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Review Article

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Brain metastases from breast cancer: Management approach

ABSTRACT

Brain metastases are a significant cause of morbidity and mortality in patients with breast cancer. HER-2 positivity is an increasingly recognized risk factor for the development of brain metastases. Although considerable progress has been made in the treatment of this complication, supportive measures like steroids, anti-seizure medication and whole-brain radiation remain the cornerstones of management in the majority of patients. The current review discusses the above and other issues like surgical excision, stereotactic radiotherapy, adjuvant radiation, radiosensitization and chemotherapy. A brief discussion of the recent evidence for the use of 'HER-1/HER-2'–targeted therapy is also present.

KEY WORDS: Brain metastases, radiation; surgery, targeted therapy

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INTRODUCTION

Brain metastases are the most common form of intracranial neoplasms and occur in about 25% of all cancer patients.[1] The most common histologies are lung, breast, melanoma and renal cell cancer.[2] This paper mainly discusses the issues related to CNS metastases from breast cancer. The prospect of being diagnosed with brain metastases, especially in HER-2+ metastatic breast disease, is terrifying, as it heralds a compromised and dependent life as a result of fatigue-inducing and memory-scrambling whole-brain radiation and personality-altering steroid treatments. The policy of not treating inactive brain metastases or not intervening for stable disease post-treatment creates anxiety and depression among the patients. This is also an area where various systemic therapies have failed to improve the dismal outcome. In the absence of effective therapies, whole-brain radiotherapy has become the mainstay of treatment for brain metastases. Yet, whole-brain radiation can leave patients with persistent fatigue, permanent hair loss, profound memory problems and other serious cognitive-deficit side effects that may worsen with time, raising serious quality-of-life issues as patients are able to live longer. The management and prevention of CNS metastases in patients whose tumors overexpress HER-2/ *neu* need to be reevaluated in the present trastuzumab era, with special consideration for prophylactic cranial irradiation, as trastuzumab is known to increase the incidence of brain metastases in this group of patients.[3-5] Alongside the effectiveness of stereotactic surgery and newer radiotherapy techniques, innovations in blood-brain barrier disruption have expanded the scope of less-damaging systemic therapies in brain cancers including metastases.[6]

Incidence

Breast cancer is the second most common cause of brain metastases (after lung cancer), occurring in 10-15% of patients with breast cancer; although autopsy studies suggest that the actual incidence is twice this figure.[7] The incidence of brain metastases is thought to be increasing, due to the introduction of more sensitive and accurate diagnostic methods, the development of improved adjuvant and palliative therapy regimens leading to improvements in survival and more frequent use of screening studies. The median time from diagnosis of cancer to the occurrence of brain metastases either to the brain parenchyma or to the leptomeninges is longer in case of breast cancer, usually 2-3 years.[8] In the majority of patients, the CNS dissemination occurs after other systemic lesions have been diagnosed. Approximately 70-80% are oligo-metastases, i.e., one to three in number.[2] Cerebrum is the most common parenchymal site of metastases, followed by cerebellum and brainstem. Supratentorial lesions are more common than infratentorial lesions, and there is a predilection for vascular border zones and the gray- and white-matter junction. This is due to the change in the caliber of vessels at these points that acts as trap for tumor emboli. Infratentorial lesions usually arise from pelvic or abdominal malignancies as they gain access through the Batson's plexus. The incidence of leptomeningeal metastases from breast cancer is 2-5%.[22]

Pathogenesis

The 'seed and soil' theory proposed by Paget, though still widely accepted,[9] fails to explain the wide range of clinical scenarios encountered. Presently the most scientifically acceptable theory that is consistent with the clinical experiences is that of multi-step pathogenesis as proposed by Hellman *et al*.[10] Gene-expression–profiling studies have identified gene signatures that predict the site of metastases as well as help in stratifying patients into risk categories.

Metastases to the brain parenchyma are thought to be hematogenous in origin whereas spread to the leptomeninges may occur via multiple routes, including hematogenous, direct extension, transport through the venous plexus and extension along nerves or perineural lymphatics.[11] Once the tumor cells reach the leptomeninges, they are thought to spread via the CSF.

Risk factors for CNS metastases

Several studies have reported that various prognostic factors (young age; receptor-negative tumors; elevated LDH; large tumor size; grade; lymphovascular invasion; number of positive lymph nodes; other sites of metastases, especially lung metastasis; HER-2 overexpressing MBC; poor Karnofsky's performance status; etc.) are associated with higher incidence of dissemination to the CNS.[12–14] HER-2 overexpression confers a greater risk of distant recurrence and overall poorer survival due to its association with steroid receptor negative status, high-grade tumors, high proliferation rate and lymph node involvement, tamoxifen resistance and reduced sensitivity to nonanthracycline chemotherapy.[15] It is also associated with increased metastatic aggressiveness to specific sites such as lung, liver and probably also brain, which is due to CXCR4/SDF-1α chemoattractant pathway.[16] Isolated CNS progression occurs in around 10% of patients on trastuzumab therapy as first line of treatment for metastatic breast cancer. This is due to the impaired penetration of trastuzumab through the blood-brain barrier owing to its high molecular weight (145 kDa). As progression in the CNS tends to be a later event than progression at other sites among patients receiving trastuzumab-based therapy, few authors have also proposed a rationale for serial radiologic screening and prophylactic cranial irradiation.[3,4]

Tham *et al*. presented the largest and most comprehensive study analyzing CNS metastases in metastatic breast cancer in relation to tumor biologic features, systemic treatment and clinical outcome. In addition to young age and ER negativity, high proliferation, p53 alterations and genomic instability in the primary tumor were associated with an increased risk for CNS metastases.[17] Interestingly, neither HER-2 overexpression in the absence of trastuzumab therapy nor adjuvant chemo-hormonal therapy increased the risk of CNS metastases. The relationship between HER-2 overexpression and the risk of brain metastasis in newly diagnosed breast cancer patients has been studied by Gabos *et al.*, who have shown that HER-2 overexpression is the most significant prognostic factor for the development of brain metastases,[4] in contrast to the results from the study by Tham *et al*. In their study, brain metastases developed in 9% of HER-2–overexpressing patients compared with only 1.9% in HER-2–negative tumors.

Clinical presentation

Parenchymal brain metastases most commonly have an insidious onset with headache (24-48%), neurological deficit in the form focal motor weakness (16-40%) or altered mental status and cognitive dysfunction (24-34%).[18] Seizures, ataxia or nausea-vomiting can also be the presenting symptoms. Acute onset is seen in hemorrhagic metastases. Leptomeningeal metastases present with nonlocalizing symptoms such as headache, nuchal rigidity or cranial neuropathies.[19]

Diagnostic evaluation

Gadolinium-enhanced magnetic resonance imaging (MRI) is more sensitive than contrast-enhanced computed tomography (CT) for identifying both parenchymal and leptomeningeal disease and is therefore the preferred noninvasive diagnostic test.[20] Contiguous thin axial slices without skips are necessary to pick up small lesions that are missed on CT, particularly in the fronto-temporal region and also in the posterior fossa and brainstem, where beam-hardening artifacts due to surrounding bone can obscure CT findings. MRI is also superior in differentiating between solitary and multiple lesions, a distinction that has critical clinical importance. Approximately 20% of patients thought to have a single brain metastasis on CT actually have multiple lesions on MRI.

Stereotactic brain biopsy must be considered whenever diagnosis of metastasis remains in doubt, especially in patients with atypical presentations, as it would lead to change in diagnosis in 11% of cases.[21] Primary brain tumors, infection, infarction and radiation necrosis are the likely alternative possibilities.

Survival statistics

Treatment of brain metastases depends on their location, number, age, performance status and localization of extra-cerebral lesions and a prediction of their response to systemic therapy. An adequate estimation of these independent prognostic factors is required to enable the clinician to decide between invasive treatments and to avoid unnecessary treatment.

The majority of cancer patients who develop metastatic brain disease present with multiple lesions, and death is attributed to uncontrolled metastatic brain disease in approximately 40%. Median survival in untreated patients with CNS involvement is 1 month; in patients administered corticosteroids, 2 months; and following CNS radiotherapy, 3-6 months. Patients with single CNS lesions and limited systemic disease amenable to surgery or radiotherapy may achieve median survival in the range of 10-16 months. Favorable prognostic factors in

patients with CNS metastases include the absence of other metastatic lesions, younger age (below 60 years), good performance status, long disease-free period after primary treatment, surgical resection of the lesion and positive steroid-receptor status. Recursive Partitioning Analysis (RPA) of data from three Radiation Therapy Oncology Group (RTOG) trials (1,200 patients) has allowed three prognostic groups to be identified [Table 1].[23] This is the most widely used prognostic scoring criteria in oncological practice.

Lorezoni *et al.* have proposed a simplified scoring system for patients treated with radiosurgery, incorporating KPS, age, number of brain lesions, largest brain lesion volume and status of extracranial disease.[24] This index called 'score index for radiosurgery' (SIR) may prove to be more accurate than the RPA classification.

RTOG have now recently proposed a new index known as Graded Prognostic Assessment (GPA) for brain metastases in the light of new data being available from the RTOG 9508 trial and the also to overcome the limitations of the RPA scoring index [Table 2]. They have reported that GPA index is as prognostic as the RPA and at the same time less subjective and easier to use.[51] Scodan *et al*. have proposed a simple prognostic score for patients with brain metastases from breast carcinoma treated with whole brain radiotherapy.[52] Using KPS (RPA class I and II vs. III), lymphopenia (>700 vs. ≤ 700) and HR status (positive vs. negative), a prognostic score was developed which classified patients into three subgroups with significantly different overall survival.

TREATMENT

A] Parenchymal metastases: The optimum therapy of brain metastases is still evolving. Corticosteroids, radiotherapy, surgical therapy and radiosurgery all have an established place in management. In addition, chemotherapy is useful in some patients.

Table 1: Recursive partitioning analysis classification for brain metastases

RPA class	Median survival
I: KPS≥70, age <65 years, controlled primary and no extracranial disease	
Single metastasis	13.5 months
Multiple metastases	6.0 months
Overall combined	7.1 months
II: All other situations.	
Single metastasis	8.1 months
Multiple metastases	4.1 months
Overall combined	4.2 months
III:KPS <70	2.3 months

Table 2: Graded prognostic assessment

	Score		
	0	**0.5**	**1.0**
Age in years	>60	50-59	<50
Karnofsky performance status	<70	70-80	90-100
No. of CNS metastases	>3	2-3	1
Extracranial metastases	Present	-	None

Symptomatic management

Corticosteroids: The anti-edema effect attributed to the reduction in the permeability of abnormal tumor capillaries and restoration of the arteriolar tone is responsible for symptomatic improvement. Dexamethasone is preferred over other steroids due to its low mineralocorticoid action, low risk of cognitive impairment and high CNS penetration. The usual dose is 4 mg every 6 h, preceded by a loading dose if clinically indicated. Asymptomatic patients on whole-brain radiotherapy do not need corticosteroids, but patients undergoing high-dose radiosurgery should preferably receive single loading dose of steroids at the time of radiosurgery.

Anti-seizure medication: About 15% of supratentorial lesions present with seizures. Antiepileptics are required only in those patients who present with seizures or develop seizures during therapy. The role of prophylactic anti-seizure medication is limited to the lesions in highly emetogenic or cortical areas.

Definitive management

Whole-brain radiotherapy alone: WBRT is the mainstay of treatment for most patients with brain metastases, which produces symptomatic relief especially of headache and seizures in 75-85% of patients. It also improves survival to about 3-6 months and quality of life and radiological response in up to 60% of cases.[23] Various dose-fractionation schedules (50 Gy/20#, 54.4 Gy/34# twice a day fractionation, 30 Gy/10#, 15 Gy/3#, 12 Gy/2#, 10 Gy/1#) have been tested in randomized studies. None of the regimen has been proved to be superior to another, either in terms of overall mortality or in terms of better symptom control. For breast cancer which responds better to WBRT and in patients with longer life expectancy (>6 months), a fraction size of less than 3 Gy is usually preferred. It reduces the incidence of late dementia, which is a rare but most undesirable side effect in long-term survivors (median latent period 4 months). The acute side effects of WBRT include alopecia, mild skin toxicity, mild-to-moderate fatigue, nausea and occasionally vomiting and transient blockage of ears; whereas ataxia, urinary incontinence and memory or cognitive disturbances are the known late side effects. Late radiation-induced dementia is a rare occurrence, in only 1.9-5.1% of patients.[25]

Surgical resection alone: Improved imaging and localization techniques have made surgery an accepted treatment option, particularly in patients with good prognostic factors. There is no direct evidence comparing WBRT alone versus surgery alone. Numerous retrospective studies have reported superiority of surgical resection over WBRT alone, but all of them had inherent selection bias, i.e., patients selected for surgery had good performance status, single metastatic lesion, young age, supratentorial location of metastases and minimal extracranial disease. However, surgical resection is generally

preferred when clinical diagnosis is doubtful (11% lesions are known to be nonmetastatic on histopathology diagnosis if CT scan is used as the preoperative diagnostic imaging modality) or there is considerable mass effect due to cystic/ hemorrhagic metastases or posterior fossa lesions. Lesions located in the brainstem, thalamus and basal ganglia are unresectable, and an attempt to biopsy can also be detrimental. The median survival in this good prognostic group is 12 months, better than that for WBRT. Further, it has been estimated that only 30% of patients with brain metastases are suitable for surgery. The role of surgery in multiple metastatic lesions is controversial. Bindal *et al.* reported excellent survival after resection of all the metastatic lesions, whereas Hazuka *et al.* indicated increased risk of perioperative morbidity due to the need of multiple craniotomies.[26,27] However, resection of large and symptomatic lesions should be considered to relieve mass effect and also in cases of life-threatening brain lesions like large compressive cerebellar lesions. The current practice is to treat multiple brain metastases with WBRT alone.

Radiotherapy after surgical resection versus surgery alone: The rationale of adjuvant radiotherapy is to sterilize the tumor bed which contains the microscopic tumor foci. It has been studied in case of single brain metastasis. Patchell *et al.* reported significantly better recurrence-free survival (70% *vs.* 18%, $P < 0.001$) and an improved quality of life (surgical resection or radiosurgery) without any overall survival benefit in a randomized study of 95 patients.[28] WBRT was given in doses of 50.40 Gy, and recurrences in the tumor bed as well as other areas of the brain were significantly reduced. Other retrospective series have also reported similar results. However, the decision of offering adjuvant radiotherapy to prevent recurrence, knowing the risk of definite but acceptable toxicity of WBRT, should be delicately balanced against the negative effect on the neurocognitive functioning of the patient.[29] The effects of recurrence are worse than the side effects of preventive treatment.

Radiotherapy after surgical resection versus radiotherapy alone: Three randomized studies have been reported in literature, two of which have shown statistically significant benefit in median survival after addition of surgery to radiation therapy. Patchell *et al.* randomly assigned 48 patients with single brain metastasis (10% with breast primaries) to surgery followed by WBRT versus WBRT alone.[30] The WBRT dose was similar in the two groups, 3,600 cGy in 12 daily fractions of 300 cGy each. Patients in the combined arm experienced a longer duration of functional independence (38 *vs.* 8 weeks) due to maintenance of KPS $\geq$70 for a longer duration of time and improved survival (40 *vs.* 15 weeks; $P < 0.01$). Noordijk *et al.* conducted a randomized trial of 63 patients (19% with breast primaries), which also reported similar results.[31] In this trial WBRT was given in nonstandard fractionation, 4,000 cGy in 200 cGy twice daily fractions for 2 weeks . Importantly, only patients with stable or absent extracranial disease benefited from combined modality therapy. Patients with progressive extracranial disease at study entry achieved a median survival of only 5 months, irrespective of the allocated treatment. One additional trial failed to demonstrate a survival or quality-of-life benefit.[32] Nearly half of the patients in this trial had extracranial disease, and 10 of 43 patients randomly assigned to radiotherapy underwent surgical resection. The imaging modality used for diagnosis was CT scan, as compared to MRI in the earlier two studies. The median survival time was 6.3 months in WBRT alone and 5.6 months in 'surgery plus WBRT' group.

Stereotactic radiotherapy: Stereotactic radiosurgery (SRS) involves the delivery of a single high-dose fraction of external radiation to a targeted lesion in the brain using multiple cobalt sources (gamma knife), modified linear accelerator (LINAC) or cyber knife. It has a potential to achieve high local tumor control and is essentially used as a substitute for surgical treatment in patients with lesions less than about 3 cm in diameter. The attractive features of SRS are lack of discomfort, minimal invasiveness (no surgical incision), reduced hospitalization time (outpatient basis) with negligible damage to the surrounding healthy tissues. SRS has gained particular attention in brain metastases as these are ideal targets for stereotaxy, being small, spherical, well defined with distinct margins on contrast enhancement and having displacing rather than infiltrative nature (unlike malignant gliomas). These characteristics help to achieve highly conformal dose distributions with minimal damage to surrounding tissues. The greatest advantage of SRS is the feasibility of using it in eloquent areas of brain which are usually inaccessible to surgical resection.

The major randomized clinical trials of SRS in brain metastases are tabulated below, in Table 3:

a) WBRT versus SRS alone: There is no randomized study directly comparing these two treatment options. Indirect conclusions can be drawn from above trials, that the three treatments may offer comparable survival benefit. However, omission of WBRT at the initial presentation is associated with an increased risk of intracranial relapse, requiring delayed WBRT and mandating strict MRI-based follow-up to diagnose relapses early.
b) WBRT with or without radiosurgery: Data indicates that survival is extended if radiosurgery is applied after WBRT in patients with a single brain metastasis than in those with two or three metastases. The median survival was 4.9 months versus 6.5 months in patients with a single metastasis treated with additional radiosurgery versus not in the RTOG 9508 trial, as reported by Andrews *et al.*[33] In this study, NSCLC and squamous histology and RPS class I patients also had significantly better survival. The 'WBRT plus SRS' group also has a significantly better local tumor control and more likelihood of having stable or improved KPS than patients receiving WBRT alone. DiLuna *et al.*, in their retrospective analysis, observed that radiosurgery had the best results in patients who had good systemic

Table 3: Major randomized trials of SRS in brain metastases

Study	Kondziolka[37]		Chougule[38]		Andrews[33]		Aoyama[36]	
Nature	Randomized		Randomized		Randomized		Randomized	
No of lesions	2 to 4		1 to 3		1 to 3		1 to 4	
Diameter	≤ 2.5 cm		≤ 4 cm		≤ 4 cm		≤ 3 cm	
Patients	Control	Case	Control	Case	Control	Case	Control	Case
	WBRT	WBRT+SRS	WBRT	SRS	WBRT	WBRT+SRS	SRS	WBRT+SRS
	30Gy/12#	16 Gy SRS	30 Gy/10#	30 Gy	37Gy/15#	15-24Gy	18-25 Gy	30 Gy/10#
Number	14	13	31	36	167	164	67	65
Survival	7.5 m	11.0 m	-	-	5.7 m	6.5 m	8.0	7.5 m
QOL	-	-			NS	NS	NS	NS
Local control	0%	92%	62%	87%	71%	82%	53.2%	23.6%
Neurologic toxicity ¾	None	None	-	-	0% acute	3% acute	2.9% acute	1.5% acute
					3% late	6% late	2.9% late	6.1% late
Functional preservation	-	-	-	-	27% at 6 m	43% at 6 m	26.9%	33.9%
							70.3%	72.1%
Neurologic deaths	None	None	-	-	0%	1%	19.3%	22.8%

control, breast cancer, one to three metastases and a total intracerebral tumor volume of <5 cc.[34] Similarly, Varlotto *et al*. reviewed the medical records of brain metastases patients undergoing SRS and concluded that the addition of concurrent WBRT to SRS was associated with an improved local control rate in patient subsets with tumor volume >2 cc, peripheral dose <16 Gy, single metastases, nonradioresistant tumors and specifically lung cancer metastases.[35]

c) SRS with or without WBRT: The rationale of omitting WBRT stems from the philosophy that patient with truly limited intracranial disease (oligometastatic state) can be managed effectively with focal therapies in the form of neurosurgical resection or radiosurgery. The only randomized trial that evaluated this approach observed no significant difference between SRS alone versus 'SRS plus WBRT' in terms of median survival, acute or late neurotoxicity and neurologic functional preservation rates.[36] But the 'SRS alone' group suffered from more recurrences and required salvage therapy at a later date more often than the 'SRS plus WBRT' group. These data are analogous to the surgical randomized trial by Patchell, which showed no survival advantage with adjuvant RT but reported significantly decreased tumor recurrences (70% *vs*. 18%). Several retrospective and prospective studies have also compared SRS alone with 'WBRT plus an SRS boost' and suggested that the omission of WBRT in the initial management of patients who underwent SRS did not compromise survival or intracranial control. Therefore, SRS alone appears to be effective in the treatment of a limited number of brain metastases and in good prognostic subgroup (RPA class I and II). Muacevic *et al.* reported similar findings in retrospective review of 151 patients of multiple brain metastases from breast cancer.[39]

Whole-brain radiotherapy with radiosensitizers: Whole-brain radiotherapy is the main treatment modality for multiple brain metastases as radiosurgery has not shown to improve survival in this group of patients. However, as majority of metastatic brain lesions are not ideal candidates for SRS due to their location, size or extracranial disease status, whole-brain radiotherapy remains the standard treatment in most patients. But the relatively suboptimal results of radiotherapy alone in eradication of brain metastases have led to studies combining radiotherapy with drugs that act on the radioresistant hypoxic clones with rationale of improving local tumor control. The drugs used initially for radiosensitization (metronidazole, misonidazole and 5 bromodeoxyuridine) failed to improve the results of WBRT alone. Novel radiosensitizers – Motexafin gadolinium, a redox active drug; and efaproxiral, a synthetic allosteric modifier of hemoglobin – have been studied that selectively target hypoxic tumor cells. Motexafin has been shown to improve median time to neurological progression without an overall survival benefit and with substantially low-grade (3 and 4) neurotoxicity in a subgroup of patients

with lung cancer. A phase III trial, randomized trial RT-009, also called Radiation Enhancing Allosteric Compound for Hypoxic Brain Metastases (REACH), demonstrated improved response rates and prolonged survival in breast cancer patients with CNS metastases treated with combination of WBRT and efaproxiral.[40] The efficacy of efaproxiral is related to the concentration of the drug in red blood cell (E-RBC). Brain metastases patients achieving sufficient E-RBC ($\geq$483 μg/ml) and receiving at least seven of ten efaproxiral doses were most likely to experience survival and response benefits. Patients with breast cancer primary tumors generally achieve the target efaproxiral exposure and therefore gain greater benefit from efaproxiral treatment.[41] As the number of breast cancer cases was relatively small in this study, a confirmatory trial in patients with brain metastases from breast cancer is ongoing (ENRICH), which would allow more meaningful conclusions to be drawn.

Intracavitary and interstitial brain irradiation: The United States Food and Drug Administration (US FDA) -approved GliaSite Radiation Therapy System (Cytyc Corporation, Marlborough, MA), a device for delivering intracavitary radiation, is undergoing phase II evaluation in resected solitary brain metastasis with the intent of achieving optimal tumor control. The preliminary results have been reported by Rogers *et al.*, in 62 patients, half of them being NSCLC. The prescribed dose was 60 Gy to a depth of 1 cm.[42] The local control rate was 82-87% with a median survival time of 40 weeks and a reoperation rate for suspected tumor recurrence or radiation necrosis of 25%.

Chemotherapy for brain metastases: The impermeability of the blood-brain barrier to ionized water-soluble compounds >180 Da and the presence of the P-glycoprotein efflux pump at the luminal surface of the brain capillaries result in lack of penetration of the chemotherapeutic drugs. Though breast cancer is a chemosensitive disease, there is limited data on the use of chemotherapy for breast cancer metastatic to brain. Most commonly used are cyclophosphamide-based regimens (along with methotrexate, 5 FU, prednisolone, etc.), producing response rates of 17-61% and median duration of response of 7 months.[43] High-dose intravenous methotrexate has resulted in overall response rates of 56%.[44] There are case reports and phase I study on the efficacy of capecitabine, an oral analogue of 5 FU alone or in combination with temozolamide, for treatment of parenchymal as well as leptomeningeal metastases. Topotecan has not been shown to be effective in brain metastases other than that from small-cell lung cancer. Recently, temozolamide is being extensively evaluated in phase I and II studies, either alone or in combination with other chemotherapeutic drugs (vinorelbine, cisplatin, capecitabine), for recurrent and progressive brain metastases from solid tumors, including breast cancer.[45,46] These studies have shown median survival time of 4-7 months. The toxicity includes hematological (grade 3 or 4 thrombocytopenic leucopenia) and non-hematological (pneumonitis, constipation, elevated liver enzymes).

Targeted therapies for brain metastases: The increased incidence of brain metastases in patients with HER-2–positive tumors has already been discussed above. Recently the 'HER-1/ HER-2'–targeted dual tyrosine kinase inhibitor lapatinib has been found to have significant activity in these tumors. More recently, this drug has also been shown to have activity in HER-2–positive patients with brain metastases. A phase II multicentric study (EGF105084) that enrolled 241 HER-2–positive patients with brain metastases who had previously been treated with trastuzumab and cranial RT and who had documented CNS disease progression was presented at ASCO 2007.[47] The primary outcome measure was the composite 'CNS Objective Response Criteria,' which included assessment of target and nontarget lesion volume, new lesions, steroid use and neurological symptoms. The majority of patients (87%) had non-CNS disease, and 88% had received $\geq$3 previous therapies. The main findings of the study showed a partial response/ stabilization rate of 48% with a 6-month PFS rate of 22% in this heavily pre-treated population.

Novel drug delivery techniques: Various approaches have been advocated to improve the drug delivery across the BBB. Temporary osmotic damaging of the blood-brain barrier, achieved by mannitol or a novel bradykinin agonist Cereport, is one of such methods. Surgical adjuncts such as BCNU (carmustine) wafers have also been used after surgical resection to enhance local control. Encouraging results have also been observed with intra-arterial chemotherapy in conjunction with blood-brain barrier disruption for multiple brain metastases in ovarian and lung cancer and also systemic lymphoma. Such strategies should also be evaluated for breast cancer metastasizing to brain. However, BBBD should be applied with caution in patients with significant mass effect as the transient increase in the interstitial brain water content increases the risk of herniation.

Chemoradiotherapy: This approach has been studied in a randomized phase II trial by Antonaduo *et al*.[48] The study randomized 52 patients with previously untreated brain metastases from solid tumors to oral temozolomide (75 mg/m^2/day) concurrent with 40-Gy fractionated conventional external-beam radiotherapy (2 Gy, 5 days/wk) for 4 weeks followed by adjuvant continued temozolomide therapy (200 mg/m^2/day) for 5 days every 28 days for an additional six cycles versus 40-Gy radiotherapy alone. The group receiving temozolomide and radiotherapy had significantly improved response rate, improved functional status and decreased corticosteroid use but did not have improved overall survival. Though this study supports the efficacy and safety of TMZ and RT in the treatment of patients with previously untreated brain metastases, these observations need to be confirmed in a large phase III randomized trial.

'WBRT plus supportive care' versus supportive care alone: The only trial which compared 'WBRT plus supportive care' (oral prednisone) versus supportive care alone is that reported

by Horton *et al*.[49] Median survival in the 'prednisone alone' arm was 10 weeks compared with 14 weeks in the combined arm (*P*-value not stated), and there was no difference in the proportion of patients with an improvement in performance status (63% versus 61% respectively). However, this trial should be interpreted with caution as data on tumor response, intracranial progression-free duration, quality of life and toxicity were not reported.

B) Leptomeningeal metastases: Breast cancer is the most common cause of metastases to the leptomeninges, especially from a lobular carcinoma.[50] Most common presenting symptoms are headache, vomiting, ataxia, lethargy, spinal symptoms, cranial nerve palsies and very rarely seizures. Even after multimodality therapy, median survival is only 12 weeks. Definitive diagnosis is by CSF examination for presence of malignant cells or raised tumor markers. Imaging should include screening of the entire spine as well as brain to rule out simultaneous parenchymal metastases and to map out the extent of spinal disease. Focal radiotherapy is given to symptomatic and bulky sites. The treatment of the entire neuraxis results in unacceptable toxicity, mainly leukoencephalopathy and dementia. Those whose extracranial disease is reasonably controlled, intrathecal therapy can be delivered preferably through an Ommaya reservoir or via lumbar puncture. The chemotherapeutic drugs most commonly used in IT therapy are methotrexate, thiotepa and, more recently, liposomal cytarabine (DepoCyt).[43]

CONCLUSIONS

The development of brain metastases is the end stage of the natural history of a malignant disease course. CNS metastases is a common occurrence among breast cancer patients, with rates increasing over time The incidence has increased due to the use of trastuzumab, a monoclonal antibody which does not cross BBB, produces systemic responses and enhanced survival, without a clear effect on brain metastases. In standard care, no routine brain screening is performed in asymptomatic patients, as there are no convincing data to support the benefit related to early diagnosis and treatment of CNS metastases. Indeed, the overall survival of patients with symptomatic and asymptomatic CNS metastases seems to be similar and related predominantly to progression of extra-cerebral lesions. The goal of management of brain metastases is both symptom palliation and prolongation of life. The majority of patients with controlled intracranial metastases will expire from systemic disease rather than from recurrence of these metastases. The choice of appropriate therapy for brain metastases also depends on prognostic factors, including the age of the patient, the Karnofsky's performance score, the number of brain metastases and the presence of systemic disease. Single brain metastasis should be treated with surgical resection or stereotactic radiosurgery, though it is unclear at this time if one modality is more effective than the other. Surgical resection is preferred when a pathologic diagnosis is needed, for tumors larger than 3.5 cm or when immediate tumor mass decompression is required. Stereotactic radiosurgery (SRS) should be applied for single tumors less than 3.5 cm in surgically inaccessible areas and for patients who are not surgical candidates. Small tumors (i.e., <3.5 cm) that cause minimal edema and are surgically accessible may be treated with either surgery or SRS. Surgical adjuncts such as BCNU (carmustine) wafers and the GliaSite Radiation System (Cytyc Corporation, Marlborough, MA) may be useful in the future in achieving optimal local tumor control. There is controversy over whether whole-brain radiation therapy (WBRT) can be omitted following surgical resection or SRS. Omission of WBRT increases intracranial tumor recurrence; however, this has not been correlated with decreased survival. Clinicians who choose to omit upfront WBRT are obligated to monitor the patient closely for intracranial recurrence, at which time further salvage therapy in the form of surgery, SRS or WBRT may be considered. In patients who have two to four metastases, stereotactic focal radiotherapy (i.e., radiosurgery) with or without WBRT is usually indicated. In the remainder of patients, WBRT alone provides adequate palliation. Chemotherapy has been demonstrated to improve response rates when used as an adjunct to radiation therapy. Although breast carcinoma is sensitive to chemotherapy, the role of chemotherapy in the treatment of brain metastases is still unclear. Objective responses after cyclophosphamide-based therapies were reported in studies performed in the 1980s. Recently, capecitabine- and temozolamide-based regimens have shown encouraging results in phase I and II studies. However, these improvements in response rates have not been correlated with an improvement in median survival. Noncytotoxic radiosensitizing agent efaproxiral has shown promise in a phase III randomized trial in patients with metastatic breast cancer in terms of improvement of response rates and also median survival. Targeted therapies offer promise in achieving therapeutic efficacy while minimizing side effects. Given the prevalence of brain metastases in patients with metastatic breast cancer in contemporary series, the rationale for clinical trials of CNS screening and prophylactic cranial irradiation should be developed in HER-2/ *neu* overexpressing patients receiving trastuzumab. The increasing prevalence and economic burden associated with brain metastases suggests an unmet need that could be filled with newer treatments that improve breast cancer outcomes, including the prevention or delay of brain metastases. 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.

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