Review Article

Genomic profiling of brain metastases: current knowledge and new frontiers

Martha R. Neagu*, Corey M. Gill*, Tracy T. Batchelor, Priscilla K. Brastianos

Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

*These authors contributed equally to this article.

Correspondence to: Priscilla K. Brastianos, MD. Division of Neuro-Oncology, Stephen E. and Catherine Pappas Center for Neuro-Oncology, Harvard Medical School, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, USA. Email: pbrastianos@partners.org.

Abstract: Brain metastases (BM) constitute the majority of intracranial cancers and carry with them a dismal prognosis. Several common cancers have a particular predilection for spread to the brain, amongst them lung cancer, breast cancer, melanoma, renal cell carcinoma (RCC), and more rarely gastrointestinal (GI) cancers. While prognosis has historically been poor and multimodality treatment combining surgery and radiation therapy was the mainstay of treatment, the genomic revolution in cancer therapy is finding increasing applications in treatment of central nervous system (CNS) disease. Targeted therapy, combined with advances in the evaluation of BM for targetable mutations, is showing increased efficacy. Developments in the understanding of brain tropism and targetable signaling pathways in metastasis are elucidating entirely new treatment approaches. This review focuses on advances made in the understanding of the genomics of BM and how this may change the role of targeted therapeutics in this common complication of cancer.

Keywords: Brain metastases (BM); genomics; targeted therapies; sequencing

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Introduction

Comprising the majority of central nervous system (CNS) malignancies, CNS metastases from systemic cancers are a common and devastating complication in adult cancer patients. Up to 19% of cancer patients develop complications from brain metastases (BM), and at autopsy over 25% are found to have metastases to the CNS (1,2). Most metastatic disease affects the brain parenchyma with 80% of BM found supratentorially and 20% infratentorially (15% in the cerebellum and 5% in the brainstem), with the spinal cord most infrequently involved (3,4). In about 4-15% of patients with CNS disease, cerebrospinal fluid and leptomeninges are involved with devastating sequelae (3,4).

Common cancers to metastasize to the CNS include, lung (40-50%) and breast cancer (15-30%), followed by melanoma (5-20%), renal cell cancer (2-4%), colorectal cancer (3-8%), and less frequently, ovarian cancer (1%) (5,6). Cancers that metastasize the brain need to undergo multiple steps, including invasion, intravasation into the blood stream, extravasion, survival and proliferation (5). Although an area of active investigation, it is hypothesized that invasion and proliferation into the CNS may be associated with specific molecular programs that may be common in BM (7,8) and likely dependent upon tumor microenvironment (9).

A diagnosis of brain metastasis carries with it a dismal prognosis, especially in cases of poor performance status (Karnofsky performance score, KPS <70) where median overall survival (OS) is 2.3 months (10,11). For younger patients (age <65) with good performance status (KPS >70) OS is about 7.1 months. To date, treatment regimens have included neurosurgical resection of a single lesion when possible or when tissue diagnosis is required, stereotactic radiosurgery (SRS) in oligometastatic disease, as well as whole brain radiotherapy (WBRT) for oligometastatic

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or widespread disease (12,13). While WBRT has been the standard treatment of metastatic disease to the CNS for several decades, neurotoxicity occurs in up to 45% of patients and negatively impacts quality of life (14), highlighting the need for alternative therapies. A substantial obstacle in chemotherapeutic approaches is the difficulty in achieving therapeutic doses in the CNS due to limited BBB penetration (15). With the genomic revolution leading to targeted systemic therapies, targeted agents are assuming an increasingly central role in treatment of brain metastasis with early success in oncogene-addicted cancers such as EGFR or ALK positive non-small cell lung cancer (NSCLC), $BRAF^{V600E}$ expressing melanoma, and HER2/Neu expressing breast cancer (3,4). Because craniotomies are indicated in only a subset of patients, exploring the genomic differences between BM and matched primary tumors has been challenging. This review focuses on advances made in the understanding of the genetics of BM and their primary tumors and how these advances may change the role for systemic therapies in this common complication of cancer.

Brain metastases (BM) from melanoma

While the cumulative incidence of brain metastasis in melanoma patients is less than 10% (16,17), patients with advanced melanoma have a particularly high incidence of BM with brain involvement in 45-50% of patients, rising to 75% at autopsy (18-20). Upon detection of BM, median survival has historically been approximately 4 months (21). Conventional treatment strategies, including surgical removal when possible and radiotherapy (either SRS or WBRT), have been disappointing in disease control since melanoma is not radiosensitive (20,22). Approximately 1-5% of melanoma patients present with leptomeningeal disease, which is associated with an especially dismal prognosis (23). Conventional chemotherapy (including temozolomide, thalidomide, and sorafenib) has also proved disappointing with an objective response rate of 3-5% for temozolomide monotherapy (24,25), increased to 9-44% when combined with WBRT (26,27). Targeted therapies and immunotherapies have revolutionized the management of advanced melanoma, including BM.

BRAF

Approximately 50% of metastatic melanomas have *BRAF* mutations, the majority of which are the V600E mutation resulting in constitutive activation. The mutation prevalence of BRAF is similar between CNS metastases and extracranial sites (3,28). Vemurafenib, a small-molecule inhibitor of the serine-threonine kinase activity of *BRAF* and its downstream MAP-kinase pathway activation, was FDA-approved for the treatment of $BRAF^{V600E}$ positive metastatic melanoma in 2011 (21). The seminal trial (29) that leaded to FDA approval of vemurafenib unfortunately excluded patients with active BM. In a pilot study of 24 patients with melanoma metastatic to the CNS treated with vemurafenib, median PFS was 3.9 months, and median OS was 5.3 with an overall PR at both intracranial and extracranial sites achieved in 42% of patients and SD in 38% patients (30). Resistance to therapy with BRAF kinase inhibitors is associated with reactivation of the mitogen-activated protein kinase (MAPK) pathway. Combining BRAF and MEK inhibitor has resulted in increased efficacy compared to BRAF monotherapy (31). The BRAF inhibitor, dabrafenib, in combination with the *MEK* inhibitor, trametinib, was FDA approved in 2014 for advanced melanoma. Dabrafenib has promising activity in the brain as demonstrated by a Phase 2 trial in patients with $BRAF^{V600E/V600K}$ BM (32).

Immunotherapy in melanoma

Ipilimumab was FDA approved for treatment of metastatic melanoma in 2011 (21). Ipilimumab is a humanized monoclonal antibody blocking the function of the cytotoxic T-lymphocyte antigen 4 (CTLA-4) receptor on T cells, allowing for increased and sustained T cell activation, thus counteracting immune evasion by the tumor (33). In a phase III trial which included patients with treated and radiographically stable melanoma BM, patients treated with ipilimumab had a median survival of 11.2 months compared to 9.8 months for the control arm and 20.8% of patients were alive at three years compared to 12.2% in the control arm, showing capacity for a durable effect (34,35). Promising results were demonstrated in a phase II trial in patients with BM receiving ipilimumab; intracranial disease control was achieved in 18% of patients with asymptomatic BM (36). Whole exome sequencing of tumor tissue from patients with melanoma and treated with anti-CTLA-4 blockade demonstrated a specific neo-antigen landscape in tumors that responded to therapy (37). Whether this same signature correlates with response in BM will need to be evaluated.

Another immunotherapy-based strategy is to target

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programmed cell death-1 (PD-1), an inhibitory signal to activated T cells that is engaged by the programmed cell death ligand-1 (PDL-1) expressed on tumor cells (38). The PD-1 inhibitors nivolumab and pembrolizumab have demonstrated remarkable efficacy in advanced melanoma (38-40). Notably, melanoma BM frequently express PD-1 and PDL-1 (41) and clinical trials evaluating the efficacy of pembrolizumab in CNS metastases are underway (NCT02085070).

Future targets

Likely secondary to ultraviolet light mutagenesis, melanoma has a significantly higher mutation rate compared to other cancers (42). Mutations in *CDKN2A/p16*^{INK4a} appear to be initiators in oncogenesis (43), mutated in 10-25% of sporadic melanomas (43). Accumulation of other somatic mutations in melanoma oncogenesis may provide future targets for therapies and include amplifications in *MYC*, loss of *PTEN*, and mutations in *STK19*, *ARID2*, *APAF-1*, *PKB/AKT*, *N-RAS*, *GRM-3*, *CHRM3*, and *GPR98* (42). The role of these alterations in melanoma progression needs to be explored. BM from melanoma are genomically complex and large scale sequencing studies exploring these differences are being performed (44). Molecular profiling of 16 matched CNS and extracranial metastases showed that CNS metastases distinguished themselves through specific molecular differences in the activation of the PI3K/mTOR/Akt pathway through mechanisms that are under further investigation (45). Preclinical mouse studies demonstrated that treatment of mice harboring intracranial human melanoma with the PI3K inhibitor BKM120 improved OS (45). These findings have been repeated in several melanoma xenografts as well as genetically engineered mouse models (46). These studies highlight the potential of adding PI3K inhibitors as adjunct targeted therapy in the treatment of CNS melanoma metastases.

Lung cancer

NSCLC is the most common lung cancer (>85% of all lung cancers) and has a propensity for CNS spread (47). BM will develop in up to 40% of patients and indicate a poor prognosis. Survival ranges from 2 months if treated symptomatically with glucocorticoids to 14 months if treated with SRS, WBRT, and/or neurosurgical resection (48,49). Systemic therapy has fallen short to date, with platinum-based therapy showing response rates of 28-45% in the up-front treatment of NSCLC metastatic to the CNS (50-54). Temozolomide, an alkylating agent with BBB penetration, which has activity in primary brain tumors (55), demonstrates only modest effects in NSCLC BM (56,57). The antifolate, pemetrexed, has promising activity as combination therapy with cisplatin (58) and as monotherapy (59).

With the discovery of targetable genetic alterations in the treatment of NSCLC, patients are now stratified based on genetic alterations in the primary tumor including the epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and translocations involving the echinoderm microtubule-associated protein like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) genes (60). In a retrospective study of 89 patients with NSCLC treated with SRS for BM, addition of targeted therapies was associated with significantly better outcomes. Patients treated with targeted therapy (against *EGFR* or *ALK*) had a median survival of 21 months compared with 11 months for patients who did not receive targeted therapy (60).

EGFR

Approximately 10% of patients with NSCLC harbor activating mutations in *EGFR* with higher rates found in East Asians, non—or light former smokers, women, and in adenocarcinomas (61,62). Mutations in *EGFR* predict sensitivity to the small molecule tyrosine kinase inhibitors (TKI) gefitinib and erlotinib (3,4). When *EGFR* mutation rates were compared in matched tumor and metastases, discordance rates were reported in up to a third of cases (63-65); specifically, the rate of discordance was 27% in BM compared to their primary tumors (63).

Erlotinib shows promise for treatment of BM in patients with NSCLC. In a study of 69 NSCLC patients with BM, 17 harbored the *EGFR* mutation and were predictive of benefit from EGFR-targeted therapy in systemic metastatic disease. Of this subgroup, 82.4% had a response to therapy and time to progression in the brain was 11.7 months compared to 5.8 months in patients without an activating mutation (66). In a study of erlotinib with WBRT in a cohort of newly diagnosed NSCLC patients, 50% of whom harbored an *EGFR* mutation, response rates were 86% (67). In a randomized study comparing WBRT *vs.* WBRT with erlotinib in unselected patients with newly diagnosed brain metastasis, only 3% of which harbored *EGFR* mutations, there was no improvement in survival in the erlotinib arm (68).

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In addition to the success seen with erlotinib treatment, gefitinib has demonstrated promise in the management of BM from NSCLC. In heavily-pretreated unselected patients with recurrent BM, gefitinib showed a response rate of 10% (69), and in a selected population of non-smokers of Asian origin, a response rate of 32% (70). When combined with WBRT, gefitinib showed an 81% response rate in a prospective study of Asian patients with newly diagnosed metastatic NSCLC (71). Given the limited response in studies of unselected patient groups, treatment with EGFR-targeted therapy should be reserved for patients harboring actionable mutations in *EGFR* (72).

ALK rearrangements

The *EML4-ALK* translocation results in a cytoplasmic protein with constitutively active kinase activity (73) and is found in 2-7% of all NSCLC with a higher prevalence in light or never smokers, younger patients, and adenocarcinomas (74). *EML4-ALK* translocation predicts sensitivity to the small molecule TKI, crizotinib, and responses have been seen in patients with *EML4-ALK* translocation with lung cancer BM (75,76). *ALK* translocations were reported to be 100% concordant between primary tumor and BM. *ALK* amplifications, however, are more frequently found in BM compared to primary tumors with a discordance rate of 12.5% in matched primary tumor and brain metastasis studies (77). Progression of BM in patients with *ALK* translocations receiving crizotinib have been reported (78), and a highly selective and potent ALK inhibitor with strong CNS efficacy, alectinib, is showing promising results in crizotinib-resistant NSCLC metastases (79,80). In a study of 47 patients who progressed on or were intolerant to crizotinib, alectinib was well tolerated: objective responses rates were 55% with 2% complete response (CR), 52% partial response (PR), and 36% stable disease (SD) (80). Of the 21 patients with baseline BM, intracranial responses were found in 52%, with 29% showing CR, making alectinib an attractive salvage therapy in the setting of crizotinib failure (80). NCT02075840 is a phase III trial comparing crizotinib and alectinib in treatment-naïve patients (72).

Other candidate targets in systemic treatment of NSCLC BM

With immunomodulatory agents showing durable responses in advanced NSCLC (81), trials are underway to explore the role of these therapies in NSCLC BM (NCT02085070). Comprehensive genetic assays have also uncovered many additional candidate genes that are now crystallizing as potential future predictive biomarkers or therapeutic targets in NSCLC (65,82,83). Sequencing of squamous cell carcinomas demonstrated that *PI3K* pathway alterations are associated with more aggressive disease and with the development of BM (84). The v-Ros avian UR2 sarcoma virus oncogene homolog 1 (*ROS1*) harbors mutations in 1.3% in NSCLC BM and predicts response to crizotinib (85), providing a further target for systemic therapy. Mutations in *BRAF* have been reported in ~3% of NSCLC and 0.3% of NSCLC BM (28,86). Additionally, *LKB1* copy number alterations combined with *KRAS* mutations indeed are predictive of brain metastasis in NSCLC (87). Gene expression analysis suggests the importance of the WNT/TCF pathway in the formation of brain and bone metastases; knockdown of the two WNT genes, *HOXB9* and *LEF1*, decreased brain metastasis formation in mice (88). Overexpression of Oct4, a stemness gene encoding a transcription factor, may correlate with poor disease-free survival and metastasis (89). Approximately 45% of NSCLC BM show overexpression of *C-MET* that encodes the hepatocyte growth factor receptor (*HGFR*) with gene amplification found in 21.6% of NSCLC (83). With multiple c-Met inhibitors under development, this is a further attractive target for therapy. Finally, the relatively high rate of *FGFR1* amplifications, reported in 19% of BM from squamous cell lung carcinoma and 15% of BM from adenocarcinomas, makes *FGFR1* inhibitors a promising target for drug development (82). While many of these multiple potential targets may not always be expressed in a high proportion of lung cancer BM, the potentially potent response in individual patients harboring actionable mutations in either the primary tumors or the BM highlights the need for sequencing of lung cancer BM and adoption of personalized treatment for patients.

Breast cancer

Ten to thirty percent of breast cancer patients develop BM, with younger age and the presence of lung metastases as risk factors for CNS spread (90,91). Breast cancer is a histologically and genetically heterogeneous disease, classified by expression of the estrogen (ER) and progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2/neu).

HER2-amplifed tumors have a high rate of spread to

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the CNS (92). Similarly, triple negative breast cancer has a propensity for CNS spread and up to 46% of patients with advanced triple negative disease develop BM (4). Cytotoxic therapies in breast cancer BM have been employed with some success. Phase II trials of methotrexate or cyclophosphamide containing regimens show response rates of 17-59% (93,94), cisplatin combined with etoposide show responses of 38-55% (52,95), and topotecan (96) and capecitabine (97,98) have activity in small studies and case reports.

Steroid hormone receptors

About 60% of breast cancers are ER and/or PR positive and respond to endocrine treatment (99). Modulation of steroid hormone receptors is one of the earliest targeted therapies used in CNS metastases (100). Tamoxifen, a selective estrogen receptor modulator, harbors activity in the CNS (100). Case reports have also described activity of letrozole in the CNS (101,102). Loss of hormone receptor expression occurs in up to 50% of BM in a retrospective series of matched primary and BM pairs (103). Heterogeneous expression of ER/PR in patients with multiple BM may lead to mixed responses to hormone treatment (3).

HER2

HER2-positive breast cancer has a higher risk of CNS spread and up to 30% of patients with HER2-positive breast cancer will develop BM (4,92,104,105) with up to 50% of these patients succumbing to CNS disease (106). Protein overexpression or gene amplification of HER2 is found in ~15% of breast cancer and strong HER2 overexpression (3+ by IHC) predicts response to HER2-targeted agents such as trastuzumab, lapatinib and T-DM1 (3,107,108). HER2 discordance between primary tumors and metastases is associated with decreased OS and occurs in up to 24% of cases (109,110), with up to 14% of BM patients showing a change in HER2 status (111). Lapatinib, a small molecule TKI of HER2 and HER1 is FDA approved in combination with capecitabine for the treatment of trastuzumab-resistant metastatic HER2 positive breast cancer (4). While lapatinib monotherapy showed a CNS response rate of only 6% (112), combination with capecitabine increased response rate to 65% in newly diagnosed HER2 positive BM (113) and 20% in patients pre-treated with WBRT or SRS (112). T-DM1 is an antibody-cytotoxic drug conjugate of trastuzumab and emtansine (4). Case reports showing shrinkage of HER2-positive BM (114,115) have led to a phase 1 clinical trial of T-DM1 in combination with WBRT (NCT02135159) for treatment of HER2-positive BM. Leptomeningeal carcinomatosis occurs in 2-5% of HER2-positive breast cancer patients with a high concordance rate of HER2 expression in CSF tumor cells and primary tumors (3,116). Trials are underway to investigate the use of intrathecal trastuzumab in this setting (NCT01325207).

Triple-negative disease

Triple-negative breast cancer poses a special treatment challenge, lacking actionable targets to date. Because patients with triple negative disease have a high extracranial metastatic burden, they typically succumb from systemic disease (117). Since BM are common in these patients and median OS is a dismal 5 months (117,118), targetable genetic alterations in triple-negative breast cancer is an active area of investigation (44). Recent genomic profiling studies have focused on identifying metastases specific pathway alterations (119,120) with advances made in stratifying triple-negative breast cancer into four molecular subtypes, offering future therapeutic targets (121). Whole genome sequencing of metastatic triple-negative breast cancer found recurrent mutations in *TP53*, *LRP1B*, *HERC1*, *CDH5*, *RB1*, and *NF1*; while RNA sequencing resulted in the finding of consistent overexpression of the FOXM1 gene (122). Moreover, 20% of triple-negative breast cancers show expression of PDL-1 (123), resulting in checkpoint-blockade immunotherapy as an attractive option for patients with triple-negative BM (3). Methylome sequencing in triple-negative breast cancer showed distinct methylation profiles which correlate with prognosis (124). Characterization of methylation patterns may help identify additional predictive biomarkers in the future.

Future targets

Angiogenesis plays a key role in brain metastasis formation and in mouse models of breast cancer BM, increased VEGF expression contributed to BM formation (125). Bevacizumab is an antiangiogenic humanized monoclonal antibody targeting the vascular endothelial growth factor A that is being investigated for the treatment of breast cancer BM (126,127). Newer targets are also emerging as genomics are broadly applied to primary and metastatic breast cancers. Large-scale genomic characterization of primary breast tumors demonstrated that the only genes to

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occur at more than 10% incidence across all subtypes were *TP53*, *PIK3CA*, and *GATA3* (128). Other genes recurrently mutated in breast cancers include *AKT1*, *CDH1*, *MAP3K1*, *PTEN*, *CDH1*, *RB1* and *CDKN1B*. Notably, the PI3K-mamalian target of rapamycin (mTOR) pathway shows consistent activation in breast cancer BM (129,130) and clinical trials of small molecule inhibitors of the PI3K/mTOR pathway for treatment of breast cancer CNS metastases are underway (NCT01783756). Analysis of BRCA-1 and 2 mutations is an important avenue, as these tumors are particularly sensitive to PARP inhibitors such as olaparib (131), which penetrates the BBB (132), making this drug an attractive targeted therapy in the treatment of BRCA-1 and 2 mutated BM. Furthermore, gene expression and functional analyses in *in vitro* and *in vivo* models identified *ST6GALNAC5*, *COX2* and *HBEGF* as potential mediators of CNS metastasis (133). The role of these genes as potential therapeutic targets needs to be explored.

Gastrointestinal (GI) malignancies

Morbidity and mortality resulting from advanced GI cancers are most commonly associated with systemic metastases, but clinically significant metastatic involvement of the CNS is seen in all types of GI cancers, with an estimated overall incidence of 3-8% (134). The reported frequency of diagnosed CNS metastases in GI cancers varies by primary site. In a large, retrospective analysis of CNS metastases in cancer patients, BM were detected in 1.8-3% of patients with colorectal carcinoma (CRC) (16,135). CNS disease is also found in association with esophageal cancer (82% of CNS metastases with adenocarcinoma histology), and the incidence of BM was greater in patients who had received systemic therapy (neoadjuvant 8.4%, adjuvant 7.0%, or both 18.4%) than in those treated with surgery only (2.5%) (136). BM appears to be a rare complication of gastric cancer in 0.16-0.69% of patients (137,138).

Presentation of CNS involvement in GI primary tumors tends to occur late, usually in the setting of extracranial systemic disease, and is associated with poor prognosis. Median survival for patients with CRC BM is approximately 6 months (139,140). In patients with esophageal cancer and CNS involvement, median survival is 3.8 months (141) with survival rates at 12 and 24 months of 14% and 3%, respectively (142). In a case series of gastric cancer patients with BM, it was estimated that in unresectable patients, median survival was less than two months, while patients who underwent resection survived an average of 5.4 months (143).

As with all BM, current treatment options include resection, SRS with or without subsequent WBRT, and WBRT alone. For patients with CRC BM, SRS provided local tumor control in 94% with a median OS of 9 months from CNS diagnosis and 5 months from the date of SRS in one case series (144). A number of chemotherapeutic agents have been used in CNS metastatic disease of GI origin, including capecitabine, topotecan, dacarbazine, and temozolomide, which were chosen for some degree of CNS penetration, relative tolerability, and activity in a variety of tumor types that commonly metastasize to the brain as well as primary CNS neoplasms. The most studied agent has been temozolomide, but temozolomide monotherapy showed no benefit in patients with CRC (56,145,146). Targeted therapy for GI BM has been disappointing to date, partly because commonly found mutations lack effective small molecule inhibitors.

Colorectal carcinoma (CRC)

Up to 50% of metastatic CRC show mutations in *RAS* which are associated with a shorter OS and a higher incidence of BM (147). Development of RAS inhibitors has been unsuccessful to date, and drugs targeting RAS processing (R115777/Zanestra, SCH66336/Sarasar, L778,123, BMS-214662) as well as RAS antisense nucleotides (ISIS 2503 and 5732) have been disappointing in clinical trials (148). Targeting MEK (Cl-1040/PD184352) and RAF (BAY43-9006), the immediate upstream effectors of RAF, has shown more promise, but trials in CNS metastatic disease are lacking (148). Notwithstanding, intense efforts at developing RAS inhibitors are underway and are targeting different enzymes required for post-translational RAS processing, inhibition of RAS localization to plasma membrane, and disruption of protein-protein interactions required for RAS signaling (148). $BRAF^{V600E}$ mutations, found in up to 10% of CRC and 5.5% of CRC BM, are associated with unfavorable prognosis and may influence the efficacy of EGFR inhibitors (3,28,149). In a phase I trial of dabrafenib for treatment of melanoma, untreated BM, and other solid tumors, apparent antitumor activity was noted in one case of CRC, making BRAF targeting a potentially useful tool in treatment of *BRAF* mutated CRC BM (149).

Mutations in the PI3K pathway were reported in 10-15% of patients with metastatic CRC (147,150). Approximately 10% of patients have alterations in both the RAS/RAF and PI3K pathway. Whether PI3K pathway

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alterations are independently correlative with prognosis and pattern of metastatic spread (specifically to the CNS) is still an active area of investigation (147,150). While genomic characterization between matched primary and liver metastasis identified shared mutations in *APC*, *KRAS*, *ARID1A*, as well as *PIK3CA* (151), the relationship between primary CRC and BM is currently unknown.

Gastroesophageal cancer

Up to 15% of gastroesophageal adenocarcinomas harbor HER2 overexpression or amplification (3,152). HER2 overexpression is also found in ~14% of gastroesophageal CNS metastases (153). Discordant HER2 overexpression between primary tumors and matched metastases may be an independent predictor of poor OS (154). HER2 overexpression and amplification predicts response to anti-HER2 therapy in gastroesophageal cancer. In a randomized, multicenter phase III trial of 594 patients with advanced HER2 positive gastric or gastroesophageal cancer were randomized to receive trastuzumab with chemotherapy or chemotherapy alone; the addition of trastuzumab increased median OS to 13.8 versus 11.1 months with chemotherapy alone (152). However, this trial excluded patients with BM. Given the poor prognosis of gastroesophageal cancer in the CNS, anti-HER2 therapy, particularly agents that have blood brain barrier penetration, should be considered for selected patients.

Exome and genome sequencing of primary esophageal adenocarcinoma identified recurrent mutations in *TP53*, *CDKN2A*, *SMAD4*, *ARID1A*, *PIK3CA*, *ELMO1*, *TLR4*, and *DOCK2*, many of which are potential therapeutic targets (155). Further work is needed to characterize driver mutations between primary site and BM in gastroesophageal cancers.

Renal cell carcinoma (RCC)

Two to four percent of BM derive from RCC and pose an interesting scientific challenge, since they respond to a variety of targeted therapies, but reliable biomarkers for response have not been identified to date, possibly due to the heterogeneity of RCC, which consists of several subtypes (3,156). Comprehensive sequencing studies in primary RCC have demonstrated the importance of the PI3K/AKT/mTOR pathway in the development of renal cell cancer (157,158). A study exploring genetic differences in four patients with renal cell primaries and matched extracranial metastases using whole exome sequencing, chromosome aberration analysis and ploidy profiling demonstrated significant intratumoral heterogeneity, particularly within the primary tumor (159). This heterogeneity likely accounts for differential therapeutic responses observed in the clinic. Current clinical practice employs a gamut of targeted agents and immunotherapies ranging from TKIs (sunitinib, sorafenib), immune modulators (IL-2, IFN-alpha) (160), bevacizumab, as well as immune checkpoint inhibitors including PD-1 inhibitors (3,161). Indeed, targeted therapies in RCC brain metastasis management have not been associated with an increase in neurologic adverse events (162). Notwithstanding relative efficacy of various therapies, resistance occurs especially to TKIs and active efforts to identify predictive molecular markers for targeted therapy are essential (156).

Ovarian carcinoma

Ovarian carcinoma is the most common gynecologic malignancy with a rare predilection to develop BM (1.19%) (6). While there is a documented association between BM incidence from primary ovarian carcinoma and loss of BRCA1 function, little is known of the genomic makeup of these CNS metastases (163). Subtype stratification of ovarian carcinoma BM is currently limited to histology, namely between high-grade serous carcinoma, clear cell carcinoma, carcinosarcoma, and high-grade adenocarcinoma (164). Comprehensive genomic analyses of primary ovarian carcinomas revealed *TP53* mutations in 96% of the high-grade serous subtype (165). Additional recurrent somatic mutations across all subtypes included *NF1*, *BRCA1*, *BRCA2*, *RB1*, and *CDK12*. Furthermore, changes in NOTCH and FOXM1 signaling are indeed important in serous ovarian cancers. Beyond these now characterized genomic aberrations in the primary tumor, too little is currently known about the genomics of systemic and CNS metastases from ovarian carcinoma to offer a potential pathway for targeted therapeutics in this disease.

Conclusions

Given the increasingly prominent role that molecular genetics and targeted therapy are playing in metastatic CNS disease treatment, there is a rising need for reliable and affordable genetic testing as well as for biomarkers of treatment effect in an era when our understanding of the molecular heterogeneity of cancer and its interaction

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with the local microenvironment is changing dramatically. With the increase of effective small molecule inhibitors, paralleled by the increase in known actionable genetic alterations, high-throughput whole genome sequencing, copy number assessment, and genome-wide methylation screens are increasingly incorporated into clinical practice and are vastly expanding the clinical trial landscape for CNS metastatic disease. The genetic signature of CNS and systemic metastases can differ, however, from the primary tumor and may be shaped by the microenvironment and changes in clone-specific gene expression. For both breast and melanoma CNS metastatic disease, the PI3K/AKT/mTOR pathway is activated compared to primary tumors, revealing targetable mutations that may be induced by the CNS microenvironment (112,114,115,118,130). Further studies are now honing in on common mutations. An expanded repertoire of targeted therapies for CNS BM combined with rapidly improving high throughput genomic analysis point to a future of personalized medicine in CNS metastases.

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