Review Article

Management of lung cancer brain metastasis: An overview

ABSTRACT

With the improvements in systemic treatment for lung cancer, distant metastasis to sanctuary sites such as brain has become an increasingly more important issue. The management of these patients consists of supportive care and disease-directed treatment. Combined modality treatment (surgical resection or radiosurgery, followed by whole brain radiotherapy) of brain metastases has greatly improved the local control of disease in patients with single lesion, good functional performance status, and controlled extracranial disease as demonstrated in prospective randomized studies. For patients with multiple brain metastases, conventional fractionated whole brain radiotherapy continues to be a standard and efficacious treatment. At present, experience with the use of molecularly targeted tyrosine kinase inhibitors in nonsmall cell lung cancer patients with activating mutations in the epidermal growth factor receptor gene and anaplastic lymphoma kinase gene is growing. However, their effectiveness in patients with brain metastases is not well established. In the arena of targeted therapies, vascular endothelial growth factor pathway inhibitors such as bevacizumab have shown some activity in brain metastases. Further prospective studies are necessary to facilitate selection of patient subpopulation for targeted agents in future studies.

Keywords: Bevacizumab, brain neoplasms, combined modality therapy, epidermal growth factor receptor, nonsmall cell lung carcinoma, receptor protein tyrosine kinase

INTRODUCTION

Lung cancer remains the most common cause of cancer-related deaths in men worldwide. Out of the estimated 1.8 million new cases in 2012 (12.9% of the total), 58% occurred in the less developed regions with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5/100,000) and Eastern Asia (50.4/100,000).[1] In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer-related deaths in both sexes.[2] Lung carcinomas have been classified based on histopathological subtypes into small cell lung cancer (SCLC) and non-SCLC (NSCLC). Brain metastasis is one of the most important causes of treatment failure in patients with lung cancer. Approximately 10% of lung cancer patients present with brain metastasis at diagnosis and an estimated 40% will eventually develop brain metastasis during the course of the disease.[3] Most of which occurs within 2 years with a median survival of 4–5 months.[4,5] Keeping the increasing incidence and mortality associated with lung cancer brain metastasis (LCBM), we undertook this review to summarize the experience till date with respect to current treatment options and future novel approaches for the treatment of LCBM.

BRAIN METASTASIS IN SMALL CELL LUNG CANCER

SCLC is neuroendocrine carcinoma accounting for approximately 10%–15% of lung cancer. The Veterans Administration Lung Cancer Study Group staged SCLC into limited (stage) disease (LD) or extensive (stage) disease (ED). Characteristic features of SCLC includes its aggressive behavior, rapid growth, early spread to distant sites, exquisite sensitivity to chemotherapy (CT) and radiation therapy (RT),

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and frequent association with distinct paraneoplastic syndromes.[6,7] Without treatment, SCLC has the most aggressive clinical course of all histopathological types.[8] Around two-thirds of all SCLC patients are diagnosed with ED, with metastasis commonly observed in the contralateral lung, liver, brain, and bones.[9] In spite of the late detection of SCLC, a good initial response to CT and RT is observed in the majority of the patients.[10] Unfortunately, even with this good initial response, the 5-year survival rate remains low at <7% overall, and most patients survive less than a year after diagnosis.[11,12] Brain metastasis has been reported as a common event in SCLC and is considered a major clinical challenge. The increasing incidence of brain metastasis is directly related to patients surviving long enough after a primary cancer diagnosis to experience brain metastasis due to the improvements in the treatment of systemic disease.[13]

BRAIN METASTASIS IN NONSMALL CELL LUNG CANCER

NSCLC comprises several subclasses that include adenocarcinomas, squamous cell carcinomas, and large cell carcinomas constituting for approximately 80%–85% of lung cancer.[14] The molecular targeted agents that inhibit epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) are approved for the treatment of NSCLC harboring genetic alterations in the genes encoding these proteins.[15] Although the management of NSCLC patients has improved over time, due to the development of these molecular targeted agents with a better knowledge of prognostic factors,[13] brain metastases still remain a common and lethal complication for these patients.[16] In particular, this increased incidence of brain metastases has been attributed to: (1) the routine use of magnetic resonance imaging for staging purposes, even in patients with metastatic NSCLC, resulting in the identification of small asymptomatic lesions that would otherwise have gone unnoticed. (2) With the availability of more effective systemic therapy for patients with resected NSCLC and locally advanced NSCLC, the brain as a single site or as the first site of relapse is becoming more common.[17-19] About 7%–10% of NSCLC patients present with brain metastasis at the time of initial diagnosis[3,20,21] and approximately 25%–30% of newly diagnosed NSCLC patients develop brain metastasis at some point during their illness.[22] The overall survival (OS) time for NSCLC patients with brain metastasis is <3–6 months when left untreated.[23]

MANAGEMENT OF LUNG CANCER BRAIN METASTASIS

In general, the initial management and prognosis of patients with brain metastasis depends on age, performance status, control of primary tumor, extent of extracranial disease, number of brain metastases, aggressive treatment modalities such as surgery or radiosurgery, and biomarkers such as expression levels of vascular endothelial growth factor (VEGF), cyclooxygenase-2, EGFR overexpression, and EGFR mutations.[23] The treatment options for patients with LCBM are limited including surgical resection, whole brain RT (WBRT), stereotactic radiosurgery (SRS) alone, and potentially, systemic or targeted therapy, based on the above-mentioned factors.

MEDICAL TREATMENT

Medical management of brain metastasis is considered an essential component requiring a prompt intervention to minimize progressive neurologic injury.[24] Early integration of palliative care has demonstrated improvement in quality of life and mood, with improved survival despite less aggressive end-of-life treatment.[25] In addition, patients with brain metastasis need supportive medications such as corticosteroids and anticonvulsants. Corticosteroids are vital for the improvement of symptoms by decreasing capillary permeability, thereby reducing intracranial edema. A systematic review by Ryken *et al*.[26] has made the following recommendations:

- If corticosteroids are given, dexamethasone is the best choice
- Starting doses of 4–8 mg of dexamethasone should be given for temporary relief of symptoms related to increased intracranial pressure. In more severe cases where symptoms suggest impending herniation, doses of 16 mg/day or more may be considered
- There is insufficient evidence to guide treatment recommendations for asymptomatic brain metastasis.

Anticonvulsants are clearly known to impact negatively on quality of life and neurocognition. A systematic review on the role of prophylactic anticonvulsants in the management of brain metastasis found only one trial stratifying patients by metastasis versus primary pathology. This study reported a Level 3 recommendation of not to use routine prophylactic anticonvulsants, explained by the fact that anticonvulsant use can have significant adverse effects and by the lack of evidence suggesting any benefit from the prophylactic use of anticonvulsants for patients with brain metastasis. The key conclusion from these guidelines recommends that in view of the lack of a clear and robust benefit from the routine prophylactic use of anticonvulsants, they should be avoided.[27]

Careful attention should be paid with regard to concurrent anticonvulsant medications when administering systemic therapy to patients with brain metastasis. The pharmacokinetic interactions between various chemotherapeutic agents and

enzyme-inducing antiepileptic drugs including phenytoin, carbamazepine, and phenobarbital reduce the overall systemic exposure responsible for increased metabolism of chemotherapeutic agents leading to worsened clinical outcome.[28,29] As levetiracetam is not an enzyme inducer, it is an attractive anticonvulsant in this setting.[30]

RADIATION THERAPY

WBRT is the most widely accepted treatment for patients with brain metastasis. The rationale for this treatment approach is based on the presumption that micrometastatic deposits of tumor cells are present elsewhere in the brain. WBRT palliates the associated neurological symptoms and may prevent the growth of new metastases. There are no randomized, controlled clinical trials establishing a survival benefit from WBRT in NSCLC patients.[31] In view of neurotoxic risks associated with WBRT and ability of SRS in very efficiently controlling few metastases, there is growing reliance on SRS for patients who have a limited number of brain metastases (usually 1–3).[32,33] However, WBRT still holds an important therapeutic role because of the easy availability and cost-effectiveness.

There are no randomized trials comparing SRS with traditional surgical resection. Surgical resection is recommended mainly for patients with a single brain metastasis in an accessible location, especially when the tumor size is large and causing a considerable mass effect or obstructive hydrocephalus. Surgery is also favored in patients with good performance status, who are functionally independent, and in whom systemic disease is limited or absent.[34] In a systematic review of studies on managing single brain metastasis in various types of cancer, Gaspar *et al*. found that the combination of surgical resection plus WBRT was superior to either approach alone in patients with good performance status and who had few sites of extracranial disease.[35] A low quality evidence regarding the addition of upfront WBRT to surgery or to SRS in decreasing any intracranial disease progression at 1 year has been provided by Cochrane review.[36] The debate over whether to use SRS or WBRT as frontline treatment for brain metastasis still continues. Multiple randomized controlled trials failed to show OS benefit of adding WBRT to SRS.[16,37,38] The NCCN guidelines for treating a single brain metastasis in NSCLC recommend surgery followed by WBRT or SRS, SRS followed by WBRT, or SRS alone, depending on the individual patient.[37]

Whole brain radiotherapy is generally the standard of care in patients with multiple brain metastases, as it addresses both macroscopic and microscopic disease. WBRT has resulted in an improvement in symptoms in 64%–85% of patients.[39,40]

The role of SRS in multiple brain metastases, especially those with ≥4 tumors, remains controversial. The literature is emerging, and the limited evidence suggests that the local control benefit is independent of the number of metastases, and that patients with more than four brain metastases have similar OS compared to those with 2–4 lesions.[41,42]

Till date, there has been no consensus on the optimal dose and fractionation schedule for WBRT. Eight randomized controlled trials comparing the standard dose schedule (30 Gy divided into 10 fractions) with altered dose schedules on patients with brain metastases from various primary cancers including NSCLC reported no significant differences in OS and symptom control.[39] A total of 30 Gy in ten fractions continue to be the standard for a vast majority of patients. A shorter fractionation scheme of 20 Gy in five fractions should be considered in CT refractory patients.

ROLE OF PROPHYLACTIC CRANIAL IRRADIATION IN SMALL CELL LUNG CANCER AND NONSMALL CELL LUNG CANCER

Prophylactic cranial irradiation (PCI) was first tested for patients with SCLC in the 1970s following the recognition that the blood–brain barrier (BBB) appeared to restrict the penetration of most chemotherapeutics into the brain leaving it as a sanctuary site for relapse.[43] A meta-analysis of five randomized controlled trials compared brain metastasis incidence and OS between PCI and no PCI in patients with SCLC. The results indicated that PCI decreases brain metastasis incidence and improves survival in SCLC patients. This systematic review suggested that PCI should be considered a part of standard care for all patients with SCLC who have a good response to initial CT.[5] At present, the standard therapy for LD-SCLC is concurrent chemoradiotherapy and PCI for those who achieve complete response or good partial response with initial therapy, whereas the standard therapy for ED-SCLC is CT only.[44] A Japanese Phase III study failed to confirm the usefulness of PCI for patients with ED-SCLC.[45] In the 2014 edition of the Guidelines for the Treatment of Lung Cancer from the Japan Lung Cancer Society, use of PCI for patients with ED-SCLC has been changed from "recommended" to "not recommended," and the guidelines only recommend PCI for patients with LD-SCLC who achieve complete response after initial treatment (Grade A recommendation) and patients with ED-SCLC who achieve complete response after initial treatment (Grade B recommendation) indicating appropriate selection of patients for PCI of paramount importance.[45] A population-based analysis on the role of PCI among NSCLC patients at higher risk of brain metastasis (<60 years, adenocarcinoma, or stage IIIB) suggested no OS benefit of PCI even among high-risk patients.[46]

SYSTEMIC CHEMOTHERAPY

Systemic CT is not routinely used in the treatment of LCBM as the large, hydrophilic molecules cannot penetrate the BBB[32] and due to the presence of drug efflux mechanisms.[47] In view of the dismal prognosis leading to exclusion of these patients in clinical trials, we are left with limited data on the efficacy of chemotherapeutic agents. Edelman *et al*. reported similar outcomes with regard to OS and median survival in patients receiving CT with a slight trend favoring patients without brain metastasis.[48] In a meta-analysis of six randomized controlled trials involving 910 participants of LCBM, the results indicated that CT concurrent with WBRT was more effective at improving response rate than WBRT alone, but it did not improve median survival time or time of neurological progression. Since most of the studies included in the meta-analysis were retrospective or single arm-study and limited randomized controlled trials, the role of CT in LCBM remains controversial with no proven survival benefit.[49]

The most extensively studied chemotherapeutic drugs with WBRT are temozolomide (TMZ) and the radiation sensitizer, motexafin gadolinium. Recent studies have raised concerns of worse outcomes with the combination of TMZ and WBRT in NSCLC patients. In the RT Oncology Group 0302 study, patients in the WBRT/SRS plus TMZ arm experienced shorter survival compared with those receiving WBRT/SRS alone (6.3 vs. 13.4 months) with increased toxicity.[50] None of the other agents have shown evidence of significant improvement in response rate or survival. At present, concurrent CT with WBRT is not indicated outside of the context of a clinical trial.

ROLE OF TARGETED THERAPY

Molecular targeted tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have proven to be effective in patients with activating mutations in the EGFR gene and chromosomal rearrangements involving the ALK gene. Despite their efficacy in systemic disease control, their effectiveness in patients with brain metastasis is not well established since data on the use of erlotinib or gefitinib are available from retrospective and nonrandomized studies with a limited number of patients.[51,52] A Chinese study of 136 NSCLC patients with resected brain metastasis identified an EGFR mutation in 57% of the brain metastases, with a concordance rate of 93.3% in the EGFR mutation status between the primary tumor and brain metastasis. This suggested that the primary tumor EGFR status is a very good surrogate for EGFR mutation status of the brain metastasis.[53] There is mounting evidence that treatment with TKIs results in high response rates (70%–89%), increased OS and progression-free survival (PFS) (12.9–19.8 months and 6.6–23.3 months, respectively) demonstrating an improved clinical outcome in selected populations of EGFR-mutated NSCLC patients with brain metastasis.[54,55] Therefore, EGFR and ALK-TKIs are among valid options for patients with asymptomatic brain metastases from NSCLC, especially those with EGFR-activating mutations or harboring ALK-rearrangement.[56]

For EGFR-mutant NSCLC patients with asymptomatic brain metastasis who do not require urgent symptom relief, the proper treatment schedule is not well established. In a retrospective study on patients with asymptomatic brain metastasis without prior TKI treatment, first-line brain RT failed to improve long-term survival in TKI-naive EGFR mutant NSCLC patients with asymptomatic brain metastases.[57]

The question of whether erlotinib or gefitinib can delay or obviate the need for brain radiation appears quite appealing.[52] To answer this, a meta-analysis on EGFR-mutant NSCLC patients with brain metastasis was undertaken. The authors reported improved PFS and OS with the use of upfront cranial RT although with more neurological adverse effects than with TKIs alone. This meta-analysis provided evidence, albeit of low quality, that upfront cranial RT may improve intracranial disease control and survival outcomes compared with TKIs alone.[58] Negative results were reported recently with the use of upfront EGFR-TKIs, with the deferral of SRS or WBRT resulting in inferior OS in patients with EGFR-mutant NSCLC who develop brain metastasis.[59] Similarly, no significant difference in OS was reported in 110 patients with EGFR-mutant lung adenocarcinoma subjected to erlotinib versus RT for brain metastasis (median, 35 vs. 26 months; $P = 0.62$).[60] However, this study underscored the role of WBRT in producing durable intracranial disease control in comparison with erlotinib. The results of above-mentioned studies suggest that local therapy may still be important for the treatment of brain metastases in patients with EGFR mutations.

Another issue of major importance is whether WBRT enhances the activity of EGFR inhibitors by, for example, disrupting the BBB and thus allowing a higher drug concentration to be achieved in brain metastasis. An intracerebral response rate of 75%–89% versus 84% has been reported in patients treated with EGFR-TKI alone and on combining EGFR-TKI with WBRT, respectively. This response rate was considerably higher as compared to what was expected from standard approaches such as CT and WBRT alone.[23] However, this hypothesis has yet to be confirmed by sound data in prospective trials in the future.

Alterations in the ALK gene occur in 2%–7% of NSCLC patients[61] and confer sensitivity to selective TKIs. Crizotinib is the first ALK inhibitor approved for the treatment of patients with metastatic NSCLC whose tumors harbor ALK rearrangement. However, it is important to note that patients develop resistance to crizotinib because of the weak penetration of the BBB by this drug.[62] Although EGFR-TKIs produce lower drug concentrations in cerebrospinal fluid than in plasma, they achieve higher levels relative to crizotinib.[51] Keeping the data till date in mind, it is suggested that crizotinib may not be the best ALK inhibitor for patients with brain metastases. However, promising responses in the central nervous system (CNS) in crizotinib-resistant brain metastases have been seen with second-generation ALK inhibitor, alectinib.[63] Future studies are needed to clarify optimal sequencing of the above-mentioned TKIs in patients with CNS disease and whether these will be effective and safe in multimodality therapies such as in combination with radiation. Furthermore, a study evaluating immunotherapy in CNS metastases from NSCLC is underway (clinicaltrials.gov identifier: NCT02085070).

Another targeted approach studied in the treatment of brain metastases with NSCLC is the use of bevacizumab (BVZ), a recombinant humanized monoclonal antibody that obstructs VEGF pathway. Despite its extensive employment in the treatment of lung cancer, its role in LCBM is very limited. This is because of the exclusion of patients with brain metastases from BVZ clinical trials after the occurrence of a fatal cerebral hemorrhage in the Phase I study.[64] However, the brain metastases as an exclusion criteria contradiction were removed after the retrospective analysis of clinical trial data suggested an equal risk of intracranial bleeding in patients with brain metastases treated with or without BVZ therapy.[65,66] BVZ administration to NSCLC patients with symptomatic brain lesions, who were not suitable candidates for a specific local therapy, the PFS and OS data were very encouraging with symptomatic benefit due to BVZ's high capacity to provide a long-lasting decrease in perilesional edema.[67] The results so far have suggested that a BVZ-based regimen is capable of eliciting an intracranial response and might offer an alternative treatment option for patients with brain metastases from NSCLC.[68] There still remain several unanswered questions in view of the lack of prospectively conducted trials of BVZ in these patients.

CONCLUSIONS

With the advances in the management of lung cancer and better survival, more patients are likely to develop brain metastases. These patients have poor median survival, and more effective therapies are urgently required. The goal of treatment for these patients is longer survival with improved quality of life and preservation of neurocognitive function. PCI for patients without detectable brain metastases decreases the frequency of subsequent intracranial relapse and improves survival for patients with LD-SCLC. There is no proven role of PCI for patients with locally advanced NSCLC, not even among patients at higher risk of brain metastases. Local RT is still an important component of treatment for brain metastases in NSCLC patients with EGFR and ALK mutations. Current research is focused on various novel treatment approaches including the use of targeted therapies, using targeted therapy concurrent with radiation, and finally utilizing immunotherapy in patients with LCBM.

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Conflicts of interest

There are no conflicts of interest.

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