Emergent immunotherapy approaches for brain metastases

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Abstract

Brain metastases from solid tumors are increasing in incidence, especially as outcomes of systemic therapies continue to extend patients' overall survival. The long-held notion that the brain is an immune sanctuary has now been largely refuted with increasing evidence that immunotherapy can induce durable responses in brain metastases. Single agent immune checkpoint inhibition with anti-CTLA4 and anti-PD1 antibodies induces durable responses in 15%–20% in melanoma brain metastases as long as patients are asymptomatic and do not require corticosteroids. The combination of anti-CTLA4 with anti-PD-1 antibodies induces an intracranial response in over 50% of asymptomatic melanoma patients, and much lower rate of otherwise durable responses (20%) in symptomatic patients or those on steroids. Data in other cancers, such as renal cell carcinoma, are accumulating indicating a role for immunotherapy. Emerging immunotherapy approaches will have to focus on increasing response rates, decreasing toxicity, and decreasing steroid dependency. The path to those advances will have to include a better understanding of the mechanisms of response and resistance to immunotherapy in brain metastases, the use of novel agents such as anti-LAG3 checkpoint inhibitors, targeted therapy (oncogene directed or TKIs), and possibly surgery and SRS to improve the outcomes of patients with brain metastases.

Recent advances in systemic therapies of solid tumors have dramatically improved the outcomes of patients achieving prolonged survival with the use of novel targeted therapies and immunotherapies. This has paradoxically resulted in patients living longer at the risk of developing metastases to the central nervous system (CNS) and indeed can manifest in increased incidence of one of the most devastating complication of solid tumors. The occurrence of a CNS metastasis dramatically alters the trajectory of therapy and worsens outcomes in patients with metastatic cancer. The traditional approach to CNS metastases is rooted in the lack of effectiveness of systemic agents and the urgency of intervention to prevent rapid neurological deterioration and possibly neurological death. Therefore, surgery, radiation, or both have been the mainstay of the management of CNS metastases. Systemic chemotherapeutic agents have historically been ineffective against CNS metastases, either because of inherent lack of efficacy against cancer in general, or because they have been developed to preclude CNS penetration to limit their toxicity. However, there is growing evidence that a new generation of systemic agents, including small molecule inhibitors and modern immunotherapy, can achieve clinical benefit through their antitumor activity against brain metastases providing a foundation for new combinatorial approaches of therapies and modalities for patients with CNS metastases. Specifically, the use of immune checkpoint inhibitors has resulted a high rate of durable intracranial responses and stands

to change the therapeutic paradigm into a genuinely multi-disciplinary multi-modality approach.

As the role of systemic therapy for brain metastases evolves, targeted therapies are already establishing their roles in treating brain metastases from EGFR-, and ALK/ROS-mutant non-small cell lung cancer, as well HER2-positive breast cancer. However, the impact of immune checkpoint inhibitors remains unclear. The data in NSCLS remain largely retrospective and reviewed comprehensively by Santamaria et al. in 2020.[1] Since immune checkpoint inhibitors only recently gained regulatory approval in breast cancer (TNBC), the data are even more scarce and reviewed by Watase et al. in 2021.[2] In this review, we will focus on melanoma and genitourinary malignancies to examine the role of immunotherapy in managing patients with brain metastases and highlight the challenges and emerging opportunities for immuno-oncology (IO) drug development in this population.

Incidence of Brain Metastases in Melanoma

Melanoma has the highest propensity of all common malignancies to metastasize to the brain, with 40% of advanced melanoma patients expected to have brain metastases at the time of diagnosis of metastatic disease and up to 70% at the time of death.[3]

Systemic therapy for metastatic melanoma has been revolutionized over the last decade with the development of multiple effective mutationally targeted and immune-based therapies.[4] In clinical trials, these new regimens have increased the 1-year survival for metastatic melanoma patients without CNS involvement from 25% to over 80%, and responses lasting longer than 5 years are becoming commonplace. There is reason to hope that this progress will also extend to metastatic melanoma patients with CNS involvement. Indeed, in a recent review of a large, nonacademic database, Iorgulescu et al. reported markedly improved outcomes for patients with melanoma metastatic to the brain in the era of the new therapeutic landscape for this disease (data from 2010 to 2015).[5] In this National Cancer Database, 36% of metastatic melanoma patients had brain metastases at the time of diagnosis of metastatic disease. This study highlighted the value of screening patients with advanced solid tumors at the time of diagnosis rather than imaging only upon the development of CNS symptoms. In addition, even with such short timeline after checkpoint inhibitors gained wide utilization in melanoma, there was a doubling of 4-year overall survival MBM patients who were treated with immune checkpoint blockade in the real world.[6]

Review of Clinical Data in Melanoma

Anti-CTLA4 and anti-PD-1 checkpoint inhibitors have revolutionized the field of cancer therapeutics. Two case reports in 2008 and 2010 initially showed a response of MBM to immunotherapy which led to further investigations.[7,8] A phase II trial of ipilimumab, targeting CTLA4, in 2012 showed improvement in overall survival and durable responses.[9] This study conducted by the Cytokine Working Group established the intracranial activity of ipilimumab with ORR, PFS, and OS very comparable to patients without CNS involvement. In addition, it included a cohort of patients with MBM that were on steroids where ipilimumab had little to no activity, and this cohort was stopped for futility. Another study by the Italian NIBIT group combining ipilimumab with fotemustine (a nitrosourea alkylating agent) had similar outcomes and led to a Phase III study comparing ipilimumab to ipilimumab and fotemustine, and later amended to include an arm of ipilimumab and nivolumab.[10] Anti-PD-1 antibodies soon followed suite and a Phase II trial of pembrolizumab in a small number of patients with NSCLC or melanoma (*n* = 23) with brain metastasis was reported in 2016.[11] A majority of patients in this study had multiple prior therapies and the intracranial response rate was ~22%. Interestingly, unlike some of the targeted therapy trials in this population, immunotherapy trials tend to show concordance between intracranial and extracranial disease response indicating likely similar immulomodulation between intra and extra-cranial melanoma. Additionally, Engelhardt and Ransohoff[12] and others have postulated that activated cytotoxic T-cells from outside the CNS traffic through the BBB inducing responses and resulting in therapeutic efficacy.

Combination immunotherapy trials have shown improved response rates over single-agent anti-PD-1. The CheckMate-204 trial conducted in the United States evaluated the rate of intracranial clinical benefit in metastatic melanoma patients, asymptomatic from CNS disease and with at least one measurable and nonirradiated intracranial lesion (0.5–3 cm).[13] Ninety-four patients had median follow-up of 14 months and rate of intracranial benefit was found to be 57% (95% CI 47–68). Intracranial benefit was defined as stable disease for at least 6 months, complete response (CR) or partial response (PR). CRs were noted in 26%. Updated results from CheckMate-204 with longer follow-up and with inclusion of symptomatic patients and/or those who required corticosteroids had shown the asymptomatic cohort (*n* = 101, Cohort A) who received a median 3 doses of combination immunotherapy had intracranial clinical benefit rate (CBR) of 58.4%. Medial PFS and OS were not reached at the medial 21-month follow-up period. In contrast, Cohort B which included 18 patients with symptomatic CNS disease and/or requiring steroids had an intracranial CBR 22.2%. These patients had received median one dose of combination immunotherapy; OS and median intracranial PFS was 8.7 and 1.2 months, respectively.[14] Importantly, the toxicity profile observed with this regimen in a population with brain metastases was almost identical to the toxicity profile in patients without brain metastases, mostly immune-mediated hepatitis, colitis, and endocrinopathies. The incidence of neurological toxicities was 6.7% with most being attributable to disease (headaches, syncope, etc.), and 2% of patients experienced brain edema on treatment. One case of immune-mediated peripheral neuropathy was also reported separately, a toxicity observed with combination immunotherapy and not necessarily indicating a relationship with the presence of CNS metastases. Taken together, these updated results

show durable responses in 55% of patients with asymptomatic CNS disease treated with combination ipilimumab/nivolumab, and that patients with symptomatic CNS disease and/or steroid dependence are less likely to benefit.[14]

In 2018, Long GV and colleagues reported the results of the ABC trial out of Australia where patients treated with combination nivolumab + ipilimumab had improved intracranial responses compared to nivolumab alone.[15] In this study, asymptomatic MBM patients without prior CNS-directed treatment had been randomized to receive nivolumab + ipilimumab (Cohort A; $n = 36$) at standard dose for 4 cycles followed by maintenance nivolumab, or nivolumab alone (Cohort B; $n = 27$). A third cohort (C; $n = 16$) included nonrandomized patients with symptomatic disease, leptomeningeal disease or those in whom local therapies had failed. At median follow-up of 17 months, 46% (95% CI 29–63) had intracranial response in the combination arm compared to 20% (95% CI 7–41) with nivolumab alone. Complete intracranial response was noted in 17% in cohort A and 12% in cohort B and none in cohort C.

Decreased efficacy was noted in the initial phase II study of Ipilimumab described above in patients who were on glucocorticoids. Though it is unclear if this patient population has more advanced or aggressive disease characteristics and therefore a worse outcome, or if steroids reduce the anti-tumor effects of immunotherapy, or a combination of both, typically successive large trials have excluded patients who require the use of steroids. Bevacizumab has been put forth as a steroid-sparing agent which may be applicable during immunotherapy with the ability to reduce required dexamethasone doses by >50% in some patients as a result of its effects in reducing edema. Adverse events such as hypertension and hemorrhage, both intracranial and gastrointestinal, would require monitoring with anti-angiogenic therapy.[16] In an institutional study at our center, bevacizumab used for treatment of radionecrosis following SRS with or without WBRT resulted in symptom improvement and quality of life improvement with 2–6 doses of bevacizumab, and radiographic improvement in the majority of patients. In this small cohort, no intra or extracranial bleeding episodes had occurred warranting further investigation into the use of bevacizumab with immunotherapy.[17]

Combination therapy heralds a higher rate of immune-related toxicity with grade 3 or 4 toxicity in 55% of patients in CheckMate-204 with a 20% discontinuation rate in this group. Similarly, 54% of patients in the combination arm (cohort A) of the ABC trial experienced a grade 3 or 4 toxicity. In the prior single-agent immunotherapy trials, the most common grade 3 toxicity noted was diarrhea and fatigue (12% each). Single-agent anti-PD-1 trials have shown ~10%–15% grade 3/4 adverse events.

Mechanisms of Resistance to Immunotherapy in Melanoma Brain Metastases

The central nervous system has classically been viewed as an immune privileged site under normal conditions. However, recent evidence shows that although the immune system in the brain might be quite different than in other organs, a system of immune cells capable of fighting disease and tumor cells does exist in the normal brain and reacts in response to injury, infection, or tumor. Invasion of cells from the peripheral immune system also occurs in the setting of injury. Lymphatic drainage, initially thought to be absent in the brain, was only recently identified.[18,19] However, during infection or inflammation, peripheral immune cells also cross the permeable blood–brain barrier or tumor–brain barrier to respond to pathogens or malignant cells. Macrophages and inflammatory T cells have been shown to migrate into the central nervous system in response to injury.[20]

Understanding other mechanisms of resistance can aid in the design of combination therapies to further improve patient outcomes. Comparison of extracranial and concordant brain metastases offers the ability to identify molecular and immune differences that could underlie a difference in the immune response. For instance, increased levels of PI3K/AKT and decreased expression of PTEN have been observed in MBM when compared with extracranial sites.[4,5] Despite these differences, patients with stage IV melanoma containing *BRAF* or *NRAS* mutations have a higher incidence of brain metastasis at time of diagnosis (24 and 23%, respectively) in comparison to wild-type tumors (12%; $P = .008$).[6,21]

Furthermore, multiple preclinical studies have noted hyperactivation of the AKT and loss of PTEN expression in CNS metastasis compared to extracranial sites.[22–28] Inhibition of PI3K-AKT pathway in a vemurafenib-resistant cell line showed improved growth inhibition compared to vemurafenib alone.[25] Taken together, such data indicates a role for AKT in the pathogenesis of MBM and resistance to *BRAF* mutation-directed therapy in the CNS. PTEN loss has also been shown in vitro and in vivo preclinical models of melanoma to decrease both T-cell trafficking to tumors and T-cell-mediated tumor cell destruction conferring a resistance to T-cell-mediated anti-tumor effects.[29,30] Strategies to target this pathway with PI3K and mTOR inhibitors are currently under way.

OxPhos Pathway

There is increasing evidence to suggest significant differences in the pathophysiology and molecular determinants of CNS metastasis in melanoma in comparison to extracranial metastasis. In a recent analysis by Fisher et al.,[22] RNA sequencing was performed on 88 samples of resected melanoma brain metastasis and 42 matched extracranial metastatic tumor samples from a subset of the same patients. Four hundred and ninety-four differentially expressed genes had been identified in the matched analysis. The oxidative phosphorylation (OxPhos) pathway had been significantly enriched in their analysis. The authors validated this finding via inhibition of OxPhos in xenograft mouse models which had acquired (A375-R1) and de novo (SKMEL5) resistance to BRAF/MEK inhibition. Treatment with the OxPhos inhibitor IACS-010759 was noted to significantly improve survival in both murine models (HR, 0.197; 95% CI, 0.075–0.519, $P = .001$) and (HR, 0.072; 95%

CI, 0.024–0.214, P < .0001) in A375-R1 and SKMEL5 mice, respectively. Incidence of MBM was also significantly reduced (P = .035) in an immunocompetent mouse model of spontaneous lung and brain metastasis in comparison to control while no change in rate of primary tumor growth or lung metastasis formation was noted.[22]

Those findings were consistent in brain metastases from lung cancer, breast cancer, and renal cell carcinoma which were also characterized by decreased immune infiltrates, increased OXPHOS, increased activation of the PI3K-AKT pathway (previously demonstrated by our group and others in MBMs), and increased sensitivity to IACS-010759, similar to our analysis of MBMs.[31] Additional studies were performed to further understand the functional significance of OXPHOS in MBMs. While OXPHOS was significantly higher in MBMs than in ECMs, there was heterogeneity of OXPHOS levels (by a gene expression score) among this cohort of MBMs. Thus, molecular and immune features were compared between MBMs with High versus Low OXPHOS to further understand the impact of this metabolic state. These analyses demonstrated that OXPHOS correlated with increased mTOR activity, increased glutamine metabolism (consistent with previous studies of melanoma cell lines with acquired resistance to MAPK pathway inhibitors with high OXPHOS), and decreased immune activation.[32]

Combinations of Targeted Therapy with Immunotherapy

Combining targeted and immune checkpoint inhibition is another emerging therapeutic strategy in metastatic melanoma with future application to MBM. Increased T-cell infiltration as well as PD-L1 and tumor antigen expression have been seen post BRAF/MEK inhibition and preclinical models have shown increased anti-tumor effect with the combination of anti-PD-1 checkpoint inhibition and BRAF/MEK inhibition.[33] In a Phase 1 trial of 15 patients with *BRAF V600* mutations treated with dabrafenib, trametinib, and pembrolizumab, ORR was seen in 11/15 (73%) of patients and 40% continued to have response at 27 months median follow-up.[34] In the phase 2 setting, the triplet combination showed a trend toward improved PFS when compared to the placebo arm with dabrafenib/trametinib (16.0 months vs 10.3 months) though statistical significance had not been reached.[35] Fifty-eight percent of patients in the triplet arm experienced grade 3/4 toxicities compared with 27% in the doublet arm.

This includes the phase III IMspire 150 study of vemurafenib/cobimetinib with atezolizumab or placebo where a significant improvement in PFS was seen in the triplet arm (15.1 vs 10.6 months; HR 0.78; 95% CI 0.63–0.97; P = .025) in patients with untreated *BRAF V600E* mutation positive metastatic melanoma.[36] Patients with actively progressing or untreated CNS metastatic disease were excluded from the study; though 2%–3% with previously treated MBM were included in each arm. Interestingly, a recent analysis of this study indicated that triplet therapy may indeed delay the occurrence of

CNS metastases compared to targeted therapy alone.[37] An ongoing global study is evaluating this combination in patients with active untreated brain metastases (TRICOTEL, NCT03625141). Part 3 of the COMBI-i trial was a randomized, placebo-controlled phase III study that evaluated spartalizumab (anti-PD-1) versus placebo in combination with dabrafenib and trametinib in *BRAF V600* mutation positive metastatic melanoma (NCT02967692).[38] Again clinically active MBM patients were not included. This study failed to meet its primary endpoint and the triplet arm did now show improved investigator-assessed PFS compared to the doublet at 24-month follow-up. Additionally, a higher number of discontinuation/dose modifications were noted in the triplet arm. The initial safety and efficacy results of the phase II study TRIDeNT (TRIplet combination of Nivolumab with Dabrafenib and Trametinib in BRAF-mutated metastatic melanoma (n = 26)) which allowed for patients with asymptomatic CNS disease had an ORR of 91%.[21] At time of enrollment, 8 patients had CNS disease. Of 6 evaluable patients, 67% had noted intracranial response with 2 complete responses noted. No significant difference in outcomes had been noted in patients with and without CNS metastasis advocating for more studies incorporating patients with CNS disease in their inclusion criteria [NCT02910700].

The LEAP-004 phase II study of lenvtinib + pembrolizumab in previously treated metastatic melanoma showed activity in patients previously treated with PD-1/L1 inhibitor or combination with anti-CTLA-4 therapy.[39] Active MBM was excluded though 67% had M1c/M1d disease (NCT03776136). An ongoing phase II study is also evaluating pembrolizumab + bevacizumab in the treatment of asymptomatic CNS metastases in melanoma and NSCLC not requiring local therapy at time of enrollment (NCT02681549).

Combination with Radiation and Surgery—Multimodality Therapies

Combining radiation therapy and immunotherapy can result in an "abscopal" phenomenon, defined as regression of the tumor at sites distant from the target lesion receiving the radiation, which has been described in the brain and body.[40] Initially, case studies suggested potential improved anti-tumor effect of combining immunotherapy with SRS.[41] A retrospective review of 77 patients treated with definitive radiosurgery for melanoma brain metastasis showed increased median OS in those who had also received ipilimumab (n = 27) from 4.9 to 21.3 months.[42] Approximately 37% of these patients received ipilimumab prior to SRS and 63% received it after. No significant differences in sequencing SRS and immunotherapy had been noted in this study. Another retrospective study of 70 patients who received either WBRT or SRS were analyzed for those who did (n = 33) or did not (n = 37) also receive ipilimumab.[43] Average time between first dose of ipilimumab and radiation therapy was 23 weeks. This study found SRS and ipilimumab to be significant predictors of improved OS with the magnitude of benefit (of ~16 months

though small sample sizes were used) suggesting a possible synergism between SRS and ipilimumab.

Though the former study had adjusted for performance status, both of these retrospective studies are relatively small sample sizes subjected to selection bias toward patients with better performance status and perhaps more indolent course. Certain other retrospective analyses have shown no significant difference in adverse events such as hemorrhage or necrosis but without statistically significant differences in overall survival or disease control, though trends toward improved OS had been noted depending on timing of ipilimumab with SRS.[22] A more recent retrospective analyses of 1104 patients from the National Cancer Database where 192 patients had received radiation therapy and immunotherapy versus 912 who had received radiation therapy alone for MBM had shown a significant improvement in medial OS (11.1 months [95% CI 8.9–13.4] versus 6.2 months [95% CI 5.6–6.8]; *P* < .001) favoring combination therapy.[23] Taken together, these data warrant prospective trials of combination immunotherapy and radiation therapy to minimize selection bias in the evaluation of outcomes, and to evaluate effects of sequencing and timing of the combination. An appropriate concern has been the suggestion that the combination of immunotherapy and SRS can increase the incidence of radiation necrosis. While several studies independently demonstrated this association, they all remain retrospective, and given the many confounding factors, do not confirm conclusively this association.[24–26] There are several factors that can contribute to those findings, for instance, the fact that patients treated with both modalities could be surviving longer and therefore are at an increased risk of this form of delayed toxicity, or the fact that immunotherapy could exaggerate the inflammatory response to SRS and perhaps more so on imaging than in a necessarily symptomatic or clinically relevant phenomenon. In addition, one could argue that immunotherapy can reduce breast cancer CNS checkpoint inhibitors size and number of CNS lesions, which are 2 important predictors for the risk of radiation necrosis. Only prospectively collected and consistently analyzed data will be able to answer this difficult question. Indeed, several trials combining radiation therapy with immune checkpoint inhibitors (ABC-X; NCT03340129) or targeted therapy (concurrent dabrafenib/trametinib with SRS; NCT02974803) are currently ongoing.

A recent study from MGH addressed the issue of patients with symptomatic brain metastases that are requiring steroids, and therefore unlikely to benefit from immunotherapy. In those patients where the symptomatic lesions were surgically resectable, the approach was to utilize surgery as a bridge to immunotherapy and surgery was indeed at eliminating the need for steroids and rendering patients eligible for and more likely to benefit from combination immunotherapy.[27] This and other novel surgical approaches such as laser interstitial thermal therapy (LITT) could prove critical in symptomatic patients either as a bridge to or in combination with checkpoint inhibitors. This study clearly highlights the ability of multi-modality approaches to synergize and maximize the therapeutic benefit for patients with brain metastases.

Brain Metastases from Genitourinary Malignancies

Introduction

Among genitourinary (GU) malignancies, renal cell carcinoma (RCC) has the highest propensity to metastasize to the brain. According to one study, around 6.5% of brain metastases were from RCC, which is only third after lung primary (19.9%) and melanoma (6.9%).[28] The incidence of brain metastases from urothelial cancer (UC) has increased from 1% in pre-cisplatin era to 3-16% after the introduction of platinum-based chemo regimen.[29] Around 1%–2% of germ cell tumor (GCT) patients develop brain metastaes; however, the incidence soars to 10%–15% in patients with advanced stage GCT.[30] Prostate cancer is among the primary tumors with least tendency to spread to brain; in one retrospective analysis, 0.13% (18 of the 13,547) of patients with prostate adenocarcinoma developed brain metastases.[44] With the improvement in systemic treatment, the incidence of brain metastases from GU malignancies will be on the rise as patients will survive longer. The management strategies of brain metastases need to be improved to meet the clinical needs of this patient population.

Similar to other primary tumors, brain metastases from GU malignancies are usually treated with local therapies including surgery, stereotactic radiosurgery (SRS) and whole brain radiation WBRT). The role of systemic treatment remains to be defined despite ongoing and accelerating efforts. Here we will focus our discussion on the current status and new development in systemic treatment for brain mets from RCC, UC, and GCT.

Renal Cell Carcinoma

An increasing number of studies are investigating the role of systemic treatment in renal cell carcinoma patients with brain mets.

In the era of tyrosine kinase inhibitor(TKI), a few studies examined sunitinib and sorafenib without being conclusive as their intracranial acitiviy.[45] Cabozantinib is a potent TKI that targets MET, VEGFR2, AXL, approved by FDA as first-line treatment for metastatic RCC, and was associated with significant intracranial activity in a retrospective study.[46] In fact, a single-arm phase II CABRAMET trial is recruiting RCC patients with brain mets to assess the intracranial activity of cabozantinib, 77 patients will be accrued and treated with Cabozantinib 60 mg daily (NCT03967522). This trial will help to elucidate the potential role of cabozantinib in the treatment of RCC brain mets.

Apart from TKIs, immune checkpoint inhibitor (ICI) therapy has significantly improved the outcome of RCC patients. The updated analysis of checkmate-214 showed Nivolumab plus Ipilimumab (Nivo/Ipi) produced overall survival of 48.1 months and 15% improvement in survival compared to sunitinb. The ability of ICI to overcome blood brain barrier and its proven systemic activity has generated interest in exploring its potential role in RCC brain mets management. Notably, Nivoluamb and combination of nivo/ipi have been evaluated in patients with RCC

brain mets in prospective studies. The activity and safety of nivolumab was tested in GETUG-AFU 26 NIVOREN phase II trial, in which patients with RCC brain mets who progressed on TKI were enrolled. Patients without previous local therapy (cohort A) had 1 year overall survival rate of 66.7% (95% CI, 49.6–79.1%), patients with previous local therapy (cohort B) had 1 year overall survival rate of 58.8% (95% CI, 40.6–73.2%), Median intracranial PFS was 2.7 months (95% CI, 2.3–4.6 months) in cohort A and 4.8 months (95% CI, 3.0–8.0) in cohort B. The intracranial activity of nivolumab shown in this study was low, and only four patients with limited intracranial tumor burden (up to 10 mm) (12%) out of 34 had intracranial response. Of note, intracranial progression-free survival benefits was higher in patients with previous local treatment (cohort B).[47] Combination of Nivo/Ipi was assessed in CheckMate-920 study, 28 patients with brain mets received Nivo+ipi for 4 cycles followed by nivolumab every 4 weeks, at a follow-up of 6.47 months, grade 3-4 IMAEs within 100 days of last dose were reported in 6 cases, which is consistent with previous reports, overall response rate was 28.6% (95% CI 13.2–48.7). Median PFS in all treated subjects was 9.0 months (95% CI 2.9–not estimable [NE]). Median OS has not been reached (95% CI 13.1–NE). however, intracranial objective response data with imaging for Nivo/Ipi was not captured.[48] In phase III JAVELIN renal 101 trial, 23 patients with asymptomatic brain mets were enrolled on both Axitinib+Avelumab and sunitinib arms, patients on Axitinib+Avelumab arm had a PFS of 4.9 months (95% CI: 1.6, 5.7) versus 2.8 months (95% CI: 2.3, 5.6) for patients assigned to sunitinib (HR: 0.90; 95% CI: 0.43, 1.88), but CNS activity data on Axitnib+Avelumab or sunitinib are not available.[49]

Based on the findings from previous retrospective and prospective studies, there are not enough data to support use of TKIs or ICIs to treat RCC brain mets, however, more directed investigations can potentially assess the utility of combinatorial approaches.

Urothelial Cancer

Significant progress has been made in the treatment of urothelial cancer. In addition to cisplatin-based chemotherapy, ICIs, enfortumab and sacituzimab have been approved by FDA. As patients with brain mets from urothelial cancer were historically excluded from landmark trials, little is known about whether these agents have activity in brain mets from urothelial cancer. There were several trials that allowed urothelial cancer patients with brain mets. For example, IMvigor130 trial (testing atezolizumab in UC) and KEYNOTE-361 (Phase III trial for treatment-naive mUC with pembrolizumab +/–platinum-based chemotherapy and gemcitabine) enrolled patients with brain mets, but no data available on this patient population yet. Saul trial assessed Atezolizumab in patients with locally advanced, metastatic UC or Nonurothelial Carcinoma of the Urinary Tract. 14 out of 1004 patients with CNS mets were included in the study, median OS was significantly worse (3.7 months; range 1.5–7) compared to the whole cohort (8.7 months; range 7.7–9.9), no CNS efficacy data were reported from this trial.[50] Given the CNS efficacy of Nivo/Ipi in melanoma brain mets, clinical trials testing ICIs in urothelial cancer

brain mets should be conducted to address this important clinical question.

Germ Cell Tumor

In patients with brain mets from GCT, systemic treatment with chemotherapy appeared to be beneficial with intracranial response rate of 86%–100%. It was worth noting that patients with synchronous brain mets treated with chemotherapy had improved 3-year overall survival than patients with metachronous brain mets (34.2% vs 18.8%). A pooled analysis was conducted to examine the role of local therapies (surgery/radiation) in combination with chemotherapy, in patients with brain mets at diagnosis, treatment involving local therapies is associated with better 3-year OS (60.4% vs 34%, $P < .001$), however the benefits disappear after adjusting for prognostic group classification in multivariable analysis; for patients who develop brain mets after diagnosis, multimodality treatment including local treatment had improved 3-year overall survival (35.5% vs 14.1%, $P < .001$), this benefits remained significant in multivariate analysis while adjusting for after adjusting for prognostic group classification (HR, 0.52; 95% CI, 0.37–0.73; $P = .001$).[30] However, caution needs to be taken to interpret these data to make clinical decision as it was not from prospective studies. Future randomized studies enrolling GCT patients with brain mets are needed to delineate the exact role of chemotherapy, surgical resection, and radiation in overall management. However, given the fact that immunotherapy does not have proven efficacy, the question on the impact of immunotherapy of brain metastases derived from GCT is currently not relevant. Unfortunately, other than chemotherapy, there has been no new treatment approved for GCT for years. Research aiming to develop new treatment options is necessary to improve the poor outcome of GCT patients with brain mets.

Future Directions

Renal Cell Carcinoma with Brain Mets

The landscape of RCC management changed dramatically in recent years with new treatment regimen approved in frontline setting. These treatment regimens include nivo+ipi, axitinib plus pembrolizumab, Nivolumab plus Cabozantinib, and Avelumab plus Axitinib. Additionally, combination of Nivo+ipi+cabozantinib is being tested against Nivo+ipi in phase III COSMIC-313 trial in untreated metastatic RCC patients.

As these approved regimens demonstrated proven extra-cranial activities, it is logical to investigate their potential efficacy on brain mets. Cabozantinib in combination with nivo+ipi is one of the exciting regimens for several reasons. First, both cabozantinib and Nivo+ipi are FDA approved first-line treatment for metastatic RCC; second, both cabo and Nivo+Ipi could overcome blood–brain barrier to exert anti-tumor activity; third, Nivo+ipi has proven CNS efficacy in melanoma brain mets, and cabo is reported to have intracranial activity in patients with RCC brain mets. Another exciting regimen is Lenvatinib

plus Pembrolizumab, it was compared to Lenvatinib plus everolimus and sunitinib in a phase III trial in untreated metastatic RCC, Pembrolizumab Plus lenvatinib was associated the highest response rate of 71% and longest progression-free survival 23.9 months when compared with other regimens.[51] In a preclinical anaplastic thyroid carcinoma (ATC) brain mets mouse model, Lenvatinib was able to inhibit ATC tumor cell growth and reduce microvessel density in brain lesions.[52] Taking into account the high extracranial response rate of Lenvatinib plus pembrolizumab and ability of Lenvatinib to penetrate CNS, it is very likely this regimen could induce meaningful CNS response in RCC brain mets. Testing these regimens in RCC brain mets in prospective studies will potentially improve patient's clinical outcome and enhance our understanding of this difficult to treat RCC population.

Even though there are regimens with proven extracranial activity that can be tested in RCC brain mets patients, new targeting agent are needed because extracranial activity does not necessarily translate into intracranial activity. For example, in GETUG-AFU 26 NIVOREN phase II trial, the intracranial response rate (12%) of Nivolumab is lower than the extracranial response rate (21%). This discordance could be explained by the unique biology of brain mets. Tissue-derived biomarkers of brain mets reflecting the underlying biology are essential for development of new treatment. As most brain mets from RCC are treated with SRS/WBRT, and brain lesion biopsy is not practical, the traditional biological tissue is not readily available for biomarker analysis in most patients. Recent advances in cfDNA analysis in blood and cerebrospinal fluids could be used as alternative to tissue biopsy and facilitate the discovery of biomarkers in brain mets from RCC. However, there is significant concern regarding the concordance between cfDNA in blood and brain mets. However, the liquid biopsy using CSF could prove to be very useful in identifying new targets, assessing prognosis and monitoring treatment response for patients with RCC brain mets.

Preclinical mouse models are very useful for therapeutic development in human cancers. Among different mouse models, immunocompromised mice bearing human tumor samples (PDX models) can mimic human tumor accurately and be used as a valuable tool for therapeutic development and biomarker identification. Evidently, a renal cell carcinoma brain mets PDX model is definitely needed to guide research efforts and treatment decision in the future.

Urothelial Cancer Brain Mets

So far, brain mets from urothelial cancer are deemed to be a rare condition. With more systemic treatment options available for patients with metastatic UC, the occurrence of brain mets will increase as patients survive longer. Analysis including large number of patients with metastatic UC will be needed to determine incidence and clinical outcome of patients with brain mets. Better understanding of this clinical problem will lead to possible solution.

Systemic treatment options for metastatic urothelial cancer have evolved rapidly in recent years and now include cisplatin-based chemotherapy, Ertafitinib, anti-PD-1/L1 agents, Enfortumab, and Sacituzumab. The efficacy of cisplatin-based chemotherapy on brain mets is not clear due to exclusion of brain mets in pivotal trials; it might be worthwhile to examine the intracranial activity of cisplatin-based chemo alone or combined with anti-PD-1/L1 agents in bladder cancer patients. It is not clear if enfortumab and Ertafitinib can penetrate CNS and confer anti-tumor activity; further study will be helpful to address this question. Sacituzumab Govitecan has shown encouraging results in brain metastases from breast cancer;[53] it could be a promising therapeutic agent for patients with brain mets from urothelial cancer.

Brain mets from bladder cancer is an uncharted territory that requires further studies to identify targets for treatment and biomarkers for prognosis, molecular profiling of the tumor, and analysis of cfDNA in blood and CSF will help a great deal in filling this knowledge gap. A urothelial cancer brain mets PDX model could provide valuable data and set right direction for ongoing research on the role of systemic treatment in urothelial cancer brain mets.

In summary, the advances in systemic treatment for GU malignancies rendered great opportunity to explore the role of systemic agents in management of brain mets from GU malignancies and improve patient's outcome. However, prospective studies should allow the inclusion of patients with brain mets from GU malignancies as per the recent FDA recommendations, which will allow a more efficient assessment of the role of novel therapies and combinations in this population. Furthermore, studies to unravel the molecular mechanism governing the development of brain mets derived from GU malignancies should be encouraged to identify relevant immune and signaling pathways as potential therapeutic targets that could lead to the prevention of brain mets.

Conclusions

Great strides have been made in the treatment of brain metastases over the past decades. Further improvements in patient outcomes are expected with our improved understanding into the complexities of the blood–brain and blood–tumor barrier thereby enabling application of extracranial systemic therapeutic strategies such as immune checkpoint inhibitors, as well as targeted therapies, ideally with improved intracranial penetrance. Additional improvements into our understanding of the genetic differences as well as the differences in the immune microenvironment of intracranial versus extracranial melanoma metastasis may lead to novel immunotherapeutic strategies for systemic control of intracranial disease. More and more focus is shifting to multimodality therapy with combination of targeted, immunotherapy and/or radiation therapies to improve disease control and long-term outcomes. As well, strides to improve local therapies in order to minimize neurocognitive decline should also be an important consideration in the treatment of CNS metastasis. To that end, development of dedicated brain metastasis clinics to streamline patient care is being implemented across several dedicated cancer centers including M.D. Anderson Cancer Center. In these dedicated clinics, patients meet

with neurosurgery, medical oncology, radiation oncology, and neuro-oncology consultants during the same visit allowing for a multidisciplinary evaluation and coordination of optimal patient care in an efficient manner. This patient-centered approach has been met with high patient and physician satisfaction and approximately 1 in 5 patients were found to have a major change in their treatment plan after the multidisciplinary clinic. Success of such models demonstrates the effectiveness and feasibility of a centralized approach in the treatment of this complex patient population.

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