or WBRT + tremelimumab ± and durvalumab	Non-CNS disease control rate	NCT02563925
BCBM, HER2+	II	Atezolizumab + herceptin + pertuzumab	ORR CNS; RANO-BM	NCT03417544
BCBM and lung brain metastases	I	Intratumoral injection of activated, autologous dendritic cells (DCVax-Direct)	Safety	NCT03638765
Leptomeningeal disease, HER2+	I	Bi-specific antibody (HER2Bi) armed activated T cells (HER2 BATs)	Safety	NCT03661424
Leptomeningeal disease, HER2+ breast cancer	I	HER2-chimeric antigen receptor T cells	Safety and recommended phase 2 dose	NCT03696030
Leptomeningeal disease (melanoma, lung, or breast)	Ib	Avelumab + WBRT	Safety and dose limiting toxicity	NCT03719768

clinical trial is underway (NCT03696030) to determine the safety and recommended dosing of intraventricularly administered memory-enriched autologous HER2(EQ)BBzeta/CD19t + T cells (HER2-chimeric antigen receptor T cells) in patients with histologically confirmed HER2+ cancer with brain and/or leptomeningeal metastases.

T cell redirecting therapy includes bispecific compounds that engage a tumor-associated antigen and the T cell receptor-CD3 complex, which should direct T cell cytotoxicity to the malignant cell [30]. Preclinical studies have shown that activated T cells (ATC) armed with anti-CD3 plus anti-HER2 bispecific antibody cause high levels of cytotoxicity in high and low HER2-expressing breast cancer cell lines [31]. As such, a phase I trial in 23 women with metastatic breast cancer ensued treating patients with eight infusions of anti-CD3 × anti-HER2 bispecific antibody (HER2Bi) armed anti-CD3-ATCs. The infusions were overall safe and antitumor responses were seen [32]. An innovative immunotherapy strategy is currently underway whereby activated T cells armed with anti-CD3 plus anti-HER2 bispecific antibody (HER2 BATs) are intraventricularly administered in patients with HER2+ advanced breast cancer that has metastasized to the leptomeninges (NCT03661424).

Conclusions

Immunotherapy has revolutionized the manner in which advanced solid tumors are treated over the past several years, with durable and meaningful responses. As patient outcome continues to improve, recurrence in the sanctuary site of the central nervous system is becoming more common. Lessons learned from the treatment of melanoma and NSCLC brain metastases are informing the design of clinical trials for immunotherapy for patients with BCBM across subtypes, and similarities at the preclinical level hold promise for similar clinical activity. We remain hopeful that the ongoing clinical trials evaluating immunotherapy in the setting of BCBM will provide new tools in our toolkit to improve the outcomes for our patients with BCBM in the very near future.

Compliance with Ethical Standards

Conflict of Interest Sarah Sammons reports receiving research funding from Astra Zeneca and Eli Lilly. Carey Anders reports work with PUMA, Lilly, Merck, Seattle Genetics, Nektar, Tesaro, G1-Therapeutics, Genentech, Eisai, IPSEN, UpToDate, and Jones and Bartlett during the conduct of the study. Amanda Van Swearingen declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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