Leptomeningeal Disease Treatment

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Leptomeningeal disease (LMD) is a devastating complication caused by seeding malignant cells to the cerebrospinal fluid (CSF) and the leptomeningeal membrane. LMD is diagnosed in 5–15% of patients with systemic malignancy. Management of LMD is challenging due to the biological and metabolic tumor microenvironment of LMD being largely unknown. Patients with LMD can present with a wide variety of signs and/or symptoms that could be multifocal and include headache, nausea, vomiting, diplopia, and weakness, among others. The median survival time for patients with LMD is measured in weeks and up to 3–6 months with aggressive management, and death usually occurs due to progressive neurologic dysfunction. In melanoma, LMD is associated with a suppressive immune microenvironment characterized by a high number of apoptotic and exhausted $CD4^+$ T-cells, myeloid-derived suppressor cells, and a low number of $CD8^+$ T-cells. Proteomics analysis revealed enrichment of complement cascade, which may disrupt the blood–CSF barrier. Clinical management of melanoma LMD consists primarily of radiation therapy, BRAF/MEK inhibitors as targeted therapy, and immunotherapy with anti-PD-1, anti-CTLA-4, and anti-LAG-3 immune checkpoint inhibitors.

Treatment leptomeningeal disease melanoma

1. Introduction

Leptomeningeal disease (LMD, also known as leptomeningeal carcinomatosis or carcinomatous meningitis) is the spread of cancer to the meninges surrounding the brain and the spinal cord [1]. LMD is a rare and devastating complication seen in melanoma and other advanced cancers. Patients with LMD usually have a grave prognosis, with a median survival rate ranging from weeks to a few months [2]. LMD is a challenging neuro-oncological disease for scientific researchers and clinicians as the diagnosis can be complex and effective treatments are lacking.

Malignant melanoma is the third most common solid tumor that metastasizes to the central nervous system (CNS) after lung and breast cancer [3]. Advanced melanoma is the most lethal type of skin cancer, resulting from malignantly transformed melanocytes with a high metastatic potential to migrate to different tissues, including the leptomeninges. Moreover, primary CNS melanoma can occur at the leptomeninges, which a rare but aggressive subtype of melanoma [4]. LMD is usually reported in 5% of patients with melanoma, 3–5% of patients with non-small cell lung cancer, and 10–25% of patients with breast cancer [5][6][7]. In particular, LMD from melanoma (LMM) portends an abysmal prognosis, with a mean overall survival (OS) of 3.5 months, even with aggressive treatment [8]. Retrospective studies have reported concomitant brain metastasis in 60–85% of LMM cases [9][10][11][12].

Melanoma is the 5th most common type of cancer in the United States and the 19th worldwide [13][14]. In 2020, the WHO reported 324,635 new melanoma cases and 57,043 deaths from this disease worldwide. The melanoma burden is estimated to increase to 510,000 new total cases and 96,000 deaths by 2040. Thus, the incidence of LMM is predicted to increase due to advanced treatment options for systemic disease and improved patient survival [15].

2. Radiation Therapy

Whole brain radiation therapy (WBRT) +/− focal radiation therapy (RT) to the spine to symptomatic areas is the most common approach) [16]. WBRT has shown improved survival in LMD patients with primary lung cancer [17][18]. In some LMM patients, WBRT combined with systemic therapy has shown improved survival, potentially due to managing patients' neurological symptoms [19][20]. However, WBRT as sole therapy did not significantly impact LMM patients [8][11]. Focal radiation treats symptomatic and nodular areas and mitigates CSF blockage areas in patients [2]. RT is a beneficial palliative treatment, especially in patients suffering from pain and/or obstructive hydrocephalus. Photon craniospinal irradiation (CSI) in LMD from solid malignancies has unfavorable side effects (i.e., bone marrow suppression and gastrointestinal toxicities) [21]. Proton CSI has less exit radiation, sparing anterior structures to the spinal canal. A phase 1 study of hypofractionated proton CSI in 24 patients with LMD from solid tumors resulted in a lower toxicity rate than historical photon CSI [21]. Four patients (19%) achieved CNS control for more than 12 months [21]. A recent phase II clinical trial reported that proton CSI significantly surpasses photon CSI in progression-free and overall survival (OS). The primary cohort recruited with LMD was mainly with breast and NSCLC, but six patients with LMM were also included (NCT04343573) [22]. Nevertheless, the restricted availability of proton CSI impedes its widespread application.

3. Systemic Therapy

Another option to treat LMD is systemic therapy, which can help control other disease sites and potentially prolong patient survival [23]. Depending on the driver mutation, cutaneous melanoma is classified into four genomic subtypes: BRAF-mutant, *RAS*-mutant, *NF*-loss, and triple wild-type [24]. Alteration in BRAF, NRAS, and NF1 causes activation in MAPK pathway, which activates uncontrolled cell proliferation [25]. Almost 60% of cutaneous melanoma patients have a BRAF driver mutation (most commonly V600E), which is targetable with an inhibitor of BRAF [26]. The first BRAF inhibitor approved by the FDA in 2011 (vemurafenib) significantly improved patient outcomes [27][28]. However, melanoma frequently develops drug resistance through the re-activation of MEK [29]. Thus, combining a MEK inhibitor with an inhibitor of BRAF is now the standard of care targeted therapy for BRAF-mutated metastatic melanoma [30][31][32]. Sakji-Dupré et al. have shown in a small cohort that there is a low penetration rate of BRAF inhibitor vemurafenib to the CSF, with a highly variable rate between patients [33]. However, some case reports have described improvements in LMM with BRAF/MEK inhibitor therapy [34][35] or in combination with RT [20][36][37].

During the last decade, there have been tremendous advancements in immunotherapy for treating late-stage cancer patients, particularly melanoma, renal cell carcinoma, leukemia, and lymphoma [38][39][40]. Immune checkpoint inhibitors (ICI) have revolutionized the era of cancer immunotherapy [41][42]. ICIs target regulatory pathways on T lymphocytes, enhancing the anti-tumor immune response [41]. ICI, including anti-PD-1 (nivolumab), anti-CTLA-4 (Ipilimumab), and anti-LAG-3 (relatlimab), are now FDA-approved for the treatment of unresectable or metastatic melanoma [43][44][45]. Unfortunately, many clinical trials have excluded patients with LMM due to their poor prognosis [45][46][47][48]. There is a critical need to develop trials that are more inclusive of patients with LMM.

Promising results from utilizing immunotherapy in metastatic melanoma treatment have encouraged researchers to explore the efficiency of immunotherapy for LMM patients [8][12][49][50]. Few retrospective studies have been conducted to evaluate immunotherapy's efficacy on LMM patient outcomes due to the novelty of FDA approval for metastatic melanoma immunotherapy [8][12][49][50]. Interestingly, Tétu et al. have reported improved survival of five LMM patients with concomitant brain metastasis (out of 27 LMM patients) who received anti-PD-1 +/− CTLA-4 combined with radiotherapy. Those five patients had a median follow-up of 47.4 months with a complete persistent response. The remaining population's median OS was 5.1 months [12]. Tétu et al.'s study included a total of 27 LMM patients with systemic therapy, 17 patients with immunotherapy, five patients with targeted therapy, one with chemotherapy, and four with combined therapy of anti-PD1 and a BRAF inhibitor [12]. Radiotherapy was combined with systemic treatments in nine LMM patients (31%), which included either stereotactic radiosurgery (7 patients) or WBRT (2 patients) [12].

Furthermore, an earlier study was performed on 178 LMM patients who received at least one treatment for LMM, either via radiation, systemic (chemotherapy, targeted therapy, immunotherapy), or intrathecal therapy [8]. The median OS for patients who received immunotherapy was 2.9 months, targeted therapy was 8.2 months, and radiation therapy was 4.6 months [8]. In addition, several case reports of improved survival with immunotherapy in LMM patients have been reported. A recent case report demonstrated six years of survival for a male patient diagnosed with LMM after stage IV BRAF-positive cutaneous melanoma [51]. The patient had received targeted therapy and immunotherapy systematically, in addition to intrathecal methotrexate [51]. A similar study has reported more than two years of LMM remission in a BRAF-positive melanoma patient treated with anti-PD-1 immunotherapy and radiotherapy [52]. These reports shed light on the advanced multidisciplinary treatment regimens that may improve patient outcomes and prolong their cancer-free survival. Nevertheless, ICI has been associated with various immune-related adverse effects such as arthritis, aseptic meningitis, encephalitis, and myelitis [53][54][55]. However, some of these adverse effects were manageable with corticosteroids [54][55].

Further studies are needed to uncover the factors impacting the variable response among LMM patients who received immunotherapy.

4. Intrathecal (IT) Therapy

LMD patients with normal CSF flow, as demonstrated in their neuroimaging, may benefit from IT chemotherapy as the treatment is equally distributed within the CSF compartment. However, patients with obstructed CSF flow will

have the worst prognosis, and IT therapy may be ineffective, with an increased risk of developing neurotoxicity as a higher dose of the medication will be pooled proximally to the flow obstruction site [56]. Neurotoxicity from IT therapy could result from various factors, including the therapy's type, dose, and administration route. It has been reported that frequent administration of IT via lumbar puncture can cause cord or nerve damage [57]. Furthermore, patients receiving IT therapy via the Ommaya reservoir may be subjected to aseptic or chemical meningitis (*Staphylococcus epidermidis*), leukoencephalopathy, seizures, and myelopathy [57][58].

Methotrexate, arabinofuranosyl cytidine (Ara-C), liposomal Ara-C (DepoCyt), and thiotepa are the main reported controlled trials for IT therapy. Ara-C is an antimetabolic agent which is activated intracellularly to cytarabine-5′-triphosphate. It is then incorporated into DNA during DNA synthesis, resulting in cell cycle arrest [59]. To reduce cytidine neurotoxicity, liposomal Ara-C (DepoCyt) has been alternatively used to treat leptomeningeal metastasis [60]. DepoCyt is developed through the encapsulation of cytarabine in biodegradable nano-lipid-based particles, with a gradual drug release with extended exposure in the CSF [60]. IT administration of dexamethasone with DepoCyt is necessary to reduce neurotoxic side effects. A clinical study used triple intrathecal therapy Methotrexate (12.5 mg), Cytarabine (50 mg then reduced to 15 or 25 mg) + Prednisolone (40 mg) as a prophylactic approach against leptomeningeal metastasis in patients with acute lymphoblastic leukemia [61].

In addition to chemotherapy, IT administration of immunotherapies such as IL2 and anti-PD-1 has been adopted in LMM treatment. A retrospective study on 43 patients with LMM has reported that IT administration of interleukin-2 (IL-2, important cytokines for T lymphocyte proliferation) extended the survival of these patients (median OS was 7.8 months) [62]. The range for patient survival was between 0.4 to 90.8 months which is a vast range, raising many questions regarding the patients' tumor-immune microenvironment. This has reported some toxicities associated with the IT administration of IL-2, including fever, chills, and symptoms of high intracranial pressure (headache and nausea) [62]. Currently, a dose escalation trial is ongoing, studying the concurrent administration of anti-PD-1 immunotherapy (nivolumab) intrathecally with different doses on day one, and intravenously (240 mg) on day 2 (NCT03025256) [50]. The initial results from this showed that IT administration of 20 mg nivolumab was a safe and efficient dose in LMM patient's treatment. This collects CSF from LMM patients to measure CSF pharmacokinetics. CSF pharmacokinetics after either IT or systemic therapy is highly understudied in Leptomeningeal disease. In addition to CSF pharmacodynamics, studying the CSF immune profile of patients under immunotherapy is crucial for evaluating the immune system's response and immunotherapy's efficacy. A significant alteration in the CSF immune profile of LMM patients receiving targeted or immunotherapy was previously shown in [63]. The safety and efficiency of IT administration of ICI has also been reported in patients with relapsed primary CNS, encouraging the potential therapeutic impact of ICI intrathecally [64]. On the other hand, immune-mediated colitis has been reported in one patient during IT nivolumab to treat metastatic brain melanoma. However, it was unclear whether the colitis resulted from tocilizumab (anti-IL-6) administration or IT nivolumab [55].

Overall, there is an urgent need to collect CSF from cancer patients who have the propensity to metastasize to the CNS region before and after systemic therapy (either targeted or immunotherapy) to evaluate its pharmacokinetics within the CNS. Furthermore, there is a great need for additional preclinical studies to identify superior therapeutic approaches for LMM patients. A preclinical in vivo patient-derived xenograft model for LMM has been generated by

injecting patients' CTC intrathecally in mice, which could be a relevant model to assess the novel therapeutic targets' effectiveness [65]. A murine Ommaya reservoir has been developed and could be leveraged for studying novel intrathecal therapies [65].

5. Response to Treatment

The ESMO-EANO LMD guidelines categorize eight LMD subtypes to guide treatment: I or II based on CSF cytology and A/B/C/D based on imaging features, with type (A) with linear leptomeningeal contrast enhancement only, type (B) with leptomeningeal nodules only, type (C) with both linear and nodular enhancement, and type (D) with normal MRI or hydrocephalus [2]. The Response Assessment in Neuro-Oncology (RANO) group has also provided guidelines to measure the response of patients with LMD to the treatment [66]. They reported three essential elements for RANO: neurological features examination, presence or absence of CSF circulating tumor cells (CSF cytology/flow cytometry in hematological malignancies), and neuroaxis imaging (MRI).

6. Palliative and Supportive Care

Managing and treating LMM is challenging, and multiple factors (age, tumor stage, previous therapies) can impact the treatment plan. Despite recent case reports stating that combined therapeutic approaches succeed in prolonging remission in LMM patients [12][51][52], several cases with relapsed LMD may require urgent surgical intervention and medications to alleviate neurological deficits and improve quality of life.

One of the medical emergencies that develops in most LMD cases is the elevation of intracranial pressure (ICP). Elevated ICP has no pathognomonic radiologic signs, and the most accurate way to measure or monitor ICP is by using an intraventricular catheter (Ommaya) [67]. Ommaya allows CSF drainage, resolving the elevated ICP; it is therefore a lifesaving procedure [68]. Moreover, Ommaya placement is used to deliver intrathecal treatment to patients [67]. Lumbar puncture is another procedure to relieve symptoms from hydrocephalus as well as allowing CSF collection for further analysis [69][70][71]. In cases of obstructive hydrocephalus, due to bulky tumor mass, palliative radiotherapy is an initial treatment option; however, sometimes RT cannot manage the patient's symptoms, and CSF diversion using ventriculoperitoneal shunting is an alternative treatment [72][73][74][75].

Pain mitigation with analgesics such as nonsteroidal anti-inflammatory drugs and opioids is critical primary supportive care offered to patients. Steroid medications can alleviate headaches and radicular pain. However, as immunosuppressive agents, steroids are not recommended to be administered with immunotherapy [8]. Patients with neuropathic pain are treated with neuropathic agents, such as duloxetine and gabapentin [76]. Antiepileptic medication is indicated only in patients who experience seizures [77].

Frequent follow-up and response evaluation are essential in melanoma patients with LMD due to rapid deterioration in neurological functions and overall poor prognosis reported with those patients [8][11]. Accordingly, treatment and supportive care goals must be reassessed to avoid further deterioration.

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