Abstract

It is estimated that 10% to 30% of patients with solid tumors are diagnosed with central nervous system (CNS) metastasis. Common primary sites include lung, breast, melanoma, kidney, and colorectal. Brain metastases are increasing, due to the aging population, detection of subclinical disease, and control of systemic disease. CNS metastases are a major cause of morbidity and mortality affecting survival, neurocognition, speech, coordination, behavior, and quality of life. In pediatric acute lymphocytic leukemia event-free survival rates are >80% and the CNS is an important source of extramedullary relapse. CNS metastases are an increasing problem in solid tumors. In this CCR Focus series, four main topics are reviewed: (a) HER-2+ positive breast cancer as a paradigm for the problem; (b) model systems for brain metastasis and mechanistic insights into the pathogenesis of brain metastasis; (c) the unique physiology of the blood brain barrier; (d) and the evolving role of radiotherapy in CNS disease and strategies to improve the therapeutic index. Areas for future research include the need for an understanding of site-specific metastasis, effective anticancer strategies for sanctuary sites, assays to detect drug accumulation in sanctuary sites, prevention of CNS metastasis, improving the therapeutic ratio of systemic and CNS-directed therapies, behavioral tools for anticipating/measuring long-term neurocognitive defects, and quality of life assessment of the long-term effect of systemic and CNS-directed therapies.

A 64-year-old female of Indian descent from Trinidad was diagnosed with a stage II-B infiltrating ductal carcinoma of the left breast in August 2000. She underwent a modified radical mastectomy. Pathology was remarkable for invasive ductal carcinoma, noted to be nuclear grade 3, estrogen receptor negative, progesterone receptor negative, and HER-2 positive (3+ by immunohistochemistry). Three of 11 lymph nodes were positive. She was treated with four cycles of doxorubicin and cyclophosphamide chemotherapy followed by four cycles of paclitaxel. She was free of disease until August 2002 when metastatic disease manifested in the left supravacicular lymph nodes and multiple lung nodules. She was then treated with a combination of weekly 90 mg/m² paclitaxel and 2 mg/kg trastuzumab weekly for 11 cycles from October 2002 until August 2003. She had an excellent response in her pulmonary disease with resolution of adenopathy (Fig. 1). From August 2003 until March 2004, she received 3-week cycles of single-agent trastuzumab. She was doing well until March 2004 when she developed new neurologic symptoms of left-sided weakness, facial droop, and numbness. Magnetic resonance imaging of the brain revealed two sites of metastatic disease (Fig. 2). In March 2004, she underwent primary resection of the two metastatic lesions followed by postoperative whole-brain radiation accumulating to a total dose of 3750 cGy. She continued receiving 6 mg/kg trastuzumab dose every 3 weeks throughout her follow-up, when she was noted to have nodular enhancement along the resection cavity margins of the left parietal lobe with persistent surrounding edema necessitating re-excision of the left parietal lesion in January 2005. No further radiotherapy was done. She remained neurologically intact after the second craniotomy. In November 2006, she showed no recurrence of intraparenchymal brain metastases. She remains with no evidence of disease 51 months after diagnosis of metastatic breast cancer and 21 months after diagnosis of brain metastasis. She continues trastuzumab therapy.

With the advent of effective therapies for the control of systemic disease, clinicians are increasingly treating patients with central nervous system (CNS) metastasis. Just 15 years ago, expected survival in patients, such as the one described above, would have been only a few months (1). Many patients would have succumbed to uncontrolled systemic disease before CNS metastasis became clinically apparent. Today, it is estimated that 10% to 30% of patients with solid tumors are diagnosed with CNS metastasis. Common sources of CNS metastasis include melanoma and primary sites in the lung, breast, kidney, and colon (2). Why metastases from these primary sites have an increased predilection for brain tissue is not yet understood. The incidence of brain metastases has been increasing, thought to be due to the aging population, increased detection of subclinical disease with better imaging, and better control of systemic disease. CNS metastases are a major cause of morbidity and mortality in patients with solid tumors affecting survival, neurocognition, speech, coordination, behavior, and quality of life. The major treatment modalities for CNS metastases are shown in Table 1.
Metastatic disease to the CNS is not a new problem, but an old problem in a new guise. Our pediatric hematology oncology colleagues have been addressing this issue for decades. In pediatric acute lymphocytic leukemia (ALL), event-free survival rates have risen to >80%, and extramedullary relapses have become exceedingly rare (3). The CNS, traditionally an important source of extramedullary relapse, is a sanctuary site in ALL, due to the role of the blood-brain barrier (BBB) in protecting the CNS from exposure to xenobiotic toxins. To improve relapse-free survival sites in ALL, strategies to penetrate the BBB were needed. This led to the use of prophylactic cranial irradiation, which was effective in preventing CNS relapse in ALL. However, long-term sequelae, including decreased cognitive function, endocrinopathy, and secondary malignancies with prophylactic cranial irradiation, were vexing. Thus, attempts were made to avoid prophylactic cranial irradiation whenever possible through the use of intrathecal therapy and more intensive systemic therapies. High-dose methotrexate was considered a strategy to circumvent the BBB. This intervention had the unexpected beneficial effect of decreasing the risk of relapse at another sanctuary site (the testicle; ref. 4). With current approaches, approximately 2% to 10% of patients can be expected to develop CNS relapse (5). Therapy in ALL to prevent CNS relapse is therefore given early in the course of treatment. The intensity of systemic therapy and whether cranial irradiation is used is dependent on the risk of relapse (6).

Lessons learned in ALL may help guide future trials in adult solid tumor oncology. Similar to ALL, improved therapies are leading to better control of systemic disease. Relapses in the sanctuary site of the CNS are increasingly being recognized as an obstacle to what might otherwise be curative therapy in some patients. In this CCR Focus series, key aspects of this emerging problem are addressed (Table 2).

Lin and Winer (7) provide an elegant overview of HER-2-positive breast cancer as a paradigm for the problem. It is now recognized that breast cancer is composed of several subtypes. The overexpression of HER-2 identifies a more aggressive subtype of breast cancer (8). In the era before routine administration of chemotherapy, the mean survival of patients with early-stage HER-2–positive breast cancer was only 29 months compared with 110 months in women who had tumors without HER-2 expression, with a 10-year survival rate of 31% versus 48%, respectively (9). Although median follow-ups with the use of trastuzumab in the adjuvant setting are relatively short, the 4-year survival rate has been reported as 91.4% with combined anthracycline- and taxane-based chemotherapy with trastuzumab versus 86.6% for chemotherapy alone (10). In addition to clinical improvements in the treatment of early-stage breast cancer, the prognosis of patients with HER-2–positive metastatic breast cancer in the post-trastuzumab era has also improved (11). Lin and Winer review evidence supporting the hypothesis that before the availability of effective targeted therapies, failure to control systemic disease was the major factor limiting the survival of women with HER-2–positive metastatic breast cancer. This is shown even in patients with metastatic CNS disease, where a survival advantage is seen in patients with HER-2–overexpressing tumors, probably as a result of better control of extracranial systemic disease in response to trastuzumab (12). With the advent of better systemic therapies, CNS relapse is emerging as an increasing clinical problem. In a retrospective series of 21 patients who died among 122 treated with trastuzumab, 52% seemed to succumb from CNS progression, in the face of stable or responsive non-CNS disease (13). They review current strategies for chemotherapy and targeted therapy in addressing the treatment of CNS metastasis. It is noted that temozolamide, a drug with activity in primary brain cancer and good CNS penetration, has had limited activity in treating breast cancer metastatic to the brain. This raises the important point that an agent must have activity in breast cancer if it is going to be effective in treating CNS metastasis from breast cancer. Targeted therapies, such as lapatinib, a small molecule directed against HER-2 (14), may have activity in CNS disease, and antiangiogenesis agents may hold promise in this setting.

Palmieri et al. (15) review the model systems that have been developed for brain metastasis and mechanistic insights into the pathogenesis of brain metastasis. The metastatic process is complex, requiring invasion from the primary tumor into surrounding tissue; survival and extravasation into the circulatory system; and colonization and growth at a distant site (16). In addition, tumor cells may have the ability to colonize specific organ sites. The brain may represent a preferential site of metastasis as many of the currently available therapies cannot cross the BBB, even if this barrier is disrupted by tumor invasion. Thus, relapses can occur in this sanctuary site. Palmieri et al. note that although rodent systems have been developed for brain metastasis in melanoma, lung carcinoma, and breast carcinoma, they are not sufficient to represent the heterogeneity of CNS metastasis observed in the clinic. In
addition, almost no comparison has been made between the molecular characteristics of model systems and those of clinical CNS metastasis. Much needs to be learned about the pathophysiology of CNS metastasis at a molecular level. Palmieri et al. review data in support of the angiogenesis pathways, growth factors, such as HER-2, transcriptional regulation with signal transducers and activators of transcription 3, energy metabolism, and tumor cell dormancy. It is also of interest that molecular characterization of brain metastases has provided evidence for both chromosome gains and alternations in DNA methylation, suggesting that agents targeting DNA methylation or other epigenetic modifications may have promise.

Deeken and Loscher (17) describe the unique physiology of the BBB, a mechanism that is used across species to protect the brain from both endogenous and exogenous toxins. There are cellular barriers in CNS endothelial cells that are different from those in endothelial cells in the periphery (continuous tight junctions, lack of fenestrations, and very low pinocytic activity). Extracellular matrix, pericyctes, and astrocyte foot processes further mediate the impermeability of the BBB. In addition, there is a high electrical resistance in brain capillaries that increases the impermeability of the BBB to polar and ionic substrates. Deeken and Loscher discuss specific challenges that exist in developing effective strategies for overcoming the BBB, including modulation of drug transporters, nanoparticle formulations, and immunoliposomes as targeting approaches to delivering drugs across the BBB. This extremely important review succinctly provides information about the BBB not easily accessible to the cancer researcher.

Finally, implications of CNS therapy are reviewed by Mehta and Patel (18). Conventional treatment has been whole-brain radiotherapy, which can improve symptoms but potentially results in neurocognitive deficits. Topics covered in this review include the evolving role of radiotherapy in CNS disease and strategies to improve the therapeutic ratio. Mehta and Patel discuss research focused on enhancing the efficacy of whole-brain radiotherapy, thereby increasing the time to neurologic failure, as well as promising new systemic agents that synergize

Table 1. Therapeutic approaches to CNS disease

- Surgical excision
- Radiosurgery
- Radiation sensitizers
- Cytotoxic chemotherapy
- Targeted therapies
- Novel drug delivery techniques

Table 2. Critical areas for research

- Preclinical models for site-specific metastasis
- Molecular profiling of tumors with site-specific metastases
- Host effects, including pharmacogenomics
- Effective anticancer strategies for sanctuary sites
- Assays to detect drug accumulation in CNS or other sanctuary site
- Therapeutic strategies for treatment of micrometastatic disease (prevention of CNS metastasis)
- Strategies to avoid long-term CNS complications of therapy (systemic and CNS directed)
- Behavioral tools for anticipating/measuring long-term neurocognitive defects
- Quality of life assessment of long-term effect of systemic and CNS-directed therapies
(or are additive) with radiation by potentially crossing the BBB. These agents are early in the clinical testing phase but could potentially also be used to treat micrometastatic disease in a so-called “prophylactic” setting in high-risk patients, thereby reducing the overt development and manifestation of brain metastases. The introduction of highly advanced radiation delivery methods affords optimal conformal avoidance of eloquent areas of the brain, such as the hippocampus, which are at low risk of harboring microscopic disease but are critical in maintaining neurocognitive function. Several pharmacologic agents with the potential for reducing neurologic injury are beginning to be tested with radiation therapy.

CNS relapse is an old problem in a new guise. Not all patients with brain metastasis have an equally poor prognosis. Relapses in the CNS are a barrier to 100% cure in ALL and is barrier to cure in some patients with breast cancer and other solid tumors. Prophylactic cranial irradiation, although effective, may have unacceptable long-term sequelae in adults with the life expectancies in the decades following effective cancer treatment. Studying the CNS is difficult, paramount is identification of patients at highest risk of relapse through both tumor and host factors. Studies in patients with brain metastasis need to be conducted with the same rigor in patients with primary brain metastasis. Challenges for the oncology community are formidable; there is a need to recognize the problem, understand the pathophysiology of this disease (both the site-specific properties of the tumor cell and the unique microenvironment of the CNS), develop effective therapies with an acceptable therapeutic ratio, and optimally, prevent the occurrence of this devastating outcome.

References

CNS Metastasis: An Old Problem in a New Guise

Jeanny B. Aragon-Ching and Jo Anne Zujewski


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/13/6/1644

Cited articles
This article cites 17 articles, 9 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/13/6/1644.full.html#ref-list-1

Citing articles
This article has been cited by 9 HighWire-hosted articles. Access the articles at:
/content/13/6/1644.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.