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Brain Metastases as a First Site of Recurrence in Patients Receiving Chemotherapy with Controlled Systemic Cancer: a Critical but Under-Recognized Clinical Scenario

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Abstract

Purpose of review As the treatment of many malignancies has improved, brain metastases (BM) have been observed as a site of the first recurrence in patients with controlled systemic cancers. This suggests that while the administered chemotherapy is effective against systemic cancer, drug concentrations in the central nervous system (CNS) are likely too low to be effective. These findings are in accord with data suggesting that more than 98% of FDA-approved drugs on the market today are unable to cross the blood-brain barrier (BBB).

Recent findings This retrospective literature review was conducted to estimate the proportion of patients with non-small lung cancer, breast cancer, and melanoma who develop BM as their initial site of recurrence while their systemic cancers are well controlled. Of 267 studies screened, 12 studies fit criteria for inclusion. These 12 studies reported on 923

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patients. According to compiled data across these studies, 16% of patients on chemotherapy with stable or responding systemic cancer developed isolated BM as their initial site of relapse.
Summary These findings strongly suggest that while chemotherapy controlled systemic cancer, drug concentrations within the CNS were low enough to allow disease progression. Ultimately, reducing the incidence of BM in these patients will require novel therapeutic approaches that facilitate drug entry through an intact BBB early in their treatment.

Introduction

Brain metastases (BM) are a feared and frequent complication of certain malignancies. Historically, the progression of most solid cancers to the central nervous system (CNS) has been associated with a poor response to therapy and therefore poor prognosis. However, as the treatment of solid tumors has improved, BM have been observed as a site of first recurrence in patients with controlled or responding systemic cancers. This suggests that while chemotherapy is effective for the systemic disease, drug concentrations in the CNS are likely subtherapeutic. These findings are in accord with data suggesting that over 98% of FDA-approved drugs are unable to penetrate the blood-brain barrier (BBB) [1].

Isolated CNS recurrence is already a known problem in select malignancies, such as leukemia and small cell lung cancer (SCLC). Patients with those cancers tend to develop BM early and often—and recognizing this has shaped treatment protocols. In SCLC, for example, the standard of care has included prophylactic cranial irradiation in those patients who show a good clinical response to chemotherapy. The same is true of acute lymphoblastic leukemia (ALL), in which post-remission therapy has included radiation and/or intrathecal chemotherapy to prevent CNS recurrence. But in other malignancies—particularly in solid tumors—prevention of BM is not a focus of early treatment.

Brain metastases occur in 8–10% of all cancer patients and in 40% of patients with metastatic disease [2•]. In those solid tumors with the highest predilection for CNS metastasis, BM occurrences are even higher: 50% in non-small cell lung cancer (NSCLC) cases, 25–46% of triple-negative breast cancer cases, 38% of HER-2-positive breast cancer cases, and 55–75% of stage IV melanoma cases [2•]. Other common solid tumors known to invade the CNS include colorectal and renal cancer, both of which have shown an increasing incidence of brain metastases in the last few decades. In a retrospective analysis comparing two cohorts of patients with brain metastases, one from 1983 to 1989 and the other from 2005 to 2009, there was a statistically significant increase in the number of patients developing BM with colorectal and kidney primaries (24% vs 8%, $P = .002$). Breast and lung cancers persistently showed the highest incidence of CNS metastasis [3].

While most BM are diagnosed in the setting of progressive metastatic disease, there is an under-recognized population among patients with BM who have isolated recurrence in the CNS while their extra-cranial sites remain controlled. In a retrospective analysis of 1953 patients with BM, 45% had a controlled primary tumor at the time of BM diagnosis [4•]. This suggests that a substantial number of patients recur in the CNS while they are receiving chemotherapy.

Purpose of review

In this manuscript, we review the literature in treatable cancers with a high predilection for BM—NSCLC, breast cancer, and melanoma—in order to identify how often patients relapse in the CNS while their primary cancer is controlled. Given that prognosis after BM diagnosis remains dismal, these patients

might derive a crucial benefit from improved delivery of initial systemic therapy to the CNS.

More than 260 studies were screened for inclusion in this PubMed retrospective literature review. Studies were selected that included patients with NSCLC, breast cancer (all subtypes), and melanoma as these cancers have high rates of BM. Only studies in which all patients received chemotherapy or in which findings were reported separately for patients treated with chemotherapy were included. Only studies that reported the first site of recurrence after or during chemotherapy treatment or that specifically reported BM occurrence while primary cancer was controlled were selected. Some studies reported this as a "first site of recurrence," while others reported "isolated" relapse in the CNS. Studies that specified the state of the primary cancer at the time of BM diagnosis—either responding to therapy, stable, or progressing—were included. Primary disease that was either responding to therapy or stable at the time of BM diagnosis was considered "controlled" for the purposes of this review.

A total of 12 papers met our pre-specified criteria for analysis of including data on patients who received chemotherapy for either NSCLC, breast cancer, or melanoma and later developed CNS metastasis while their primary disease was controlled.

Recent findings

NSCLC

Three retrospective analyses of patients with advanced NSCLC were reviewed (see Table 1). In total, data for recurrence patterns of 244 patients treated with chemotherapy for stage III NSCLC was available. The studies showed a range of 22–43% of patients had initial recurrence in the CNS with stable or responding systemic disease. The authors of this paper calculated that a compiled average of 27% ($N = 65$) of the reported 244 patients had first recurrence in the CNS without extra-cerebral progression at the time of diagnosis.

Breast

Six retrospective analyses of patients with breast cancer of all stages and subtypes were reviewed (see Table 2). Four of the six studies selected patients who

Table 1. Non-small cell lung cancer, stage III

Paper	*N* total evaluated	Study type	Treatment	BM first site of disease progression with controlled systemic disease
Ceresoli et al. [5]	112	Retrospective analysis	Chemotherapy + resection; or chemotherapy + radiation	22% ($N = 25$)
Andre et al. [6]	81	Retrospective analysis	Chemotherapy + resection	22% ($N = 18$)
Chen et al. [7]	51	Retrospective analysis	Chemotherapy + resection; or chemoradiotherapy + resection	43% ($N = 22$)

Table 2. Breast cancer

Paper	*N* total evaluated	Study type	Cancer subtype	Treatment	BM first site of disease progression with controlled systemic disease
Bendell et al. [8]	122	Retrospective analysis	Stage IV HER-2-positive breast cancer	Trastuzumab ± other chemotherapy	17% (*N* = 21)
Lin et al. [9]	116	Retrospective analysis	Triple-negative breast cancer	Chemotherapy, ± surgery, ± radiation	8% (*N* = 9)
Paterson et al. [10]	115	Retrospective analysis	Not specified	Chemotherapy + surgery	4% (*N* = 5)
Clayton et al. [11]	93	Retrospective analysis	Metastatic breast cancer	Trastuzumab ± other chemotherapy	19% (*N* = 18)
Yau et al. [12]	87	Retrospective analysis	HER-2-positive advanced breast cancer	Trastuzumab ± other chemotherapy	10% (*N* = 9)
Okines et al. [13]	39	Retrospective analysis	HER-2-positive advanced breast cancer	Ado-trastuzumab emtansine (T-DM1) ± other chemotherapy	10% (*N* = 4)

had received trastuzumab with or without other chemotherapy, one looked at triple-negative breast cancer patients, and one study looked at all-comers with breast cancer who received surgery and adjuvant chemotherapy.

In total, these studies included 542 patients with breast cancer of multiple subtypes, including triple-negative, HER-2-positive, and unspecified. Isolated recurrence in the CNS with stable or improving systemic disease was reported in a range of 4–21% of patients. A compiled total of 69 patients, or 13% of reported cases, had CNS recurrence while their primary disease was controlled.

Table 3. Melanoma, stage IV

Paper	*N* total evaluated	Study type	Treatment	BM first site of disease progression with controlled systemic disease
Majer et al. [14]	50	Retrospective analysis	Biochemotherapy	8% (*N* = 4)
Atkins et al. [15]	48	Phase II pilot trial	Biochemotherapy	4% (*N* = 2)
McDermott et al. [16]	44	Phase II pilot trial	Biochemotherapy	25% (*N* = 11)

Melanoma

Three studies of patients with melanoma were reviewed (see Table 3). Two were phase II pilot trials and one was a retrospective analysis. These three studies included a total of 137 patients who had stage IV melanoma without CNS disease at the time of initial presentation. Data showed a range of 4–28% of patients recurred in the CNS while systemic disease was stable or responding to therapy. Of the total 137 patients evaluated, 12% ($N = 17$) had isolated metastasis to the CNS while extra-cranial disease remained controlled.

Summary

Compiled data from the papers reviewed reveal that 27% of NSCLC patients, 13% of breast cancer patients, and 12% of melanoma patients who were treated with chemotherapy had disease progression in the brain while their primary disease was controlled. This suggests that while systemic therapy has improved the control of extra-cranial solid tumors, the effective agents are not reaching the CNS in therapeutic concentrations. As a result, the brain remains a sanctuary site for disease despite promising responses elsewhere in the body.

Once patients with non-CNS primary solid tumors develop BM, prognosis is poor. In a large retrospective review of 1953 patients who developed BM (all types of primary cancers), the median survival for all patients was 6.4 months. Only 2.9% of patients survived > 5 years and 1.2% survived > 10 years from BM diagnosis [4•]. Treatment options for BM are limited to surgery, radiation, and stereotactic radiosurgery. Systemic chemotherapy is unfortunately not very effective in controlling established intracranial metastases.

In malignancies such as ALL and small cell lung cancer, prevention of BM has been shown to provide superior outcomes when compared with treatment of documented intracranial metastases. Recognizing that 27% of NSCLC patients, 13% of breast cancer patients, and 12% of melanoma patients will have isolated recurrence in the CNS, these patients may also benefit from an emphasis on the prevention of BM early in treatment. This would likely require more effective ways to increase penetration of effective chemotherapeutic agents through the BBB early in their disease.

The BBB, composed of endothelial cells forming tight junctions and efflux transporters, is an anatomic barrier that most systemic therapies, including most molecularly targeted agents, cannot cross. A molecule's ability to cross the BBB depends on its electric charge, its lipid solubility, whether it is bound or unbound to protein, and its molecular weight. In general, molecules greater than 400 Da are too large for passive diffusion across the intact BBB. Once a drug does cross the BBB, efflux transporters such as P-glycoprotein actively restrict drug accumulation [17].

Past efforts to improve drug delivery to the CNS have not been very effective or widely adopted into medical practice. These have included injecting chemotherapy directly into the cerebrospinal fluid (CSF) through lumbar puncture. Unfortunately, intrathecally administered drugs are rapidly cleared by the flow of CSF and the concentrations of drug within brain parenchyma remain very low [17]. Other attempts at directly placing drugs into the CNS include the use of surgically implanted catheters attached to a delivery pump (convection-enhanced delivery) or the implantation of

biodegradable chemotherapy-laden polymeric wafers placed into the surgical cavity at the time of tumor resection. Neither of these approaches is relevant to the prevention of brain metastases [17]. Extensive efforts to synthesize novel compounds or prodrugs to improve CNS penetration have also been largely unsuccessful.

Another approach has included attempts to transiently open the BBB coincident to the administration of systemic chemotherapy. Decades of laboratory and clinical studies have focused on opening the BBB using intra-arterial injections of mannitol into the carotid or vertebral arteries, causing osmotic contraction of the endothelial cells. This opens the BBB for 30–120 min but requires general anesthesia, significant toxicities, and only disrupts the vascular distribution of the catheterized vessel making it poorly suited to prevent the development of BM [17]. Research is ongoing to investigate whether MRI-guided focused ultrasound or radiotherapy can be used to increase BBB permeability for chemotherapy delivery, although this approach focuses on isolated areas of the brain with active disease and is less suited for prevention. Another appealing approach to transiently disrupting the BBB to improve CNS drug delivery has focused on the use of vasoactive peptides, such as a bradykinin analogue or an adenosine receptor agonist. Pre-clinical studies have demonstrated that these are capable of increasing drug delivery into the brain and clinical trials are now underway to determine the most effective dose of an FDA-approved adenosine receptor agonist in opening the BBB [18•, 19•]. In theory, co-administration of an agent to temporarily disrupt the BBB with systemically administered chemotherapy could increase drug concentrations in the brain of patients with solid tumors that are known to frequently metastasize to the CNS. This novel approach currently is an appealing research option with the potential to reduce the incidence of brain metastases in patients who are responding to systemic chemotherapy. A high priority should be placed on research efforts directed at the prevention of brain metastases in high-risk populations with chemotherapy responsive cancers.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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