Melanoma brain metastases immunotherapy

- Novel fusion superkine, IL-24S/IL-15, enhances immunotherapy of brain cancer
- Management outcomes for biopsy-proven radiation necrosis in patients with brain metastases in the era of immune-checkpoint blockade
- T lymphocyte heterogeneity in NSCLC: implications for biomarker development and therapeutic innovation
- Combined immunotherapy with nivolumab and ipilimumab with and without sequential or concomitant stereotactic radiotherapy in patients with melanoma brain metastasis: An international retrospective study
- The Effect of Concomitant Immunotherapy and Stereotactic Radiotherapy, and of Location on Survival in Patients With Brain Metastases From Melanoma
- A population-level real-world analysis and single-center validation of melanoma brain metastasis epidemiology following dual-agent immunotherapy
- Re-resection of brain metastases - outcomes of an institutional cohort study and literature review
- New Standards in the Treatment of Advanced Metastatic Melanoma: Immunotherapy and BRAF-Targeted Therapies as Emerging Paradigms

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a) ipilimumab (Yervoy®): monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4) antigen. More effective in patients who do not require corticosteroids.

b) interleukin-2 (IL-2): has shown minimal activity in brain mets, and trials have usually excluded patients with untreated or uncontrolled brain mets due to risk of cerebral edema and hemorrhage from capillary leak [1) 2) 3)]

3. BRAF inhibitors (BRAFi): inhibits BRAF kinase (a protein that participates in the regulation of cell division & differentiation), useful in tumors with BRAF oncogene mutation (as opposed to BRAF wildtype) which is common in melanoma

a) dabrafenib:phase II trial (NCT01266967)

b) vemurafenib: promising results in heavily treated patients.Phase II trial(NCT01378975)

4. anti-PD-1 drug (monoclonal antibody to PD-1 programmed cell death receptor): pembrolizumab (Keytruda) approved for advanced or unresectable melanoma not responding to other drugs [4)].

The use of these new treatment modalities, which include immune checkpoint inhibitors and small molecule BRAF inhibitors, lead to increased overall survival and better outcomes. Although revolutionary, these therapies are often less effective against melanoma brain metastases, and frequently the CNS is the major site of treatment failure. The development of brain metastases remains a serious complication of advanced melanoma that is associated with significant morbidity and mortality. New approaches to both prevent the development of brain metastases and treat established disease are urgently needed [5)].

Novel therapeutic agents such as immunotherapy (IMT) consisting of anti-CTLA-4 and/or anti-PD-1 therapy and targeted agents, consisting of BRAF and MEK inhibitors, have been shown to improve overall survival (OS) in patients with advanced melanoma, shifting the treatment paradigm away from conventional chemotherapy [6) 7) 8) 9)].

Over time, acquired resistance to these modalities inexorably develops, providing new challenges to overcome [10)].

Systematic reviews

Twenty-two studies were included for a total of 2153 patients. Median OS was 7.9months in phase I-II-III trials and 7.7months in “real world” studies. In clinical trials, median OS was 7.0months for patients treated with immunotherapy and 7.9months for patients treated with BRAF inhibitors. In “real world” studies, median OS was 4.3months and 7.7months for patients treated with immunotherapy and BRAF inhibitors, respectively. Evidence of clinical activity exists for both immunotherapy and Mitogen activated protein kinase.

MAP-kinase inhibitors and immunologic checkpoint blockade antibodies have clinical activity and may achieve improved OS in patients with metastatic melanoma and BM. These results support the inclusion of patients with BM in investigations of new agents and new treatment regimens for metastatic melanoma [11)].

Case series

2017

A total of 72 patients with melanoma with 233 MBMs were treated between April 2006 and April 2016. The number of MBMs within each treatment group was as follows: SRS: 121; SRS + IMT: 48; and SRS + targeted therapy: 64. The median follow-up was 8.9 months. One-year distant intracranial control rates for SRS, SRS + IMT, and SRS + targeted therapy were 11.5%, 60%, and 10%, respectively (P < .001). On multivariate analysis, after adjusting for steroid use and number of MBMs, SRS + IMT remained associated with a significant reduction in distant intracranial failure compared with SRS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.29-0.80; P = .003) and compared with SRS + targeted therapy (HR, 0.41; 95% CI, 0.25-0.68; P = .001).One-year local control for SRS, SRS + IMT, and SRS + targeted therapy was 66%, 85%, and 72%, respectively (P = .044). On multivariate analysis, after adjusting for dose, SRS + IMT remained associated with a significant reduction in local failure compared with SRS alone (HR, 0.37; 95% CI, 0.14-0.95; P = .04).

CONCLUSIONS: SRS with immunotherapy is associated with decreased distant and local intracranial failure compared with SRS alone. Prospective studies are warranted to validate this result [12)].

2016

A single institution, retrospective cohort of 225 melanoma patients was analyzed to determine if

BRAF-V600 mutational status was associated with brain metastasis. Eighty-three of the 225 patients (37%) had BRAF-V600 mutations. At initial diagnosis, BRAF-V600 mutations were associated with younger age ($P \leq 0.001$), higher proportion of females ($P = 0.0037$), higher AJCC stage ($P = 0.030$), regional lymph node involvement ($P = 0.047$), and family history of cancer ($P = 0.044$). Compared to BRAF-WT, BRAF-V600 patients had an increased risk of brain metastasis in multivariate analysis (OR = 2.24; 95% CL = 1.10-4.58; $P = 0.027$). However, BRAF-V600 patients treated with a selective BRAF inhibitor (BRAFi) had a similar risk of brain metastasis compared to BRAF-WT patients (OR = 1.00; 95% CL = 0.37-2.65; $P = 0.98$). Moreover, treatment with BRAFi significantly prolonged the time from initial diagnosis to brain metastasis diagnosis (HR = 0.30; 95% CL = 0.11-0.79; $P = 0.015$). Compared to other tissues, the brain was the most frequent site of metastasis in BRAF-V600 patients without BRAFi (42±7%). The frequency of brain metastasis was lower in BRAF-WT and BRAF-V600 patients with BRAFi (25±4% and 25±8%, respectively). The proportion of patients with brain metastasis as the only site was 40%, 60%, and 0% in the BRAF-WT, BRAF-V600 without BRAFi, and BRAF-V600 with BRAFi groups, respectively. This study provides evidence on the clinical importance of BRAF-V600 mutations and BRAF inhibition in the progression to melanoma brain metastasis [13].

2015

In patients with large or symptomatic brain lesions from metastatic melanoma, the value of resection of metastases to facilitate administration of systemic ipilimumab therapy has not yet been described.

Jones et al. undertook this study to investigate whether craniotomy creates the opportunity for patients to receive and benefit from ipilimumab who would otherwise succumb to brain metastasis prior to the onset of regression.

All patients with metastatic melanoma who received ipilimumab and underwent craniotomy for metastasis resection between 2008 and 2014 at the Massachusetts General Hospital were identified through retrospective chart review. The final analysis included cases involving patients who underwent craniotomy within 3 months prior to initiation of therapy or up to 6 months after cessation of ipilimumab administration.

Twelve patients met the inclusion criteria based on timing of therapy (median age 59.2). The median number of metastases at the time of craniotomy was 2. The median number of ipilimumab doses received was 4. Eleven of 12 courses of ipilimumab were stopped for disease progression, and 1 was stopped for treatment-induced colitis. Eight of 12 patients had improvement in their performance status following craniotomy. Of the 6 patients requiring corticosteroids prior to craniotomy, 3 tolerated corticosteroid dose reduction after surgery. Ten of 12 patients had died by the time of data collection, with 1 patient lost to follow-up. The median survival after the start of ipilimumab treatment was 7 months.

In this series, patients who underwent resection of brain metastases in temporal proximity to receiving ipilimumab had qualitatively improved performance status following surgery in most cases. Surgery facilitated corticosteroid reduction in select patients. Larger analyses are required to better understand possible synergies between craniotomy for melanoma metastases and ipilimumab treatment [14].

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