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Original Article

Practical consensus recommendations on Her2 +ve breast cancer with solitary brain mets

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Abstract

Breast cancer is a common cause of brain metastases, with metastases occurring in at least 10–16% of patients. Longer survival of patients with metastatic breast cancer and the use of better imaging techniques are associated with an increased incidence of brain metastases. Current therapies include surgery, whole-brain radiation therapy, stereotactic radiosurgery, chemotherapy and targeted therapies. However, the timing and appropriate use of these therapies is controversial and careful patient selection by using available prognostic tools is extremely important. Expert oncologist discussed on the mode of treatment to extend the OS and improve the quality of life ofHER2-positivebreast cancer patients with Solitary brain metastases. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

Key words: Herceptin, stereotactic radiosurgery, surgery, TDM1, WBCR

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] Autopsy studies indicate that this figure may underestimate the true incidence since another 10% of BM are human epidermal growth factor receptor 2 (HER2)-positive cancer or triple negative breast cancer (TNBC). TNBC and HER2 positive patients have a higher risk of developing BM than patients with luminal-like disease.[3-5] Several studies have shown that HER2-positivity is associated with a biological propensity to metastasize to the brain.[6] Previous studies have identified the subgroups of patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer as having an increased risk for the development of brain metastases,[7-10] with up to half of patients with HER2-positive metastatic breast cancer experiencing brain metastases over time.[5] Tumor subtypes are also an important factor for the median time interval from primary diagnosis to development of brain metastases; a recent large study showed shorter intervals for triple negative and HER2-positive patients, and longer intervals for estrogen receptor (ER) positive tumors.[11]

Brain metastases in breast cancer patients represent a catastrophic event that portends a poor prognosis, with a median survival that ranges from 2 to 25.3 months, despite treatment.[12,13-15] Treatment options for patients with breast cancer brain metastases are limited and include surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), chemotherapy and targeted therapy.[13,16,17]

An expert group of oncologists met in the update in oncology-X-2017 to discuss on available strategies for patient having HER2 + ve with Solitary Brain Mets Breast cancer.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer.[18,19] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the present 250 oncologists, which included medical oncologists, radiation oncologists, surgical oncologists, molecular oncologists and radiologists present in the update in oncology-X-2017 was taken into consideration by the expert panel.

The expert group was chaired by Dr. Kishore Singh and Dr. Harpreet Singh whereas the discussions were moderated by Dr. NiteshRohtagi and Dr. Anusheel Munshi. The core expert group consisted Dr. Peyush Bajpai, Dr. Manisha Singh, Dr. Siddarth Sahai, and Dr. Stephen C Malamud. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[20-22] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. A total of six broad question categories were part of the expert group discussions [Table 1].

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.[23]

After the introduction of effective anti-HER2 therapy, survival after diagnosis of BM among HER2-positive patients has been

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significantly improved compared with that among patients with HER2-negative disease, mainly due to the improvement of extracranial disease control.[24,25] Several retrospective studies have reported that the median OS after diagnosis of BM is around 2 years for HER2-positive patients.[24-27] 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,[28] 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.[29]

Treatment Approach

As mentioned above, treatment approach includes symptomatic treatment, surgical excision of solitary metastasis, stereotactic radiosurgery (SRS) for small (<3 cm) lesions not amenable to surgery, whole-brain radiotherapy (WBRT) and chemotherapy [Tables 2-6].[30]

Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Case 1-40 years premenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T1N0M0. ER negative, PR negative, HER 2/neu- 3+. She is given 6 cycles of TCH and then completed 1 year trastuzumab. She remains well for 3 years, then develops headache and vomiting. MRI BRAIN reveals 2×3 cm lesion in left frontal lobe
Question 1 (I) - What is the next line of action?
Question 1 (II) - Patient undergoes surgery, what is the next line of action?
Question 1 (III) - Patient undergoes complete resection followed by SRS then What next should be done?
Question 2 (I) - Patient is given T-DM1 for 9 months, then she develops five lesions (total) in both cerebral hemispheres and cerebellum. What next?
Question 2 (II) - SRS done, what next?
Update in oncology-X-2017

ER=Estrogen receptor, PR=Progesterone receptor, HER 2=Human epidermal growth factor receptor 2, MRI=*Magnetic resonance imaging*, SRS=Stereotactic radiosurgery

Table 2: Question 1 (I) - What is the next line of action?

Options (%)	Surgery	Radiotherapy
Percentage of polled oncologists	80	20

Expert group consensus: Expert panel recommend surgery for solitary brain metastasis

Table 3: Question 1 (II) - Patient undergoes surgery, what is the next line of action?

Options (%)	WBRT	SRS followed by WBRT	SRS
Percentage of polled oncologists	40	40	20

Expert group consensus: Following surgical excision, the patient should be treated with WBCR - there is insufficient data to recommend SRS for all patients. WBRT=Whole-brain radiation therapy, SRS=Stereotactic radiosurgery

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.[31-34] Surgical resection is also used for immediate mass effect relief in patients

with limited BM (2e4 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,[35] postoperative radiation is usually recommended to improve local control.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a radiationtherapy technique using multiple intersecting beams to deliver a highly conformal and high dose of radiation to a target volume. The aim is 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 5 or more fractions [fractionated stereotactic radiotherapy (FSRT)]. For local control of BM, SRS can be used as a therapy alone or a boost after whole brain radiotherapy (WBRT).

WBRT, or an adjuvant treatment preoperatively or postoperatively.[36] Different technologies are presently available for delivering stereotactic radiosurgery, however there exists no evidence of superiority of one over the other.[37-43] The essentials for a good SRS program remain robust immobilisation, tight margins to the tumour volume, excellent quality assurance and on board CT imaging before treatment delivery[43-47]

Traditionally SRS has been used in patients with 1-3 brain metastasis (either alone or after whole brain radiotherapy). However recent evidence suggests that SRS alone can be used in patients with even upto 10 metastasis.[48]

Postoperative and Preoperative Radiation Therapy

Because of the high recurrence rate after surgical resection,[35,47] postoperative radiation is usually recommended as a boost for intracranial control. Adjuvant WBRT is the standard treatment in the postoperative setting, although focal radiotherapy (SRS/SRT) to the lesion bed with margin is also an emerging option.[49] Multiple studies have demonstrated that postoperative WBRT can significantly reduce the risk of local recurrence, distant brain recurrence, and neurologic causes of death, but has no benefit for OS.[35,47] Because of potential toxicity associated with WBRT, clinicians have used postoperative SRS to defer WBRT and to improve intracranial control. Because of the size limitation of SRS, FSRT has been used for large surgical cavities over 3 cm and has a similar control rate as SRS.[50]

Whole-brain Radiation Therapy

One of the most important treatments available for brain metastases is WBRT, particularly in the setting of multiple

Table 4: Question 1 (III) - Patient undergoes complete resection followed by stereotactic radiosurgery then what next should be done?

Options (%)	No further treatment	Trastuzumab containing regimen	Capecitabine and lapatinib	T-DM1
Percentage of polled oncologists	37.5	37.5	12.5	12.5

Expert group consensus: TDM1 is the appropriate option of choice for eligible patients

Table 5: Question 2 (I) - Patient is given T-DM1 for 9 months, then she develops five lesions (total) in both cerebral hemispheres and cerebellum. What next?

Options (%)	WBRT	SRS
Percentage of polled oncologists	77.8	22.2

Expert group consensus: Recommended treatment for multiple recurrence of brain metastasis is SRS. SRS=Stereotactic radiosurgery, WBRT=Whole-brain radiation therapy, T-DM1=???

Table 6: Question 2 (II) - Stereotactic radiosurgery done, What next?

Options (%)	Lapatinib and capecitabine	Herceptin based
Percentage of polled oncologists	50	50

Expert group consensus: Herceptin based systemic therapy is recommended for optimized overall survival

brain lesions. This approach has two main goals—the control of macroscopic metastases, and the eradication of microscopic seeding of the brain. The majority of patients are given conventional WBRT, a total dose of 30 Gy in 10 fractions with daily fractions of 3–4 Gy.[51]

The benefit of WBRT after surgical resection has been demonstrated in a prospective trial that randomized 95 patients who had single brain metastases to WBRT or observation.[51] The study showed that patients in the WBRT group had fewer recurrences both at the operative site (10 vs. 46%, $P < 0.001$) and at other sites in the brain (14 vs. 37%, $P < 0.01$), however overall survival was not increased. Controversy exists about the role of WBRT versus focal SRS/SRT in patients with few (≤4) brain metastases.[52,53] Associated toxicities with WBRT included worse neurocognitive outcomes and quality of life.[54,55] Also, there is paucity of data directly comparing hippocampal sparing WBRT techniques with focal SRS treatments. Withholding WBRT can result in risk of progressive disease in the brain, which in turn could also negatively impact cognition – factors that need to be considered in the decision making process.[56,57]

Targeted Therapy for HER2-positive Breast Cancer Brain Metastases

Unlike estrogen and progesterone status, expression of HER2 has been reported to be highly concordant between the primary and brain metastatic tumors,[58] which makes targeted therapy possible for treating patients with HER2-positive BCBM. Although the OS of patients with HER2-positive breast cancer has improved substantially in the trastuzumab (T-DM1) era,[3-5] the incidence of BM among these patients has been increasing in recent years. One of main reasons for this is that the blood brain barrier (BBB) makes the CNS a perfect sanctuary for tumor cells. The BBB is a barrier that selectively chooses molecules to enter the CNS. It consists of endothelial cells, a basement membrane, and astrocyte foot processes. The permeability of the BBB decreases 100-fold as the molecular weight of the drug increases from 200 Da to 450 Da.[59] As a large molecule (145,531 Da), trastuzumab cannot penetrate the intact BBB, but multiple factors can disrupt the BBB, including metastatic tumors, surgery, and radiotherapy, which then allows limited amounts of large molecular agents to penetrate the CNS. Because the incidence of BM is higher in patients with HER-2 positive tumors, a specific interest in this subset exists.

Standard systemic treatment of HER-2 positive disease typically includes trastuzumab, (T-DM1) which has been shown to cross a disrupted BBB in some patients (albeit in limited amounts)[60] and is associated with both longer time to the development of BM and survival after a diagnosis of BCBM.[61]

Conclusion

For patients with HER2-positive breast cancer with Solitary brain metastases, consideration should be given to treat with combination of surgery, radiotherapy, chemotherapy and anti HER2 treatments is at present the best way to extend the OS and improve the quality of life of patients.

Current care involves radiotherapy, either SRS or WBRT, and/or surgery and depends on the number, size, and site of metastases, as well as overall systemic disease control and a patient's performance status. Systemic chemotherapeutic approaches are gaining traction and are increasingly efficacious options that are being used earlier in the course of the illness. Early vigorous treatment can enhance a patient's functional status and prolong CNS disease control and survival. The output of this discussion is to provide the best and effective treatment options for patients with HER2-positive breast cancer with solitary brain metastases.

Take Home Message

For a 40 year premenopausal lady diagnosed with infiltrating duct carcinoma left breast who has: undergone modified radical mastectomy, had pathological stage T1N0M0 (ER-ve, PR-ve, Her2/Neu 3+), had received 6 cycles of TCH and then completed one year trastuzumab, was well for 3 years AND now has MRI BRAIN documented solitary brain metastasis-2×3 cm lesion in left frontal lobe.

1. Surgery is the standard of care for solitary brain metastasis
2. Following surgical excision, the patient should be treated with WBCR – currently there is insufficient data to recommend SRS for all patients
3. TDM1 is then an appropriate option of choice for eligible patients
4. If this patient responds initially and then develops multiple recurrence of brain metastasis, he/she should be treated with whole brain radiotherapy. SRS can be selectively used in such situations.
5. Following completion of radiation therapy, Herceptin based systemic therapy is recommended for such patients to optimize overall survival

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Conflicts of interest

There are no conflicts of interest.

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