Treatment of brain metastases of lung cancer in the era of precision medicine

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1. ABSTRACT

Common and deadly complications of non-small cell lung cancer (NSCLC) are brain metastases (BM). BM portends a poorer prognosis with limited effective treatment options and current management strategies present several challenges from iatrogenic complications of supportive medications, optimal delivery of drug across the blood-brain barrier, and preservation of neurocognitive function. Long term side effects and survivorship issues have become more evident in the era of targeted therapy where a systemic disease is much better controlled. Targeted therapies and immunotherapy are beginning to provide improvements in responses and survival rates. With further advancements and experience, our knowledge in this era of precision medicine will likely lead to strides in improving the quality of life and overall survival of patients with BM from NSCLC. In this review, we present the most recent updates in treatment of BM in NSCLC in regards to targeted and immunotherapy.

2. INTRODUCTION

The development of brain metastases (BM) represents the most common cause of neurologic demise experienced by patients with lung cancer leading to dramatically increased morbidity and mortality. Metastatic disease in the brain is present in 10-25% of lung cancer patients at diagnosis and may develop in up to 40% at some time during their disease course (1). Median survival following metastatic spread to the brain can be as short as 3-6 months but can be up to 12 months depending on the patients prognostic index and treatment modalities implemented (2,3). NSCLC is the most common tumor to cause BM and adenocarcinoma subtype is present in over 50% of the patients with NSCLC and BM (4). The incidence of BM is rising in part due to advances in imaging techniques that can detect smaller lesions earlier as well as improved survival following newer systemic treatments (5,6). It poses an enormous treatment problem and calls for improvements in the treatment strategies of lung cancer BM (LC-BM).

Several prognostic scoring systems for BM have been developed including the recursive partitioning analysis which utilized the common parameters of performance status, age, extent of extracranial disease and primary diagnosis, all of which delineate prognostic
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groups with differing, but poor prognoses (7–13). This has changed, to a certain degree, how patients are treated with brain metastases.

Standard local therapeutic strategies for the treatment of newly diagnosed LC-BM include whole brain radiation therapy, surgical resection, stereotactic radiosurgery, and combinations of these modalities (2,14,15). Systemic chemotherapy has played a limited role in first line therapy for BM largely because of its inability to penetrate across the blood-brain barrier (BBB) (16). However, data revealing at least partial BBB disruption in BM suggests a potential role for effective systemic therapeutics including those with limited or no penetration across an intact BBB (17). In fact, published data describes response rates of up to 40-50% following standard systemically administered cytotoxic chemotherapy in patients with BM from NSCLC (18–20).

In the new era of precision medicine and whole genome sequencing of tumors, driver mutations including EGFR, ALK and ROS-1 translocations now define important subsets of patients with NSCLC and improve outcomes with the use of novel targeted therapies. Anti-PD-1 inhibitors and immunotherapeutic approaches to NSCLC have also emerged as effective anticancer strategies (21,22). The purpose of this review is to highlight the role of these promising new systemic treatment options in patients with NSCLC and BM.

3. CHEMOTHERAPY IN NSCLC

Traditional cytotoxic chemotherapy has had a limited role in the treatment of LC-BM. There is no level 1 evidence supporting its use over local radiation and surgical therapies. Concerns about BBB penetration of systemically administered chemotherapy have limited its use in the primary treatment of BM. Pharmacologic data support this concern as high molecular weight, hydrophilic and protein-bound drugs are typically excluded from the CNS due to tight-junctions and highly regulated protein transporters of the endothelial vasculature (23). However, growing published evidence suggests that the BBB is compromised in BM. Decreased expression of P-glycoprotein, an efflux pump, which is thought to remove chemotherapy agents from the CNS, is one potential mechanism underlying BBB dysfunction in BM (17). Supporting this is an analysis by Ortuzar et al, of 2296 patients in two phase III trials which demonstrated a reduced incidence of CNS failure, 3.2% (95% CI 2.1%-4.6%) versus 6.6% (95% CI, 5.0%-8.6%) with P=0.002 for pemetrexed versus non-pemetrexed regimens (24). There are several active clinical trials trying to further evaluate the effectiveness of various combination therapies in patients with NSCLC and BM, including Cisplatin/ Pemetrexed/Bevacizumab (ClinicalTrials.gov Identifier: NCT02162537) and a phase II trial of temozolomide with topotecan (ClinicalTrials.gov Identifier: NCT01736800).

4. LOCAL THERAPY

4.1. Surgery

Surgery is a useful modality for LC-BM. The advantages of surgery include the ability to acquire a pathologic tissue sample, the rapid decompression of symptoms, and a survival advantage in some patients. However, as surgery delays systemic therapy for a period of time for wound healing and recovery of health status, patients should be properly selected. Patients with large or symptomatic metastases tend to benefit most from surgery. Patchell et al published a randomized study for patients with predominantly symptomatic brain metastases and found that patients who received surgery followed by whole brain radiotherapy (WBRT) had improved overall survival over those patients who received WBRT alone (2). Moreover, patients with a new diagnosis of brain metastasis after a disease free interval from the original lung cancer will benefit from surgical sampling because up to 10% of patients in this scenario will have pathology consistent with something other than a brain metastasis (25).

Contraindications to surgery include patients with tumors in surgically inaccessible (deep brain) regions or eloquent regions. Patients with poor prognosis are also not good surgical candidates because recovery from brain surgery may take a large portion of the remaining life expectancy. Finally patients with multifocal brain metastases may benefit more from a radiotherapeutic modality since radiation can treat all lesions simultaneously. However, if a dominant lesion exists in a setting of multifocal brain disease, surgical intervention may have a role.

Of note, surgical resection of a brain metastasis is not considered an oncologic surgery, and local recurrence after surgery is a common occurrence. Surgery alone for a brain metastasis has local failure rates as high as 50% (26). Post-operative radiotherapy either as WBRT or stereotactic radiosurgery (SRS) directed to the resection cavity can improve local control rates and decrease the likelihood of neurologic death (26,27).

4.2. Radiation therapy

For many years, WBRT had been the mainstay of treatment for patients with brain metastases from NSCLC. The advantage of WBRT includes the high response rate (50-75%) with regards to both tumor size on imaging as well as patient symptoms caused by BM (28). WBRT has significant toxicities both in the acute and late setting. The major acute toxicities include hair loss, fatigue, headaches, and decline in performance status (29,30). Despite performance status being a fairly subjective clinical judgment, it is often one of the most important tools used to determine whether a patient is an appropriate candidate for chemotherapy. Thus, toxicities
related to upfront WBRT can significantly delay the start of chemotherapy for patients' extracranial disease. The major late toxicity of WBRT is cognitive decline for which few treatments are effective (30,31). The advent of better systemic therapies along with improved technology have changed the landscape of LC-BM management for patients over the past 2 decades. With SRS, there is now a technology that allows for sparing of the toxicities associated with WBRT, while still controlling brain metastases. Multiple randomized trials have now shown that SRS is at least as effective as WBRT, and patient's survival is not affected by withholding WBRT as long as there are 4 or fewer brain metastases (32–34).

The use of SRS has increased over the recent years due to improved access to radiotherapy technology such as linear accelerator-based SRS and gamma knife radiosurgery in the community. As the role of SRS has expanded for lung cancer patients with brain metastases, it has become paramount to better define the populations that will benefit from SRS as this is a much more expensive modality (35). Multiple factors play a role in this decision including prognosis, performance status, status of extracranial disease, and histopathology. Patients with prolonged survival after WBRT are more likely to suffer from the cognitive toxicities of WBRT (30). As such, a greater life expectancy leads to a greater incentive for the use of SRS. There is evidence that patients with brain metastases are living longer than ever before (27). Moreover, lung cancer patients, even those with BM, have a high rate of dying of their disease in the chest (36). As such, because SRS does not cause a delay in therapy directed towards systemic disease, it is often seen as a favorable treatment option by medical oncologists. Finally, there is emerging data that there are differences in outcomes based on histology of lung cancer, and that these differences may even translate to how patients respond to SRS and WBRT(37,38).

There are some differences between management of lung cancer patients with brain metastases as compared to some other histologies. First of all, lung cancer patients who receive WBRT are thought to benefit more from a SRS boost. A randomized study published by Andrews et al showed that while the overall population of patients with brain metastases did not benefit from an SRS after WBRT, the lung cancer subgroup had an improvement in overall survival (5.9 vs 3.9 months, p=0.05) (39). Kuremsky et al demonstrated that the likelihood of development of new metastases after SRS alone is greater in patients with squamous cell rather than adenocarcinoma (38). This in turn caused a greater need for future WBRT in patients with squamous cell cancer. Finally, recent data suggests that the appropriate use of systemic targeted agents in lung cancer patients can not only alter survival, but also affect the development of new metastases after SRS (40).

The current standard of care, while controversial, is for SRS to be used in the upfront setting for patients with four or fewer brain metastases, while WBRT is reserved for patients who have greater number of metastases. It has been suggested that the current standard may over treat a number of patients with WBRT that otherwise would have been good candidates for SRS (41). This “over-irradiated” population includes patients with greater than 4 brain metastases that respond well to systemic chemotherapy and do not develop new brain metastases for a prolonged period. A recent large prospective Phase II clinical trial from Japan suggested that treating up to 10 metastases with SRS alone may be a reasonable option (25).

In the future, it is likely that predictive models will be used to help triage lung cancer patients with brain metastases to the proper management algorithm. The disease specific Graded Prognostic Assessment is the modern prognostic model of LC-BM. A statistical nomogram has been developed to help predict which patients may rapidly fail SRS and may be more appropriately triaged to WBRT (41). Advances in molecular profiling may also help to identify the proper treatment option for patients.

5. MOLECULAR TARGETED THERAPY

5.1. EGFR mutation

Epidermal growth factor receptor (EGFR) tyrosine kinase is a multiple domain glycoprotein that is made up of an extracellular ligand-binding domain and an intracellular tyrosine kinase domain separated by a transmembrane region. Ligand binding leads to receptor dimerization on the cell surface and leads to autophosphorylation of the intracellular tyrosine kinase domain which stimulates signal transduction pathways regulating various pathobiological functions from proliferation to angiogenesis (42). Mutations in EGFR are noted in 10-15% of NSCLC adenocarcinomas in the US, and are sensitive to EGFR tyrosine kinase inhibitors (TKIs) (43). A meta-analysis by Lee et al evaluating EGFR TKI versus platinum-based regimens demonstrated progression-free survival was significantly prolonged with hazard ratio of 0.43 (95% CI 0.38-0.49) (44). Of note, increased EGFR gene amplification has been demonstrated to be associated with improved survival and response both in the Southwest Oncology Group 0126 trial and by Cappuzzo et al (45–47). Researchers in China reported 72 of 136 NSCLC patients were found to be EGFR mutant according to resected BM specimens, which demonstrated a concordance of 93.3% between the primary tumor and BM (48). In the US, there are three currently approved EGFR TKIs, erlotinib and gefitinib which are first generation agents and afatinib a second generation irreversible TKI. Studies evaluating the efficacy of these agents against BM come from retrospective analyses and small prospective studies.
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5.1.1. First generation EGFR TKI

In 2004, Ceresoli et al demonstrated the efficacy of gefitinib in 41 heavily pretreated NSCLC patients with BM and an unknown EGFR status (49). Patients were candidates if they had failed previous whole brain radiation therapy (WBRT) or did not receive WBRT because of asymptomatic BM or if they had declined radiotherapy. Thirty-nine percent of patients had two or more previous chemotherapies and 43% received prior WBRT. Overall, disease control rate (DCR) in BM was 27%, with 10% having partial response (Table 1). Further prospective studies appeared to validate these results with DCR of 63.2% [95% CI, 52.1-74.3%] and a median overall survival (OS) of 9.9 months [95% CI, 4.9-14.8] in patients treated with gefitinib for BM (50). Eighty one percent of these patients showed comparable tumor response in intracranial and extracranial lesions. To further back these findings, Eichler et al performed a retrospective analysis and found 93 patients with BM, of which 44% had EGFR mutations, and noted median survival was 14.5 vs 7.6 months in the EGFR mutated patient with a P=0.09 (51). Multivariable analysis further demonstrated that EGFR mutation was independently associated with survival. Of note a majority of these patients were initially treated with WBRT +/- surgical resection.

Several retrospective analysis and small prospective studies have demonstrated some benefit in treating BM with gefitinib or erlotinib. A review in 2012 examined 8 phase II studies evaluating either gefitinib or erlotinib and their efficacy in treating NSCLC BM, with a total number of 411 patients (52). In all comers, gefitinib had an intracranial response rate (RR) of 27-32%, but with patients selected for an EGFR mutation a RR 43-89%. Studies evaluating Erlotinib only demonstrated an intracranial RR 56-82% with patients selected for known EGFR mutations. Further supporting that EGFR TKIs have activity against BM, a more robust response noted in the studies enriched with patients with known EGFR mutations.

Current data does not favor one EGFR TKI over another; however studies have evaluated the concentration of drugs in the CSF, trying to determine which TKI is more efficacious. Fifteen patients from Japan with NSCLC and BM had CSF tested during therapy with gefitinib or erlotinib and showed drug concentration of 3.7 +/- 1.9 ng/mL versus 28.7 +/- 16.8 ng/mL (53). This difference was found to be highly significant with a P value of 0.0008 and thus proposing that erlotinib might be more efficacious but larger controlled trials need to be performed to truly validate this hypothesis.

5.1.2. Concurrent therapy

We now know that EGFR TKIs have activity in BM from NSCLC, so combination treatment with radiation therapy could potentiate these responses. A phase II study with 40 patients with BM from NSCLC treated with concurrent erlotinib and WBRT had RR 86% and median OS 12 months, but when taking this idea to a large randomized control trial, the phase III RTOG 0302 showed worse OS and increased toxicity in the concurrent arms (54,55). Grade 3 to 5 toxicities occurred in 11% in the radiation arm versus 41-49% in the concurrent arms and OS was 13.6 vs 6.1 months. At this time there is insufficient safety data to recommend concurrent erlotinib and radiation therapy, but there are current clinical trials trying to further evaluate the role of this combination, ClinicalTrials.gov Identifier: NCT01887795.

Radiation therapy is the most effective modality in the treatment of patients with brain metastases, but given the data EGFR TKIs are appealing as first line treatment for BM. A recent retrospective analysis with 110 patients with BM and known EGFR mutations evaluated which treatment modality, EGFR TKIs or WBRT, was better

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>RR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>41</td>
<td>10</td>
<td>3.0</td>
<td>5.0</td>
<td>49</td>
</tr>
<tr>
<td>Gefitinib/erlotinib</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
<td>14.5</td>
<td>54</td>
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<tr>
<td>Erlotinib/WBRT</td>
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<td>86</td>
<td>8.0</td>
<td>19.1</td>
<td>87</td>
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<tr>
<td>WBRT/SRS/erlotinib</td>
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<td>NR</td>
<td>4.8</td>
<td>6.1</td>
<td>55</td>
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<td>16</td>
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<tr>
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</tr>
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</tr>
<tr>
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<td>NR</td>
<td>NR</td>
<td>73</td>
</tr>
<tr>
<td>Alectinib</td>
<td>21</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
<td>75</td>
</tr>
</tbody>
</table>

RR: Response rate; PFS: Progression free survival; OS: Overall survival; WBRT: Whole brain radiation therapy; SRS: Stereotactic radiation surgery; NR: Not reported
in front line treatment (56). Patients were treated with erlotinib, stereotactic radiosurgery (SRS), or WBRT and although it was noted there was no significant difference in OS with erlotinib versus WBRT with a P value of 0.62. However, there was a shorter time to intracranial progression with erlotinib (16 vs 24 months; P value 0.04) and a higher incidence of intracranial failure as site of first progression with erlotinib. This demonstrates that radiation therapy appears to still be the advantageous treatment modality.

5.1.3. Second generation EGFR TKI

As mentioned previously, alectinib is a second generation irreversible EGFR TKI with demonstrated clinical activity in patients with NSCLC in the LUX-Lung trials (57,58). In LUX-Lung 4, a phase II trial of alectinib in patients who had progressed during prior treatment with first generation EGFR TKIs, alectinib showed modest efficacy in this setting. A pre-planned subgroup analysis of the LUX-Lung 3 trial, which evaluated Aftatinib versus pemetrexed and cisplatin which allowed patients with stable BM, demonstrated a progression free survival (PFS) of 11.1 months with alectinib versus 5.4 months with chemotherapy (HR, 0.52; p value 0.13) (59). A retrospective study from earlier this year evaluated the efficacy of alectinib in the pretreated NSCLC patient with BM who had received at least one prior chemotherapy and one line of EGFR TKI (60). Of one hundred patients with BM or leptomeningeal disease, 74% having documented EGFR mutations, 35% of evaluable patients had cerebral response with 16% responding exclusively in the brain. Alectinib has demonstrated benefit in the heavily pretreated patients, even in those with previous EGFR TKIs, but we will have to await further well designed clinical trials to assess if there is definite benefit in the front line setting. The newest addition to this class of medications is the third generation irreversible EGFR TKIs, which overcome T790M mutation, an acquired resistant EGFR mutation found in 50-60% of patients on current first or second generation TKIs. AZD9291 and Rociletinib (previously CO-1686) are two of these medications with publications from phase I-II studies demonstrating efficacy in the systemic setting, future studies will hopefully better ascertain their potential role in CNS diseases (61,62).

5.2. ALK inhibitors

5.2.1. First generation ALK inhibitors

Anaplastic lymphoma kinase (ALK) gene rearrangements which form fusion oncogenes have been found to be driver mutations in NSCLC. There are multiple variants of this oncogene rearrangement but the first described was EML4-ALK which encodes for a cytoplasmic chimeric protein with constitutive kinase activity and has an incidence of 2-7% of patients with NSCLC (63). ALK oncogenes are associated with younger age, never/light smoker, adenocarcinomas and are responsive to inhibition with ALK TKIs (64). BM are frequently found in ALK-rearranged NSCLC, reported in 35% of patients in the phase III PROFILE 1007 trial (65). In addition, it is one of the most common sites of relapse, even in systemic responders, as reported in an update of the phase I PROFILE 1001 trial (66,67). A recent retrospective analysis reviewing patients with BM enrolled in the PROFILE 1005 and 1007 studies indicated limited long term efficacy in regards to treatment of BM (68). There were 31% of patients who had asymptomatic BM at time of entry and median duration of response was 8 weeks for intracranial disease versus 58 weeks for systemic disease. In addition, median time to progression (TTP) was 7.0 months for intracranial disease versus 12.5 months for systemic. The possible mechanisms underlying this high propensity to develop BM are uncertain but include secondary resistance or low concentration of drug in the CSF leading to inadequate exposure of drug to BM. Low CSF concentrations have been documented and a case report has demonstrated response to high dose crizotinib providing some support for this hypothesis (69,70). Brain-only progression is clearly not uncommon in this cohort of patients and thus treatment strategies have been developed to manage this. Potential strategies include brain directed therapy (WBRT or SRS) while continuing crizotinib in order to maintain systemic response and this appears to provide clinical benefit (71). Future studies, including PROFILE 1014, will evaluate crizotinib’s effect on the rate of CNS disease control and brain only progression compared to chemotherapy and provide better insight on its effect on CNS disease.

5.2.2. Second generation ALK inhibitors

Second generation ALK inhibitors have been developed as a result of resistance to crizotinib. They are more potent, with potential to overcome secondary acquired resistant mechanisms. Ceritinib is reported to be 20 times more potent than crizotinib and is approved for patients who have progressed on or are intolerant to crizotinib (72). Reports from ASCEND-1, a phase 1 single arm study evaluating efficacy of ceritinib in pretreated ALK-positive NSCLC patients, showed that 124 of 255 patients had known BM at initiation of study and achieved an overall response rate of 54% and tumor shrinkage was noted in 50% of those with BM who had previous ALK inhibitor treatment (73). Thus indicating activity of this agent in treatment of CNS disease but further updates on these and other studies will help us to confirm these dramatic responses in these heavily pretreated patients.

Alectinib is another highly selective ALK inhibitor that has demonstrated promising clinical activity against BM and overcomes crizotinib resistance. In a phase I/II trial in patients who were ALK inhibitor naive and treated with alectinib, an initial objective response rate of 52% in BM (74). A second phase I/II trial evaluating alectinib in patients with resistance to crizotinib found 21 patients with BM at baseline and demonstrated that in regards...
to the BM there was a 29% complete response, 24% a partial response and 38% with stable disease in addition it has been reported that a linear correlation exists between the concentrations of free alectinib in the CSF and in the serum, suggestive of a high degree of penetration (75). These are more promising results using the next generation ALK inhibitors and the updated results of the phase II portion of this trial will help to further delineate the clinical activity within the CNS. Current studies comparing alectinib and crizotinib, with time to CNS progression as a secondary endpoint (NCT02075840), in the ALK inhibitor-naive patients will help decide whether these newer agents can be moved in the front line setting. Several promising newer agents are in the pipeline that have the potential to further target CNS disease, including PF-06463922 which was designed to increase potential CNS penetration and act as a more potent ALK inhibitor, as well as X-396 which has demonstrated CNS responsiveness in phase I studies (76,77).

6. IMMUNOTHERAPY

An immune system that is intact can recognize and eliminate tumor cells through immune check-points but tumors have been able to adapt and escape this defense mechanism. One such method is PD-1 (programmed cell death protein 1), an immunoinhibitory receptor that is expressed on T cells, B cell, monocytes, natural killer cells and many tumor infiltrating lymphocytes (78). There are two ligands that have been reported, PD-L1 and PD-L2, which are noted to be expressed on a range of cells from T and B cells to endothelial cells and certain tumors have high expression of these ligands inhibiting T-cell proliferation and cytokine production (79,80). By blocking this pathway in cancer cells one could modulate the antitumor immune response. An additional theoretical advantage with addition of radiation therapy is the abscopal effect, which is an immunologic mediated effect where radiation leads to antigen release and this stimulates immune cells to induce tumor cell death outside of the radiation field (81). This can be thought of as using radiation to prime the immune response by providing antigen stimulation with the hope of improving response rates at non-irradiated sites. This is an exciting area of interest and with more experience and use of these PD-1 inhibitors we can further understand and utilize the abscopal effect.

Nivolumab, a fully human, IgG4 immune checkpoint inhibitor antibody, binds PD-1 on activated immune cells to disrupt PD-1 interaction with its ligands and augment the antitumor response. In the CheckMate 063 trial, a phase 2, single arm trial evaluated the activity of nivolumab of advanced refractory squamous NSCLC and reported 17/117 had an objective response and 30/117 had stable disease with a median time to response of 3.3 months (22). It was noted that four patients had baseline BM and there were responses noted, suggesting clinical activity, but no documentation of how many responded is noted in the study. Whether this will play a more prominent role in the management of BM will be answered with a large currently enrolling clinical trial (NCT01454102). One of the treatment arms in this study will be evaluating the activity of nivolumab in NSCLC patients with untreated, asymptomatic brain metastases with no evidence of cerebral edema. The estimated completion date is November 2017 at which time will find out if immunotherapy will add to our armamentarium against this difficult-to-treat process.

7. ANGIOGENESIS

Preclinical data from animal models support the potential role of antiangiogenic agents for the prevention and treatment of brain metastasis. Elevated VEGF expression has been linked to the development of brain metastasis in a murine model (82). The idea of targeting angiogenesis in metastatic lung cancer is supported by the idea that different tumor types have a different growth pattern, for example, lung carcinoma is highly dependent on angiogenesis and melanoma is less dependent on angiogenesis (83).

Bevacizumab is a recombinant monoclonal antibody targeting VEGF. Concern over the potential for cerebral hemorrhage generally prevented its use in patients with BM. The PASSPORT trial, phase II trial evaluating safety of bevacizumab in patients with NSCLC and previously treated BM, enrolled 115 patients and after a median of five cycles there were no reported episodes of grade ≥ 2 CNS hemorrhage (84). A retrospective analysis of bevacizumab safety in BM demonstrated a similar risk of develop of cerebral hemorrhage, with 3.3% of bevacizumab treated patients developing cerebral hemorrhage and only one control-arm patient developed cerebral hemorrhage (85). Thus from these limited studies, the use of bevacizumab in the treatment of NSCLC with treated BM seems to be safe and not predispose to a major risk of cerebral hemorrhage. The BRAIN trial, a phase II prospective study investigated the efficacy and safety of bevacizumab in chemotherapy naïve or pretreated patients with non-squamous NSCLC and asymptomatic untreated BM (86). This demonstrated acceptable safety in this population and a median overall survival of 16.0 months and PFS of 6.7 months. The data is continuing to build for the use of bevacizumab in NSCLC and BM and will await further data to support or refute this finding. Something to keep in mind is that when using bevacizumab to treat patients with glioblastoma, it’s been noted that some patients are developing relapse with a more aggressive tumor. One retrospective analysis of 37 patients with glioblastoma multiforme treated with bevacizumab noted 35% of patients with increased nonenhancing tumor and this pattern of progression was associated with shorter OS (87). Whether this will be also seen in patients with LC-BM treated with bevacizumab is
not known but is something that we should be aware of as a possible outcome.

8. SUMMARY AND PERSPECTIVE

Precision medicine is upon us and the use and investigation of additional targeted agents will continue and provide viable options for selected patients in hopes of improvements to survival. BM will continue to be a problem, even in this population. Whether a patient has an EGFR mutation or ALK fusion protein, there appears to be some response in BM, but this occurs less when using the first generations of targeted agents. There have been improved responses with advancing generations of targeted agents, with new drugs better designed to overcome various mechanisms of resistance and/or overcoming barriers to get penetrate the CNS. We are in the beginnings of understanding of how to utilize and improve these targeted agents to treat BM in conjunction with local therapies. More clinical studies are warranted to see which treatment strategies work best in BM.

Currently, patients with an actionable mutation with asymptomatic BMs have a reasonable option to delay local therapy with close monitoring and treatment with the targeted agent. But patients with symptomatic BMs generally should be treated with standard therapies including radiation therapy or surgery. In these patients, it is preferred to use SRS to avoid the toxicities of WBRT upfront. Immunotherapy also has potential in the treatment of BM and hopefully with ongoing trials and we can gain sufficient experience to clarify its role in the treatment of BM in lung cancer patients. The use of concurrent therapies of targeted agents and local therapies like SRS to treat BM with stable systemic disease offers viable options to the armamentarium against this difficult to treat complication of NSCLC.

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Treatment of brain metastases of lung cancer


87. F Iwamoto, L Abrey, K Beal, P Gutin, M

**Abbreviations:** NSCLC: non-small cell lung cancer; BM: brain metastasis; BBB: blood-brain barrier; LC-BM: lung cancer brain metastasis; WBRT: whole brain radiation therapy; SRS: stereotactic radiation surgery; TKI: tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; CNS: central nervous system; DCR: disease control rate; RR: response rate; OS: overall survival; ALK: anaplastic lymphoma kinase; TTP: time to progression; PD-1: programmed cell death protein 1; VEGF: vascular endothelial growth factor

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