Treatment of Brain Metastases

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Brain metastases are the most common brain tumor and frequently originate from primary lung cancer, breast cancer, and melanoma. Brain metastases account for a disproportionately high percentage of morbidity and mortality among patients with cancer, with dismal 2- and 5-year survival rates of 8.1 and 2.4% after diagnosis. There are an estimated 200,000 new brain metastases diagnoses per year, and this number is projected to increase as systemic treatment modalities and imaging techniques improve. Despite the increasing prevalence of brain metastases, there are limited treatment options. While radiotherapy (RT) is a mainstay to treat brain metastases, systemic therapies have historically demonstrated limited ability to penetrate the blood–brain barrier (BBB). Immune checkpoint inhibitors (ICIs) have emerged as a promising treatment option for patients with brain metastases.

brain metastases radiotherapy radiation therapy

1. Brain Metastases Treatment Management

1.1. Local Therapy

Historically, local therapies such as radiotherapy (RT) and surgery played a key role in the management of brain metastases treatment. The seminal case series by Chao et al. was the first report describing the palliative benefit of WBRT for brain metastases [1]. Patchell et al. reported that the addition of surgery to WBRT improved local control (LC) and median overall survival (OS) [2]. Then in 1998, Patchell et al. reported that WBRT after surgery reduced recurrence and neurologic death compared with observation [3]. Despite the advantages of WBRT, treatment is associated with short- and long-term neurologic complications (e.g., leukoencephalopathy, cognitive decline) [4]. The concerns related to WBRT-induced toxicity led neuro-oncologists to seek alternative treatment strategies for brain metastases. More recently, stereotactic radiosurgery (SRS) has emerged as a more precise radiation modality that spares healthy brain tissue [5].

Chang et al. reported that patients treated with SRS alone experienced better neurocognitive outcomes than patients who received SRS plus WBRT [6]. In 2014, Yamamoto et al. conducted a prospective randomized trial to determine if patients receiving SRS with 5 to 10 brain metastases had non-inferior survival outcomes to patients with 2 to 4 brain metastases [7]. Median OS for patients with 2 to 4 lesions was equivalent to median OS for patients with 5 to 10 lesions (10.8 months in both arms), suggesting SRS may be an appropriate alternative to

WBRT in patients with up to 10 brain metastases. In 2017, the NCCTG N107C/CEC·3 phase III trial compared outcomes of post-operative SRS with post-operative WBRT in patients with brain metastases [8]. This research found no difference in OS but worsened cognitive decline in the WBRT treatment group at 6 months (85% vs. 52%). Although there was not a significant survival difference between the two groups, local and distant brain control was worse in the SRS group. These findings suggested that patients with one to three brain metastases may experience durable local control with SRS and that SRS is a viable alternative to WBRT. NCCTG N0574 compared outcomes between patients with one to three brain metastases randomized to SRS plus WBRT or SRS alone [9]. The authors found the addition of WBRT led to a decline in immediate recall (31% vs. 8%), delayed recall (51% vs. 20%), and verbal fluency (19% vs. 2%). Although WBRT did not improve OS, there was greater intracranial tumor control at 12 months in the SRS plus WBRT arm (84.9% vs. 50.5%). Subsequently, the JCOG0504 phase III non-inferiority trial studied whether SRS alone was as effective as WBRT or WBRT plus SRS [10]. Although intracranial progression-free survival was longer in the WBRT arm, the median OS in both arms were equivalent (15.6 months). Furthermore, the Mini-Mental Status Examination (MMSE) score decline between the two groups was not significant, but grade 2 to 4 adverse events were higher in the WBRT arm. These findings suggested that SRS can be considered standard therapy for patients with four or fewer brain metastases.

Recognizing the toxicities associated with WBRT, research groups developed techniques to limit irradiation to the hippocampal dentate gyri and hypothesized that preserving the neural stem cells may prevent WBRT-induced cognitive toxicity [11][12]. In 2020, Brown et al. published a phase III trial (NRG Oncology CC001) comparing cognitive decline and survival outcomes in patients receiving hippocampal avoidance (HA) WBRT plus memantine or WBRT plus memantine [13]. The authors found that HA-WBRT plus memantine resulted in less executive function and learning/memory deterioration with no significant difference in intracranial PFS and OS. Based on these findings, patients with brain metastases planned for WBRT may benefit from HA-WBRT if there are no metastases in the hippocampal avoidance region.

1.2. Systemic Therapy

Common chemotherapies (e.g., cisplatin and paclitaxel) have been evaluated in clinical trials but have failed to demonstrate a significant benefit in patients with brain metastases [14][15][16]. Researchers have found that the BBB, efflux pumps, and the blood–tumor barrier may prevent the cytotoxic agents from reaching effective concentrations [17]. More recently, neuro-oncologists were able to identify molecular drivers for a variety of primary cancers that have a propensity of spreading to the brain (e.g., lung cancer, breast cancer, and melanoma). Understanding these key signaling pathways has led to the development of novel targeted treatments such as tyrosine kinase inhibitors (TKIs) and immune-related therapy that have demonstrated intracranial efficacy, especially in patients with asymptomatic brain metastases [18]. The successful utilization of systemic therapy will be discussed in greater detail below.

2. Immunotherapy in the Treatment of Brain Metastases

Despite the success of ICIs across various tumor types, patients with brain metastases have been excluded from ICI trials due to a limited CNS penetration and poor prognosis [19]. The central nervous system (CNS) was thought to be an immune-privileged site, but brain metastases were found to be surrounded by an inflammatory microenvironment, suggesting otherwise [20][21]. Previously, monoclonal antibodies were thought to be too large to cross the BBB, but some studies reported ICI efficacy in treating brain metastases [22]. This observed activity may be related to (1) leaky tumor neo-vessels and (2) anti-tumor T cells that may be primed and activated at extracerebral sites. Notable studies exploring the efficacy of ICI agents will be emphasized in this section.

2.1. Lung Cancer Brain Metastases

Lung cancer is the most common cause of brain metastases and is categorized as small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). This section will focus primarily on NSCLC studies.

Patients with NSCLC that have failed first-line treatment have historically had limited treatment options. In the search for effective therapies, researchers were interested in targeting the programmed death 1 (PD-1) receptor that is expressed on activated T cells. The PD-1 receptor engages with ligands PD-L1 and PD-L2, which are expressed by cancer cells [23]. This interaction inhibits T-cell activation, thus allowing tumor cells to escape immune system recognition [24].

Nivolumab is an IgG4 PD-1 ICI antibody that inhibits PD-1 signaling, therefore restoring anti-tumor immunity [25]. Phase I and II trials utilizing nivolumab in patients with NSCLC demonstrated an increased median OS [26][27]. A subsequent phase III study by Brahmer et al. found that the OS was greater with nivolumab versus docetaxel (9.2 vs. 6.0 months). The authors reported PD-L1 expression was not a predictor of ICI efficacy, but subsequent studies demonstrated the importance of PD-L1 expression [28][29][30]. A study by Borghaei et al. compared nivolumab and docetaxel in NSCLC patients and also found improved OS in the nivolumab arm (12.2 vs. 9.4 months) [31]. The CheckMate 227 phase III trial found nivolumab plus ipilimumab led to an increased OS compared to chemotherapy in patients with NSCLC, although this trial excluded patients with untreated or symptomatic central nervous system metastases [32].

Pembrolizumab is another PD-1 inhibitor that has been used to treat advanced NSCLC. A phase II trial that evaluated pembrolizumab in patients with NSCLC or melanoma with untreated brain metastases found with at least 1% PD-L1 expression demonstrated a 29.7% brain metastases response [33]. Other studies found pembrolizumab plus pemetrexed–platinum [34] and atezolizumab plus carboplatin and etoposide [35] resulted in an improved OS and PFS in metastatic lung cancer. A recent systematic review found anti-PD-1 therapy had an intracerebral overall response rate of 16.4% with acceptable toxicity rates [36]. Hu et al. conducted a meta-analysis that assessed the impact that the status of brain metastases had on immunotherapy efficacy in lung cancer patients [37]. In this study, the authors reported that the utilization of immunotherapy resulted in a survival advantage in patients with brain metastases (OS hazard ratio, 0.72; PFS hazard ratio, 0.68). Notably, there was not a statistically significant survival advantage difference between brain metastases and non-brain-metastases patients; this finding suggested that immunotherapy benefits lung cancer patients regardless of the status of brain metastases.

2.2. Breast Cancer Brain Metastases

Breast cancer is the second-leading precursor to brain metastases. To date, numerous chemotherapies have demonstrated the ability to reduce the tumor size in breast cancer brain metastases [38], but SRS is typically the first-line treatment. Historically, endocrine-modulating therapies have been used to treat breast cancer (e.g., tamoxifen) but have failed to provide benefit for CNS metastases [39]. Other agents such as lapatinib [40][41] and abemaciclib [42][43] have yielded encouraging results, but further studies are needed to confirm the benefit of systemic therapy [44].

The discovery of HER-2/neu (a receptor tyrosine–protein kinase) led to the development of the monoclonal antibody trastuzumab, which has become an essential part of breast cancer management [45]. Although trastuzumab failed to have a significant effect on brain metastases, the antibody–drug conjugate trastuzumab–emtansine (T-DM1) [46] has demonstrated promising CNS penetrance in case series and small cohort studies [47][48][49][50]. The HER2CLIMB trial investigated the benefit of tucatinib, which is an oral, selective HER2 TKI [51]. In this study, patients with HER2-positive metastatic breast cancer who were previously treated with trastuzumab, pertruzumab, and trastuzumab emtasine were included. The patients were randomly assigned to receive either tucatinib or placebo in combination with trastuzumab and capectiabine. PFS at 1 year (33.1% vs. 12.3%) and OS at 2 years (44.9% vs. 26.6%) were significantly greater in the tucatinib group versus the placebo group. These findings suggested tucatinib plus trastuzumab and capectiabine may be beneficial for heavily pretreated HER2-positive metastatic breast cancer patients.

The ASCENT phase III trial compared sacituzumab govitecan with single-agent chemotherapy agents in patients with metastatic triple-negative breast cancer [52]. Sacituzumab govitecan is an antibody that targets Trop-2 conjugated to SN-38, a topoisomerase I inhibitor. The antibody–drug conjugate resulted in an improved median PFS (5.6 vs. 1.7 months) and OS (12.1 vs. 6.7 months) compared to the chemotherapy arm. The KEYNOTE-355 phase III trial compared pembrolizumab plus chemotherapy with placebo plus chemotherapy in patients with metastatic triple-negative breast cancer [53]. Patients that received pembrolizumab–chemotherapy with a combined positive score (number of PD-L1-positive cells divided by total number of tumor cells × 100) of ≥10 had a significantly improved PFS (9.7 vs. 5.6 months). Although patients with stable brain metastases were included in this study, patients with active central nervous system metastases were excluded.

Recently, the IMpassion130 phase III trial evaluated atezolizumab (PD-L1 monoclonal antibody) plus nab-paclitaxel in patients with locally advanced or metastatic triple-negative breast cancer [54]. Although there was no significant OS difference between the atezolizumab and placebo groups, there was a median survival benefit for patients with PD-L1 immune-cell-positive tumors (25.0 vs. 18.0 months). This finding suggested that routine testing for PD-L1 expression in patients with unresectable, metastatic triple-negative breast cancer may aid in identifying patients who may benefit from atezolizumab plus nab-paclitaxel. IMpassion 130 did not include patients with brain metastases, but a phase II study (NCT03483012) is examining the combination of atezolizumab and SRS for patients with triple-negative breast cancer that has spread the brain.

2.3. Melanoma Brain Metastases

Melanoma is the third most common cause of brain metastases [55]. Agents targeting BRAF and MEK have demonstrated efficacy, but primarily in patients with BRAF mutations (e.g., BRAFV600E, BRAFV600) [56]. The BREAK-MB trial evaluated dabrafenib in melanoma patients with brain metastases and found most asymptomatic patients with BRAF600E mutations exhibited an intracranial response [57].

Melanoma frequently metastasizes to the brain and is particularly resistant to RT and chemotherapy agents [58]. Previously, temozolomide was a common systemic therapy for melanoma patients with brain metastases, but temozolomide has limited CNS penetrance, with approximately 10% of patients experiencing an intracranial response [59]. Prospective phase II studies have evaluated the utility of ICIs in melanoma brain metastases [58][60][61]. In a phase II study, ipilimumab, a CTLA-4 antibody, demonstrated dose-dependent efficacy in advanced melanoma patients [62]. Tawbi et al. conducted a phase II trial including melanoma patients with untreated brain metastases receiving a combination of nivolumab and ipilimumab [63]. Rates of intracranial and extracranial clinical benefit (minimum six months of follow-up) were 57% and 56%, respectively. Grade 3 or 4 adverse events were reported in 55% of patients, but the safety profile was similar to melanoma patients without brain metastases. A phase II study by Long et al. enrolled patients with active melanoma brain metastases and found patients who received ipilimumab plus nivolumab had a durable response [64].

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