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Perspective

Management of breast cancer brain metastases: Focus on human epidermal growth factor receptor 2-positive breast cancer

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Abstract

After the introduction of trastuzumab, a monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2), the overall survival (OS) among patients with HER2-positive breast cancer has been substantially improved. However, among these patients, the incidence of brain metastases (BM) has been increasing and an increased proportion of them have died of intracranial progression, which makes HER2-positive breast cancer brain metastases (BCBM) a critical issue of concern. For local control of limited BM, stereotactic radiosurgery (SRS) and surgical resection are available modalities with different clinical indications. Postoperative or preoperative radiation is usually delivered in conjunction with surgical resection to boost local control. Adjuvant whole-brain radiotherapy (WBRT) should be deferred for limited BM because of its impairment of neurocognitive function while having no benefit for OS. Although WBRT is still the standard treatment for local control of diffuse BM, SRS is a promising treatment for diffuse BM as the technique continues to improve. Although large molecules have difficulty crossing the blood brain barrier, trastuzumab-containing regimens are critical for treating HER2-positive BCBM patients because they significantly prolong OS. Tyrosine kinase inhibitors are more capable of crossing into the brain and they have been shown to be beneficial for treating BM in HER2-positive patients, especially lapatinib combined with capecitabine. The antiangiogenic agent, bevacizumab, can be applied in the HER2-positive BCBM scenario as well. In this review, we also discuss several strategies for delivering drugs into the central nervous system and several microRNAs that have the potential to become biomarkers of BCBM.

Keywords: Breast cancer brain metastases; Human epidermal growth factor receptor 2-positive breast cancer; Local control; Targeted therapy; MicroRNA

Introduction

Breast cancer is the second-leading cause of central nervous system (CNS) metastases among solid malignancies.[1] The incidence of developing brain metastases (BM) has been reported to range from 10% to 16% among advanced breast cancer patients,[2] and autopsy studies indicate that this figure may underestimate the true incidence since another 10% of BM are

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asymptomatic and not diagnosed before death.[3] Patients with human epidermal growth factor receptor 2 (HER2)-positive cancer or triple negative breast cancer (TNBC) have a higher risk of developing BM than patients with luminal-like disease.[4−6] Several studies have shown that HER2-positivity is associated with a biological propensity to metastasize to the brain.[7] After the introduction of trastuzumab, which has significantly improved overall survival (OS) among patients with HER2-positive breast cancer, the incidence of BM among HER2-positive patients (ranging from 30% to 55%[5,8−12]) has been increasing.[10,13−15] Unlike BM in TNBC, which often develops with concurrent extracranial disease progression,[16] BM often occurs in a setting of stable extracranial control among HER2-positive patients.[17]

In the past, even after treatment by whole-brain radiotherapy (WBRT), the median survival of patients with breast cancer brain metastases (BCBM) was poor, ranging from 3 to 6 months.[18] Before the trastuzumab era, the OS was shorter among patients with HER2-positive brain metastases compared with those with HER2-negative disease, which was mainly attributed to the progression of systemic disease.[19] After the introduction of effective anti-HER2 therapy, survival after diagnosis of BM among HER2-positive patients has been significantly improved compared with that among patients with HER2-negative disease, mainly due to the improvement of extracranial disease control.[20,21] Several retrospective studies have reported that the median OS after diagnosis of BM is around 2 years for HER2-positive patients.[20−23] Meanwhile, with the OS significantly prolonged, the proportion of people dying of cerebral progression has been increasing. A retrospective study reported that up to 50% of HER2-positive patients died of cerebral progression,[10] which makes BM among HER2-positive patients a critical issue. To improve management, the American Society of Clinical Oncology (ASCO) published a guideline focusing on this issue in 2014.[24]

In this review, we will discuss treatments for HER2-positive BCBM, including local treatment and targeted therapy. In addition, several cancer biomarkers for BCBM will also be discussed.

Local control

Management of limited BM (1−4 BM)

Surgery

In order to achieve long-lasting control, surgical resection is a standard treatment for patients with a favorable prognosis and a solitary lesion, especially a large lesion (over 3−4 cm). There were several randomized control trials conducted to define the role of surgical resection in solitary BM, and they demonstrated a significant survival benefit for patients receiving surgical resection.[25−28] Surgical resection is also used for immediate mass effect relief in patients with limited BM (2−4 lesions) who have a large lesion causing neurologic symptoms; however, the effect of surgery on survival of these patients with limited BM is still unknown. Since there is a high recurrence rate after surgical resection,[29] postoperative radiation is usually recommended to improve local control, which will be discussed in the postoperative and preoperative radiation therapy section.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a radiation therapy technique using intersected beams to deliver a highly conformal and high dose of radiation to a target volume in order to produce an ablative effect with minimal damage to surrounding normal tissues. SRS is usually delivered in a single fraction, but it can also be delivered in multiple fractions [fractionated stereotactic radiotherapy (FSRT)]. For local control of BM, SRS can be used as a therapy alone, a boost after WBRT, or an adjuvant treatment preoperatively or postoperatively.[30]

There are different techniques available for stereotactic radiosurgery including Gamma Knife® (GK) and CyberKnife (CK). GK used to be the standard device for SRS. It is based on an invasive head frame system coupled with cobalt-60 sources and is mainly used for intracranial indications,[31,32] while CK is based on a linear accelerator system without head fixation and can be used for both intra- and extracranial lesions.[33] Because it is frameless and has a wider range of indications, CK has become increasingly popular over the last few decades and has been shown to not be inferior to GK in the accuracy of dose delivery.[34,35] In dosimetry, CK shows a more homogeneous dose distribution across the entire lesion,[36,37] while GK shows an inhomogeneous distribution with a higher dose in the center of the lesion[36,38] that may help to minimize local tumor recurrence.[39] However, a matched-pair analysis demonstrated that the obvious differences in treatment-related parameters between GK and CK had no effect on clinical outcomes after radiosurgery.[40]

Although both SRS and surgery can treat patients with limited BM, there is no prospective randomized trial comparing these two modalities. Actually, they are not competitive modalities in most cases, but are