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Systemic therapy for brain metastases

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Abstract

Metastases from cells outside of the central nervous system are the most common cancer found in the brain and are commonly associated with poor prognosis. Although cancer treatment is improving overall, central nervous system metastases are becoming more prevalent and require finesse to properly treat. Physicians must consider the biology of the primary tumor and the complex neurological environment that the metastasis resides in. This can be further complicated by the fact that the practice of cancer management is constantly evolving and therapy that works outside of the blood-brain barrier may not be effective inside of it. Therefore, this review seeks to update the reader on recent advancements made on the three most common sources of brain metastases: lung cancer, breast cancer, and melanoma. Each of these malignancies has been the subject of intriguing and novel avenues of therapy which are reviewed here.

Keywords

Systemic therapy; Metastasis; Lung cancer; Breast cancer; Melanoma

1. Introduction

The sine qua non of cancer is the potential to spread beyond its source. This process of metastasis allows tumors to colonize diverse tissues, well beyond what could be achieved by local invasion. Although metastases can be found in any organ, they are particularly worrisome in the central nervous system (CNS) due to their propensity to cause neurological

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Author declaration

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Ethics statement

No experiments were performed on human or animal subjects in the generation of this manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

deficits (Davey, 2002; Nieder et al., 2018). Overall, tumors from foreign tissues, outside of the CNS. are much more common than primary brain cancer and only one of ten cancers found in the CNS originates there (Lassman and DeAngelis, 2003). Additionally, advancement in cancer therapy has resulted in improved survival from many malignancies and therefore more time for cancer to spread to the CNS (Davey, 2002). There has been a concordant rise in the prevalence of CNS metastases meaning that these tumors are of significant and growing concern (Nayak et al., 2012). Many different cancers can give rise to a CNS metastasis. Lung (48%) and breast (15%) cancer, along with melanoma (10%), are the three most common sources of brain metastases. Overall, 10–30% of patients with lung cancer will experience a brain metastasis, compared to 10–15% of breast cancer and up to 60% of stage 4 melanoma (Sandru et al., 2014; Leone and Leone, 2015; Niemiec et al., 2011). The incidence of brain metastases by subtype is a product of both the primary cancer's prevalence and its propensity to metastasize to the CNS.

The challenge in treating metastases arises from their marked heterogeneity of origin and therapeutic response (Nayak et al., 2012). Treating CNS metastases requires an adroit sense of oncology and an appreciation for the neurological complications that cancer, or therapy, can induce. The goal of this article is to review the current state of systemic therapy for CNS metastases, with a special emphasis on the brain. We place a particular importance on new treatments with the goal of providing a broad update on treating the three most common brain metastases.

2. Drug delivery in the context of the blood-brain barrier

Treatment of primary brain cancer, namely glioblastoma, has been hampered by the protection afforded by the semi-permeable blood-brain barrier (BBB) (Stupp et al., 2005). This barrier is composed of numerous endothelial cells and their dense network of tight junctions (Stewart, 1994). Thus, the BBB provides much more selectivity than is typically afforded by vasculature alone, and it is thought to impede 100% of large molecule and 98% of small molecule drugs (Zhang et al., 1992).

Curiously, the BBB, which acts as a major obstacle in primary brain cancer treatment, may be a relatively minor impedance in treating some metastases (Davey, 2002; Donelli et al., 1992; Lesser, 1996). Unlike primary brain tumors, many metastases appear to respond, at least partially, to drugs that have activity against the primary tumor (Lassman and DeAngelis, 2003; Lesser, 1996; Chamberlain et al., 2017). Studies aimed at teasing apart this paradox have identified that, in the process of spreading and invading the CNS, metastases disrupt the BBB and make it permeable to many systemic agents (Lesser, 1996). This gives neuro-oncologists the opportunity to apply diverse medications against brain cancer. However, disruption of the BBB is not ubiquitous across all cancers and systemic therapy plays various roles that largely depended on the primary (Chamberlain et al., 2017; Whitsett et al., 2013). Like all systemic therapy design, the identity and context of the cancer is important. As a general concept, CNS metastases appear to exhibit similar chemosensitivies as their primary tumor (Chamberlain et al., 2017; Whitsett et al., 2013). Metastases are treated based on subtype, which informs the remaining structure of this review.

3. Specific considerations for therapies by tumor type

3.1. Lung Cancer

Lung cancer is the leading cause of cancer death in the United States and the most common source of brain metastases (Barnholtz-Sloan et al., 2004; Herbst et al., 2008). These malignancies are broadly categorized into small cell lung carcinoma (SCLC), which originate from neuroendocrine cells, and non-small cell lung carcinoma (NSCLC), which includes large cell carcinoma, squamous cell carcinoma, and adenocarcinoma (Herbst et al., 2008). This division separates out the more chemosensitive SSLC from the typically more chemoresistant NSCLC – attributes that tend to carry over to metastases.

There have been a number of studies that have identified objective responses of SCLC metastases in the CNS to systemically administered chemotherapy (Chen et al., 2008; Postmus and Smit, 1999). Most notably are Twelves et al. who reported a decrease in size in 9/14 (64%) patients that were treated with a combination of cyclophosphamide, vincristine and etoposide (Twelves et al., 1990). The findings on imaging were corroborated by a concordant reduction in neurological symptoms (Twelves et al., 1990). Kristjansen et al. had similar results with a trial of multidrug chemotherapy and reported a response in 11/13 patients and a median response time of 135 days (Kristjansen et al., 1993). Both of these studies found that CNS metastases have modestly reduced response rates when compared to extra-cranial metastases. This suggests that the BBB will at least partially limit chemotherapy diffusion, or else that cells capable of metastasizing through the BBB are more resistant to typical agents (Twelves et al., 1990; Kristjansen et al., 1993). Whole brain radiotherapy (WBRT) is the most common treatment modality for SCLC brain metastases and there has been persistent interest in combining chemotherapy with radiation. However, a meta-analysis of 3 randomized control trials (RCTs) (n = 192) found no differences in overall survival (OS) in patients treated with combined WBRT and various chemotherapeutics(Reveiz et al., 2012). SCLC, like other forms of lung cancer, carries a poor prognosis independent of dissemination to the CNS. It appears that chemotherapy is able to prolong PFS in patients with intracranial metastases from SCLC, but this does not translate to improved OS (Reveiz et al., 2012).

NSCLC is typically less responsive to chemotherapy than SCLC, and this principle appears to apply to metastases as well (Herbst et al., 2008; Dempke et al., 2015). A combination of etoposide and cisplatin affected a response rate of 30% in brain metastases for previously untreated patients, which is markedly less than what is seen in SCLC (Twelves et al., 1990). Despite numerous trials using other cytotoxic drug combinations, no systemic regimen has been able to rival radiotherapy alone (Twelves et al., 1990).

However, over the past 15 years, there has been a rise in the use of small molecule inhibitors for NSCLC. The first example of these in NSCLC are the epidermal growth factor receptor tyrosine kinase (EGFR-TKI) inhibitors, erlotinib and gefitinib, which have effects on EGFR-mutated cancers (Dempke et al., 2015). These agents have been shown to produce great responses in intracranial tumors (60–80%), but ultimately appear to have a relatively transient effect (6.6–11.7 months) (Dempke et al., 2015). Currently, radiotherapy appears to have better results than EGFR-TKI inhibitors and combining these treatments does not have

an additive effect (Chamberlain et al., 2017; Dempke et al., 2015). However, more recent results out of the FLAURA trial show sustained effects with osimertinib (PFS 18.9 months), which is a third-generation EGFR-TKI inhibitor. In addition to improved PFS, the FLAURA trial found an a death hazard ratio that favored treatment with this biologic (HR: 0.63, p = 0.0068) (Vansteenkiste et al., 2017). This agent has engendered considerable optimism due to its modest side-effect profile and strong efficacy, but much of the support has yet to be substantiated outside of its initial trial (Soria et al., 2018).

Work with the ALK tyrosine kinase inhibitors, small molecule drugs that inhibit the constitutive tyrosine kinase activity that results from EML4 and ALK chromosomal fusions, has demonstrated good effects in NSCLC brain metastases. Crizotinib and alectinib have each demonstrated treatment benefit, albeit their use is limited to ALK fusion-positive cancers, which are remarkably rare (3–7% of NSCLC have this fusion) (Shaw et al., 2013; Peters et al., 2017; Pillai and Ramalingam, 2012). Peters et al. determined that alectinib, in particular, appears to have good CNS effect with 17/21 patients having a measurable response and 8/21 having a complete response (Peters et al., 2017). Alectinib will likely take the lead in ALK + NSCLC metastasis therapy and, due to the CNS efficacy, this agent often allows patients to defer surgical resection of their CNS metastases (Gadgeel et al., 2016; Tran and Klempner, 2017). The results of other notable studies on these agents have been organized into a table (Table 1) (Ceresoli, 2004; Iuchi et al., 2013; Welsh et al., 2013; Wu et al., 2013; Costa et al., 2015; Solomon et al., 2016). Lastly, there has been growing interest in the use of PD1-blocking antibodies in NSCLC (Passiglia et al., 2018). This therapy first found success in metastatic melanoma, but clinical trials with Pembrolizumab have yielded intriguing results for patients suffering from intracranial NSCLC metastases as well. Goldberg et al. performed a phase 2 clinical trial () on patients with intracranial metastases due to NSCLC or melanoma (Goldberg et al., 2016). Inclusion criteria for this study included positive PD1 staining, no neurological symptoms and no treatment with glucocorticoids. Eighteen NSCLC patients met these criteria and 6 (33.3%) had durable intracranial response (greater than 1 year). None of the NSCLC patients had neurological side-effects, but colitis and pneumonitis were notable treatment-ending outcomes. Lastly, it is worth noting that as our understanding of oncogenes and cancer genetics expands, so too does the role of more refined immunomodulator selection(Passiglia et al., 2018). However, the optimal dosage, delivery and drugs is still a source of active research (Frega et al., 2018).

In summary, SCLC and NSCLC are different entities, but systemic drugs can play a role for either of them. The role of systemic therapy in SCLC is complicated by the fact that it does not appear to prolong survival. Short of this aim, treatment may still have value as palliation or to delay surgery. However, conventional chemotherapy regimens, which SCLC responds to, have significant patient burden and are unlikely to improve quality of life – whole brain radiotherapy is likely the best option. This narrative is quite different for NSCLC, which is resistant to conventional agents, but may respond to well-selected targeted therapy. The positive findings with osimertinib (effective in EGFR-mutated cancers) are very intriguing. This agent induced enduring tumor response and minimal side-effects. A similar narrative appears to be unfolding for pembrolizumab (effective in PD-1 over-expressing cancers), which had a sustained response and favorable side-effect profile. For patients with EGFR-mutated or PD-1 overexpressing tumors, these agents can be considered.

3.2. Breast Cancer

Breast cancer is the second leading cause of metastatic cancer to the CNS and a growing number of recurrences are identified in the brain, even when no cancer burden is identified elsewhere in the body (Lassman and DeAngelis, 2003; Schouten et al., 2002). Breast cancer has many possible routes of therapy, and there is not an obvious regimen that is recommended to all patients. Regardless, a number of chemotherapeutics have shown efficacy in reducing the tumor size of metastatic breast cancer in the brain (Vick et al., 1977; Lin, 2013). Despite this responsiveness, first-line treatment of CNS metastases from breast cancer is typically stereotactic radiosurgery (SRS), whole brain radiotherapy and/or surgery – to date, there are no systemic therapies FDA-approved for treatment of CNS metastases from breast cancer (Venur and Leone, 2016). As a result, the tumor-shrinking effects of chemotherapy tend to be observed as an additional benefit of chemotherapy for other indications (Vick et al., 1977; Rosner et al., 1986). However, the branch of breast oncology has identified many unique targets in breast cancer that may be of use for CNS metastases in the future.

Endocrine modulating drugs have played a role in treating breast cancer since the 1960s (Venur and Leone, 2016; Salvati et al., 1993a). For tumors that express the estrogen receptor (ER), these agents can have marked effects on tumor growth. However, these effects do not appear to be carried over to CNS metastases (Venur and Leone, 2016; Burton, 2004). It is theorized that by the time breast metastases are identified in the CNS that they may have lost their ER expression (Salvati et al., 1993a; Burton, 2004; Salvati et al., 1993b). As a result, underwhelming effects are seen when these drugs are given. Despite a few small case studies that have identified tumor size reduction, the overall consensus is that endocrine modulation is not a suitable approach to CNS disease (Venur and Leone, 2016; Burton, 2004; Bousquet et al., 2016).

The history of breast cancer is also notable for the discovery of HER-2/neu – a potent transmembrane oncogene in the epidermal growth factor receptor (EGFR) family that is overexpressed in 30% of breast cancer patients (Lin, 2013). In the 1990s clinical trials validated this gene as an actionable target and trastuzumab became an essential drug in the management of breast cancers with Her-2/neu upregulation. In 2001 Slamon et al. demonstrated a 20% risk reduction of death in patients treated with trastuzumab in addition to standard of care cytotoxic therapy (Slamon et al., 2001). While the addition of this single agent was of great benefit to patients overall, this drug appears to have relatively minor effects on CNS metastases (Slamon et al., 2001; Hudis, 2007). However, enthusiasm for this agent has resurfaced due to the development of trastuzumab-emtansine (T-DM1), which is trastuzumab linked to the cytotoxic tubule inhibitor emtansine (Escrivá-de-Romaní et al., 2018). A growing body of case series and small cohort studies have shown a reduction in brain metastases and prolonged progression-free survival (Ricciardi et al., 2018; Keith et al., 2016; Okines et al., 2017; Bartsch et al., 2015). Most intriguing is the work by Krop et al. who performed a retrospective analysis of the phase 3 EMILIA trial and found significant survival benefit for T-DM1 when compared to capecitabine-lapatinib (HR = 0.38; P = 0.008; median, 26.8 versus 12.9 months). However, as a retrospective review, these findings are not altogether convincing and follow-up studies are needed. The role that this drug will play in

the management of brain metastases remains to be seen, but it has shown great results thus far. Recent work with lapatinib, which acts as a tyrosine kinase inhibitor of the EGFR family, including Her-2/neu, has yielded more promising results against CNS disease (Petrelli et al., 2017). In 2013 the LANDSCAPE trial, which used lapatinib in combination with capecitabine as first-line therapy, demonstrated encouraging potential for this drug (Lin et al., 2009; Bachelot et al., 2013). This work found that 29/44 (65.9%) of patients had an objective response in CNS tumor size (> 50% tumor size reduction) without new neurological deficits (Bachelot et al., 2013). While this study demonstrated clear CNS effects, there is still a need for a randomized clinical trial to determine if this finding translates to a real survival benefit. It also remains unclear how much therapeutic effect is attributable to lapatinib as opposed to the effect of capecitabine alone. Currently, further work is needed to tease apart the effects of each of these drugs and establish the value of adding lapatinib.

In summary, the narrative of systemic therapy for breast cancer is different than the story for lung cancer. With SCLC and NSCLC alike, agents that work on extracranial metastases appear to work on intracranial tumors as well, but breast cancer does not have this symmetry. This is likely due to mutations that breast cancer manifests in order to invade the BBB. At this time, there is no convincing systemic therapy for breast cancer brain metastases (Kodack et al., 2015). If breast cancer brain metastases do indeed have unique mutations, it is likely that specific drugs will have to discovered to combat them.

3.3. Melanoma

Melanoma is an exceptionally rare cancer, but it is the third most common cause of brain metastases (Johnson and Young, 1996). This malignancy has an atypical predilection for the CNS and up to 60% of patients diagnosed with stage 4 melanoma will experience a CNS metastasis (Johnson and Young, 1996). Much of the morbidity ascribed to melanoma is due to neurological damage caused by tumor spread, and CNS metastasis is the worst prognostic indicator in melanoma (Chukwueke et al., 2016). Like many other malignancies, melanoma that has spread to the CNS is partially treated with surgical resection or radiotherapy (especially stereotactic radiosurgery) (Chukwueke et al., 2016). However, melanoma treatment has seen a recent surge in novel therapeutics that also appear to be effective in treating CNS metastases

Two checkpoint inhibitors, nivolumab and pembrolizumab, are notable for their effectiveness in metastatic melanoma (Scott, 2015; Larkin et al., 2015). These monoclonal antibodies are directed against programmed cell death protein 1 (PD-1), a molecule upregulated in cancer that suppresses the immune response. These drugs prevent PD-1 from interacting with its corresponding T-cell ligand (PDL-1) and thus cancer cells are unable to suppress the cytotoxic T-cell response. These PD-1 inhibitors appear to act best in concert with another set of monoclonals, the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (Buchbinder and Desai, 2016). CTLA-4 is expressed on T-cells and interacts with ligands on dendritic cells to prevent immune responses. In the process of establishing immune quiescence, dendritic cells present tumor antigens simultaneously with the CTLA-4 ligands (CD80 and/or CD86) and immune tolerance is produced. CTLA4 antibodies act to

disrupt dendritic cells inhibiting T-cell activation in the context of tumor antigens – in short, they work by inhibiting immune tolerance to cancer markers (Buchbinder and Desai, 2016). Without these antibodies, dendritic cells inhibit T-cell activation against cancer antigens and the immune system does not respond to the malignancy (Buchbinder and Desai, 2016). The combined PD-1 and CTLA-4 blockade has had considerable success, both in the CNS and outside of it. The Checkmate 204 study, which looked at asymptomatic brain metastases, showed a 55% intracranial overall response rate (ORR) and a similar extracranial ORR of 49% (Tawbi et al., 2017). Sixty-five percent of patients had PFS at 6 months (Tawbi et al., 2017). The Australian ABC trial, which was similar to Checkmate 204 in structure, reported similarly outstanding results. This team had an intracranial ORR of 42%, an extracranial ORR of 48%, and a 6 month PFS of 46% (Long et al., 2017). This project primarily looked at patients with asymptomatic CNS metastases and there is not yet a comprehensive study identifying the benefit of these drugs in symptomatic patients. The median survival has not been identified yet, which signifies how recent these studies are and how much promise still remains in this approach.

Additional molecular targets for melanoma are enzymes in the mitogen-activated protein kinase (MAPK) pathway (Chappell et al., 2011). Drugs specifically targeting BRAF and MEK have shown independent efficacy, and combining therapy to target both of these proteins simultaneously has shown remarkable benefit (Chappell et al., 2011). The major limitation of this approach is that the more robust findings are present only in patients with BRAF mutations, namely the activating BRAFV600E or BRAFV600 K mutations (Marranci et al., 2017; Shtivelman et al., 2014). Ultimately, about 50% of patients will have a BRAF mutation, most of which are BRAFV600E. The BREAK-MB trial was the first to assess the impact that a BRAF-inhibitor, dabrafenib, had in brain metastases. This study found that 44 (58%) of asymptomatic patients with BRAF600E mutations had an intracranial response(Long et al., 2012). Impressively, even patients that were less ideal candidates due to other BRAF mutations, prior therapy, and/or neurological symptoms also had response rates ranging from 44 to 59% (Long et al., 2012).Additionally, this work found that, as a single agent, dabrafenib had a relatively modest duration of effect and it was posited that a more enduring effect could be achieved with multiple agents. The COMBI-MB trial, a multi-institutional study that combined dabrafenib and trametinib (a MEK inhibitor), explored the effects of these drugs in brain metastases(Long et al., 2012; Falchook et al., 2012; Davies et al., 2017). The median response time ranged from 4.5 to 8.3 months, depending on the patients' clinical profiles at the onset of the trial(Long et al., 2012). The treatment effect was always expected to be limited, but it was notable that intracranial response was less than the reported extracranial benefit(Long et al., 2012; Falchook et al., 2012; Davies et al., 2017). This raises the possibility that melanoma that metastasizes into the CNS evolves altered molecular targets compared to the primary tumor, or that these agents are exceptionally poor at crossing even a diseased BBB(Long et al., 2012). Regardless of the explanation, MAPK targeted dual therapy is able to induce broad, if ephemeral, remission in CNS metastases and has a favorable safety profile(Long et al., 2012, 2012; Falchook et al., 2012; Davies et al., 2017).

4. Conclusion

A key hallmark of cancer is its ability to spread and inhabit distant tissue (Hanahan and Weinberg, 2011). Malignancy that spreads to the brain can be exceptionally problematic and cause a myriad of neurological sequelae. Tumors that have migrated to the CNS may be treated with surgical resection or radiotherapy, but some may respond to systemically administered chemotherapy as well. Cytotoxic agents have historically induced modest reduction in tumor mass and will likely have a role in the management of CNS metastases alongside surgery and radiation. Many novel agents have entered the realm of CNS metastasis therapy and have expanded the options for treating these devastating tumors. Despite these advancements, there is still a great need for treatments that induce robust and sustained effects on CNS metastases.

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Table 1

Additional Studies performed on Non-Small Cell Lung Carcinoma (NSCLC).

Mechanism	Agent	Paper, Study Type	Intracranial Response	Impression/Effect	Notes	Toxicity
EGFR tyrosine kinase inhibitor	Gefitinib	Ceresoli et al., 2004 Clinical Trial	Response Rate: 10% Median PFS: 3 mo	Disease control rate higher in patients pre-treated with WBRT and with adenocarcinoma.	Did not enroll based on EGFR Status Disease control rate higher in patients pre-treated with WBRT and with adenocarcinoma.	Grade 1 and 2 skin toxicity (24%), Diarrhea (10%)
		Iuchi et al., 2013 Clinical Trial	Response Rate: 88% Median PFS: 14.5 mo	Brain metastases respond favorably to gefitinib regardless of radiation if EGFR mutation is positive.	Only included patients with EGFR mutations Exon 19 deletion associated with better outcomes when treated with gefitinib.	Grade ≥4 toxicity: 0
	Erlotinib	Welsh et al.,2013 Clinical Trial	Response Rate: 86% Median PFS: 11.8 mo EGFR wild type: 9.3 mo EGFR mutation: 19.1 mo	Erlotinib + WBRT is well tolerated and has a favorable response rate.	Eligible patients: NSCLC with brain metastases regardless of EGFR status Erlotinib + WBRT	Grade 3 rash requiring dose reduction: n = 3 Grade ≥4 toxicity: 0
		Wu et al., 2013 Clinical Trial	Response Rate 58.3% Median PFS: 10.1 mo EGFR mutation positive: 15.2 mo EGFR wild type: 4.4	Erlotinib is active and well tolerated in this patient population.	Eligible patients: asymptomatic brain metastases without extracranial progressive disease post first-line platinum doublet chemotherapy	Rash: 77.1% Paronychia: 20.8% Hyperbilirubinemia: 16.7% Diarrhea: 14.6%
ALK tyrosine kinase inhibitor	Crizotinib	Costa et al.,2015 Retrospective Review	Response Rate: 56% Median PFS: 7 mo	Those who have systemic disease control are more likely to have intracranial disease control at 12 weeks.	Eligible patients: advanced ALK-rearranged NSCLC already enrolled in clinical trial PROFILE 1005 or 1007 and randomly assigned to crizotinib retrospectively reviewed Phase III PROFILE 1014 study in ALK-positive NSCLC	N/A
		Solomon et al.,2016 Clinical Trial	Response Rate: 85% Median PFS: 9 mo	Crizotinib + chemotherapy have higher intracranial disease control rate in patients with treated brain metastases.		Safety comparable to patients without CNS metastases