CPQ Cancer (2019) 1:6
Review Article

Evolving Insights into Brain Metastases in Patients with Oncogene Mutation-Driven Non-Small Cell Lung Cancer (NSCLC)

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Received: 19 August 2019

Published: 28 August 2019

Keywords: *Non-Small Cell Lung Cancer (NSCLC); Brain Metastasis; Oncogene; EGFR; ALK*

Abstract

Brain metastases (BM) frequently develop in patients with non-small cell lung cancer (NSCLC) with a higher incidence observed in patients with oncogenic driver mutations. Management strategies for BM are rapidly evolving to reflect the advancements in lung cancer biology and the recent application of novel molecular and immunotherapies in NSCLC. In addition, emerging insights into the brain microenvironment and the mechanism of brain colonization may provide new avenues for treating and preventing BM. In this review, we discuss concepts in tumor biology and current management options for BM in NSCLC with emphasis on oncogenic-driver mutations.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and the most frequently diagnosed malignancies in both men and women [1]. Non-small cell lung cancer (NSCLC), accounting for 85% of lung cancers, is a heterogeneous disease encompassing several histologic and molecular tumor subtypes. Advancements in the understanding of tumor biology and characterization of genetic driver mutations have led to the development of novel, personalized therapies. In particular, immune checkpoint inhibitors and targeted molecular therapies have dramatically improved prognosis in select groups of patients.

Despite treatment advances, however, overall survival remains poor. Metastatic disease is present in a majority of NSCLC patients at the time of diagnosis [2], and 5-year survival is less than 25% [3]. Lung cancer most frequently metastasizes to the brain, and approximately 10% of newly diagnosed patients have brain metastases (BMs) [4]. Prognosis in these patients is also very poor. Overall, 1 in 5 patients will develop BMs; however, approximately half of all patients with cancers that harbor activating mutations of the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) will develop brain metastases [5-7]. It is not well understood how these mutations enable the emergence of features that predispose toward the growth and progression within the central nervous system (CNS).

New managements strategies will require better methods of detection and options for systemic therapies that are able to negotiate the blood brain barrier (BBB). Further investigation is needed to understand the activity of immune checkpoint inhibitors and targeted therapies within the central nervous system since limited data exists for these drugs in patients with BMs [8]. Additionally, identification of new genetic drivers and molecular targets will be required to expand the population of patients benefiting from targeted therapies [2]. In this review we provide an overview of central concepts in tumor biology and current treatment strategies for NSCLC patients with metastatic CNS disease.

Tumor Biology

Numerous mutational tumor subtypes are known to exist and contribute to the heterogeneity of NSCLC. Activating mutations are observed in receptor tyrosine kinases and RAS signaling proteins such as EGFR, ALK, HER2, KRAS and BRAF among others [9]. Identification of distinct oncogenic driver mutations has enabled development of targeted therapies and there is ongoing investigation into the extrathoracic efficacy of these drugs, particularly in the central nervous system. In addition to the numerous genetic alterations, there is considerable heterogeneity of the tumor microenvironment (TME) which has also been subjected to intense investigation. The TME includes cancer-associated fibroblasts, the extracellular matrix, vasculature and infiltrating immune cells. Ongoing research is seeking to understand how alterations in the TME supports or contributes to carcinogenesis. Elucidating these pathways may lead to utilization of TME states as biomarkers with prognostic value to determine the disease stage and predict treatment response [10].

Metastatic spread to the brain is a complex, mechanistic process that is not entirely understood though appears to be influenced by characteristics of both cancerous cells and the brain microenvironment. Malignant cells must be able to cross the blood-brain barrier (BBB) and establish a vascular supply through angiogenesis to enable macrometastasis formation [11]. However, the naïve brain microenvironment is able to eliminate

most metastatic cells through the activation of innate immune system [8]. This finding suggests that tumor cells in the BM have acquired characteristics which avoid or overcome these defenses. Compared to other NSCLC patient populations, higher rates of BMs are observed in NSCLC with activating mutations of EGFR and ALK [5-7], though the association between these oncogenic drivers and the specific characteristics that facilitate colonization of the brain have yet to be fully uncovered. Alternatively, dysregulation of defense mechanisms intrinsic to the brain microenvironment may permit metastatic colonization.

Insights into the mechanism of BM formation offer several potential therapeutic strategies targeting the critical steps of BM formation. Transmigration of the BBB involves specific molecular mediators such as Cathepsin S, which can be inhibited in vivo to reduce BM formation [12]. Similarly, angiogenesis is required for brain colonization and bevacizumab has been shown to prevent BM formation [13]. Finally, the concept of metastatic latency appears to be important in understanding BM formation. BM may develop years after initial diagnosis as mediators enable cancer cells to exit quiescence and undergo rapid growth, so future strategies may exploit these mechanisms [8,14,15].

Diagnosis of Brain Metastases

Patients developing BM may be asymptomatic or present with a variety of symptoms such as headache, seizures, or altered mental status. Imaging therefore plays an essential role in the diagnosis of BM since radiographic features can help distinguish metastatic lesions from other etiologies causing neurocognitive dysfunction including infection, infarction, and primary brain tumors. Features supporting a diagnosis of BM include a well-circumcised lesion located at the grey-white junction with significant edema and the presence of multiple lesions.

Contrast-enhanced brain MRI is the preferred imaging modality for detecting BM since it is more sensitive and FLAIR sequences can help distinguish BMs from other pathologies such as meningioma [9,16]. PET-CT, although widely used in NSCLC for detecting extra-thoracic metastases, has a limited role in the brain due high background FDG uptake and also because BM can have hyper- or hypometabolic activity [9,16,17]. Patients with early stage NSCLC and an abnormal neurologic exam should undergo MRI given the likelihood of BM. Additionally, there has been increased emphasis on early detection of BM while still asymptomatic since treatment of these lesions has been associated with improved neurological control and prolonged survival [16,18]. Consequently, routine brain imaging with MRI is also recommended for patients with stage III or IV NSCLC, including those with a negative clinical exam [16]. In cases where the diagnosis of BM is uncertain, surgery or stereotactic biopsy can be considered based on tumor accessibility.

Treatment Strategies: An Overview

Contemporary management of BM is evolving rapidly and becoming more personalized to account for the origin of the primary tumor, histologic subtype, and the presence targetable oncogenic mutations. Local therapies include neurosurgery and radiation. Systemic therapies include conventional chemotherapy, and a rapidly increasing number of targeted molecular and immunotherapies. In practice, a multimodal approach is often employed and utilizes a combination of local and systemic therapies.

Targeted Systemic Therapies Vs. Local Therapies

Historically, local therapies such as radiation were favored as an early intervention over systemic therapy. However, targeted systemic therapies with EGFR and ALK tyrosine kinase inhibitors (TKIs) are now increasingly utilized for patients with oncogene-driven NSCLC. These targeted molecular inhibitors have been reported to have superior CNS activity against brain metastases. The efficacy of these targeted therapies has significantly increase survival from the order of months to years [19,20].

Targeted Therapies

EGFR TKIs

First and second-generation EGFR TKIs such as afatinib, erlotinib, and gefitinib have low CSF concentrations of 1-5% compared to serum concentrations and thus have lower antitumor activity in patients with brain metastases. In comparison, osimertinib, a newer generation EGFR inhibitor, achieves high intracranial concentrations and has significant efficacy against brain metastases [21]. Furthermore, the FLAURA trial demonstrated that patients receiving osimertinib compared to those receiving first or second-generation EGFR inhibitors had a longer progression free survival (15.2 vs. 9.6 months) [22]. Additionally, patients with brain metastases in the FLAURA trial had an intracranial response rate of 91% with osimertinib, compared to 68% with first or second-generation EGFR inhibitors [22,23].

With the development of osimertinib, patients with EGFR-positive NSCLC and brain metastases can primarily be treated with targeted systemic therapy alone. Osimertinib is favored as initial management in these patients and avoids the complications that may arise from radiation therapy or surgery. Nonetheless, since clinical data comparing osimertinib with local therapies is lacking, some clinicians opt for early radiation therapy in conjunction with osimertinib.

For patients with progression on osimertinib, patients are treated similarly to those without a known oncogenic driver mutation. See section “Patients Lacking Oncogenic Drivers.”

ALK TKIs

ALK TKIs such as alectinib and ceritinib are highly effective in most patients with brain metastases. In particular, alectinib demonstrates significant intracranial activity [24,25]. Compared to other ALK TKI inhibitors such as crizotinib, alectinib has shown increased progression free survival in patients with ALK-positive NSCLC with brain metastases in phase III clinical trials. In patients with alectinib resistance and progression of intracranial metastases, several options exist but no specific algorithm exists. Generally, patients are treated with local therapy, dose escalation of alectinib, or with lorlatinib, a third generation ALK inhibitor which has gained FDA breakthrough therapy designation with documented CNS activity in patients who have failed second generation inhibitors.

Patients Lacking Oncogenic Drivers

Local therapy with radiation or neurosurgery is preferred for most patients with brain metastases lacking known oncogenic driver mutations. In patients with a limited number of brain metastases, stereotactic radiosurgery (SRS) is favored over the historic approach of whole-brain radiation therapy (WBRT). Cytotoxic chemotherapy is less effective for NSCLC compared to small cell lung cancer but may be effective for patients with disseminated lung cancer and asymptomatic brain metastases. In patients with poor performance status, supportive care and steroids is another alternative to radiation therapy.

Local Therapies: Neurosurgery and Radiotherapy

Local therapies are important management options and are often used as part of a multimodal approach in combination with systemic or immunotherapies, or in combination with other local therapies. The number, size, and anatomic location of BMs should be considered when deciding between surgical resection and radiation to ensure that treatment is technically feasible, safe, and durable. For limited metastatic disease, generally one BM, neurosurgery is favored versus SRS for three or less BMs [8].

Immunotherapy

Immune checkpoint inhibitors directed against programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have recently been approved for patients with advanced NSCLC. However, there is paucity of data describing immune check point inhibitors for NSCLC with brain metastases. This is because patients with active CNS disease have been excluded from many of the clinical trials with immune checkpoint inhibitors. In a phase II trial of patients with NSCLC and brain metastases, treatment with the PD-1 antibody pembrolizumab produced durable CNS responses in 33% of patients [26]. Additionally, pooled data of patients enrolled in treatment studies with the PD-L1 inhibitor atezolizumab suggests that it is well-tolerated in NSCLC patients with brain metastases with no adverse neurologic events in 79 patients [27]. This data shows the potential of immune checkpoint inhibitors in patients with NSCLC and brain metastasis. However, further studies are required to determine whether patients without known oncogenic driver mutations can safely be treated with immune checkpoint inhibitors over local therapy.

Prophylactic Cranial Irradiation (PCI)

Systemic therapies reduce the incidence of non-brain metastases but have had limited impact on reducing BMs. Additionally, advancements in the treatment of NSCLC have improved survival which in turn is associated with increased incidence of BM [28]. For these reasons, the use of PCI has generated intense interest and has been the subject of investigation in several randomized clinical trials in patients with locally advanced NSCLC [28-31]. These studies demonstrated that PCI reduces the incidence of BM, although no survival advantage has been shown to date [32]. Since patients who will not develop BM are subject to neurocognitive side effects of PCI, further investigation is therefore still needed to identify the patients at highest risk for developing BM. Nonetheless, PCI still holds promise since future trials employing the neuroprotectant memantine and risk reduction techniques such as hippocampal avoidance can mitigate radiation toxicity [32]. Finally, as consolidation immunotherapy is becoming standard of care in patients with stage III NSCLC, future trials should also investigate PCI in this population [32-34].

Conclusions

BM are common in NSCLC, particularly in patients harboring tumors with activating EGR and ALK mutations. Although the recently introduced systemic treatment modalities (i.e. targeted therapy and immune check point inhibitors) have been associated with promising outcomes, novel management strategies are still needed, especially as the incidence of BM continues to rise. Additional clinical trials investigating multimodal approaches and further investigations into tumor biology will be needed to meet this challenge.

Conflict of Interest

The authors have no conflicts of interest to report.

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