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Brain metastases in breast cancer

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INTRODUCTION

After lung cancer, metastatic breast cancer is the second most common cancer associated with brain metastases in the United States [1]. As patients with advanced breast cancer live longer, the incidence of brain metastases appears to be increasing, with one meta-analysis suggesting that approximately one-third of patients with human epidermal growth factor receptor 2 (HER2)-positive, one third of those with triple-negative, and 15 percent of those with hormone receptor-positive, HER2-negative metastatic breast cancer will develop brain metastases [2]. In a subset of women, progression in the CNS has become the major life-limiting problem.

The risk factors, prognosis, and management of brain metastases in breast cancer are presented here. An overview of the presentation, diagnosis, and management of brain metastases (across tumor types) is discussed separately.

- (See "Epidemiology, clinical manifestations, and diagnosis of brain metastases".)
- (See "Overview of the treatment of brain metastases".)
- (See "Treatment of leptomeningeal disease from solid tumors".)

RISK FACTORS FOR CENTRAL NERVOUS SYSTEM METASTASES

Advanced stage at diagnosis — The risk of central nervous system (CNS) relapse among patients with breast cancer varies significantly by disease stage. Among women presenting with early-stage breast cancer, fewer than 3 percent will develop brain metastases [1,3]. By contrast,

symptomatic brain metastases are diagnosed at time of initial diagnosis in 10 to 16 percent of patients with metastatic breast cancer [1,4].

Breast cancer subtype — Breast cancer subtype is associated with the incidence of brain metastases [3,5-17].

In a cohort study of 1434 women treated with breast-conserving therapy plus systemic chemotherapy, brain metastases developed in 36 (2.5 percent) [3]. However, the risk of brain metastases at 10 years differed by breast cancer subtype:

- Luminal A – 0.7 percent
- Luminal B – 12 percent
- Luminal human epidermal growth factor receptor 2 (HER2)-positive – 8 percent
- HER2 – 12 percent
- Triple-negative – 7 percent

Specific considerations regarding HER2-positive and triple-negative subtypes are discussed below.

- **HER2-positive disease** – Over time, up to one-half of patients with HER2-positive, metastatic breast cancer will develop brain metastases [18]. The brain is frequently reported as the first site of relapse in women with HER2-positive breast cancer treated with trastuzumab, whether administered in the adjuvant [19,20] or metastatic settings [6-10]. However, the relationship between CNS events and receipt of HER2-directed agents (eg, trastuzumab) for women with HER2-positive metastatic breast cancer is not clear. Because trastuzumab was shown to reduce recurrence rates in the adjuvant setting, the higher rate of CNS events is related to the increased survival of patients, a biologic predilection for CNS metastases, and a relative "sanctuary site" in the CNS [11].

  The association between the use of trastuzumab and CNS events is illustrated in these examples:

  - A 2011 meta-analysis of adjuvant trastuzumab trials reported an increased incidence of brain metastases associated with adjuvant trastuzumab use (odds ratio 1.58, 95% CI 1.08-2.30) [19]. However, the overall risk of brain metastases was low in both of the trastuzumab and control groups in all of the trials.

- By contrast, a separate analysis of over 3400 patients who participated in the HERA randomized trial of adjuvant trastuzumab versus observation reported that adjuvant trastuzumab did not increase the risk of a CNS event as the initial recurrence (2 percent in both arms) [20]. Among patients in the HERA trial who subsequently died, there was actually a trend towards decreased CNS events among patients treated with trastuzumab versus no trastuzumab (47 versus 57 percent, respectively), although this difference was not statistically significant.

- Other data do not suggest a higher rate of CNS relapse with trastuzumab versus other HER2-directed therapy. In the KATHERINE clinical trial, 1486 patients who had residual disease after neoadjuvant HER2-directed therapy were randomized to either continue trastuzumab or to switch to trastuzumab-emtansine (T-DM1). The overall study demonstrated a significant reduction in distant metastasis events with T-DM1; however, there was no reduction in the risk of CNS as first site of relapse, which occurred in approximately 5 percent of patients in both arms [21]. (See "Adjuvant systemic therapy for HER2-positive breast cancer", section on 'Residual disease'.)

- **Triple-negative disease** – Patients with triple-negative breast cancer also have an increased risk of brain metastases as the initial site of metastases or following a diagnosis of breast cancer. In one study, the five-year cumulative incidence of brain metastases as a first site of recurrence was 3, 5, and 10 percent with stage I, II, and III disease, respectively [16]. In other studies, the incidence of brain metastases at or following the diagnosis of metastatic breast cancer ranges between 25 and 46 percent [5,17].

Germline BRCA1/2 mutation — Patients with metastatic breast cancer in the setting of a germline breast cancer susceptibility gene 1 or 2 (*BRCA1* or *BRCA2*) mutation may have a higher-than-expected risk of CNS metastases [22,23]. In one study, 53 percent of *BRCA1* carriers and 50 percent of *BRCA2* carriers developed CNS metastases [23]. In *BRCA1* carriers, this risk largely seems related to the increased likelihood of the triple-negative subtype.

Other possible factors — Other factors associated with an increased likelihood of CNS relapse include age under 40 years, pulmonary metastases, and African American ancestry [1,4,5,18,24,25]. However, these, too, are factors more often associated with triple-negative breast cancer, and whether they are independent risk factors for CNS relapse remains unclear.

LOCAL CONTROL OF INTRACRANIAL DISEASE

For most patients with a favorable prognosis (eg, Karnofsky Performance Score [KPS] 70 or higher (table 1), age <65 years, controlled primary tumor, and controlled or absent extracranial metastases), **aggressive local treatment** is indicated. The choice between surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery is discussed elsewhere. Important factors to consider include number, size, and location of brain metastases; degree of mass effect and edema; presence or absence of symptoms, functional status, and extent of systemic disease; and patient preferences with regard to invasive therapy (see "Overview of the treatment of brain metastases", section on 'Patients with good performance status'):

- However, for those with human epidermal growth factor receptor 2 (HER2)-positive metastatic disease and limited, asymptomatic intracranial disease, upfront systemic therapy is discussed below. (See 'Choosing between options' below.)
    - It should be noted, however, that most studies of initial systemic therapy in patients with previously untreated brain metastases only enrolled asymptomatic or minimally symptomatic patients not requiring corticosteroids for symptom control.
- For patients with a poor prognosis (eg, KPS <70), WBRT, or consideration of best supportive care, is the preferred treatment approach.
- For those with refractory brain metastases, further treatment decisions are made within the context of a multidisciplinary discussion, taking into account prior radiotherapy (RT), symptoms, size and location of lesions, status of a patient's extracranial disease, and patient preference. The approach to patients without a feasible local therapy option is discussed below. (See 'For those with progressive extracranial disease or no local therapy option' below.)

In addition, symptom control is of primary importance for patients with brain metastases. This includes:

- Control of peritumoral edema and increased intracranial pressure. (See "Management of vasogenic edema in patients with primary and metastatic brain tumors".)
- The management and prevention of venous thromboembolic disease. (See "Treatment and prevention of venous thromboembolism in patients with brain tumors".)
- However, for most patients with brain metastases from breast cancer, particularly those who have not had a prior seizure, routine seizure prophylaxis is not indicated. (See "Seizures in patients with primary and metastatic brain tumors", section on 'Patients without seizures'.)

SYSTEMIC THERAPY

For those without extracranial disease — For patients who have no evidence of extracranial disease and achieve an excellent clinical response after local treatment (ie, surgery and/or radiation therapy [RT]) for brain metastases, there are no prospective data to inform the benefits of systemic treatment.

- For patients with hormone receptor-positive breast cancer, the role of endocrine therapy should be individualized based on prior treatments and patient preference. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

- For patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, we typically suggest trastuzumab monotherapy, or trastuzumab/pertuzumab therapy, though we acknowledge the lack of prospective data to inform the efficacy of this approach. In general, we do not administer HER2 tyrosine kinase inhibitor (TKI) plus capecitabine in this setting outside of a clinical trial because of the potential for treatment-related toxicities in the setting of unknown clinical benefit.

  The decision on how long to continue HER2-directed therapy should be individualized, as there are no prospective data to inform this issue. Further discussion on duration of therapy is discussed elsewhere. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Optimal treatment duration of a HER2-directed agent'.)

The approach to patients in whom local therapy is not feasible is discussed below. (See 'For those with progressive extracranial disease or no local therapy option' below.)

For those with stable/responding extracranial disease — In general, for patients with a new or progressive intracranial lesion and stable or responding extracranial disease, we continue the existing line of systemic treatment, provided that it has been well tolerated and there is a reasonable local therapy option to address the patient's intracranial disease. If there is no feasible local therapy option, the approach to systemic therapy is discussed below. (See 'For those with progressive extracranial disease or no local therapy option' below.)

Endocrine therapies and anti-HER2 antibodies (eg, trastuzumab/pertuzumab) are typically continued throughout RT, while chemotherapy and immunotherapy are held during RT and resumed one to two weeks following treatment.

If systemic therapy had been poorly tolerated, however, we move to the next line of systemic therapy. (See 'For those with progressive extracranial disease or no local therapy option' below.)

The approach to patients with no remaining extracranial disease is discussed above. (See 'Systemic therapy' above.)

For those with progressive extracranial disease or no local therapy option — For patients in whom there is both new/progressive intracranial disease and progression of the extracranial disease, we change systemic therapies after local treatment has been administered to the brain metastases.

Additionally, if a patient has progressive intracranial disease but does not have a feasible local therapy option, or does not require urgent local therapy, a switch of systemic therapy for the purpose of treating both the intracranial and extracranial disease could be considered. Of note, there are no trials directly comparing RT versus systemic therapy in patients with progressive intracranial disease.

Options for therapy are discussed below.

HER2-negative disease

Single-agent chemotherapy for most patients — Although few of the commonly used agents for breast cancer penetrate the intact blood-brain barrier to a significant degree, many of the same agents (fluorouracil, and derivatives such as capecitabine, platinums, doxorubicin) have been described to have activity against central nervous system (CNS) metastases, likely as a result of increased vessel permeability associated with tumor vasculature (table 2) [26-29].

In a relatively older case series of 100 consecutive breast cancer patients with symptomatic brain metastases treated with a variety of chemotherapy regimens, an objective response rate (ORR) of 50 percent in the brain metastases was observed, with a median duration of response of seven months [30]. However, in this study, patients were untreated compared with the modern era: less than 10 percent of patients had received adjuvant chemotherapy, and approximately one-half had not received chemotherapy for metastatic disease.

Other cytotoxic agents that have been investigated in the treatment of brain metastases include temozolomide and etoposide [28,29,31-34]. A number of agents are in clinical trials, including GRN1005 and several irinotecan derivatives.

Other options in specific subsets

- **Hormone receptor-positive disease** – Responses of both parenchymal and leptomeningeal metastases have been documented in case reports to multiple hormonal therapies, including tamoxifen, megestrol acetate, and the aromatase inhibitors [35-37]. In general, however, endocrine therapy alone is not appropriate primary management of

brain metastases from hormone receptor-positive breast cancer, and local therapies are necessary. Upon completion of local therapy, next-line systemic therapy depends upon previous treatments as well as tumor phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) status. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

Cyclin-dependent kinase 4/6 inhibitors abemaciclib and palbociclib have shown intracranial activity in small, early-phase trials [38-40]. As an example, in a phase II study enrolling heavily pretreated patients with estrogen receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer with active brain metastases, the intracranial ORR was 5.2 percent and the intracranial clinical benefit rate was 24 percent [39].

- **Triple-negative disease** – Although systemic therapies have not supplanted local treatments of brain metastases in triple-negative breast cancer, a number of agents including immune checkpoint inhibitors, inhibitors of poly(ADP-ribose) polymerase, and sacituzumab govitecan are being evaluated in clinical trials for potential intracranial efficacy. Choice of therapy after local treatment of brain metastases should be based on previous treatment, breast cancer susceptibility gene mutation status, and tumor expression of programmed cell death ligand 1. (See "ER/PR negative, HER2-negative (triple-negative) breast cancer", section on 'Metastatic disease'.)

HER2-positive disease

Choosing between options — For initial therapy of newly diagnosed brain metastases, **RT** remains the standard of care. However, the role of systemic therapy in patients with brain metastases is evolving for those with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

- For the initial treatment of brain metastases for patients with HER2-positive disease:
  - We suggest upfront RT. Of note, there are no trials directly comparing upfront RT versus upfront systemic therapy.
    - **However**, some UpToDate experts and guideline committees consider systemic therapy (particularly with tucatinib plus capecitabine plus trastuzumab) as an appropriate alternative to upfront radiation for select asymptomatic patients [41], assuming close follow-up and appropriate patient counseling. Appropriate candidates for this approach include those with limited lesions, no symptoms (brain metastases were usually detected incidentally on staging scans), a

preference to defer radiation, and who have had sufficiently few prior therapies that there is a high likelihood of treatment response.

- In regards to systemic therapy, available options include:

  - Tucatinib-capecitabine-trastuzumab,
  - Fam-trastuzumab deruxtecan (T-DXd), or
  - Trastuzumab-emtansine (T-DM1), depending on prior therapy exposure at the time of brain metastasis diagnosis/progression

  Each regimen has demonstrated activity among patients with treated brain metastases, as well as active, untreated brain metastases. Because of the significant overall survival benefit observed with the addition of tucatinib to capecitabine/trastuzumab in the HER2CLIMB trial, our preference is for the tucatinib-capecitabine-trastuzumab regimen, particularly among those with active brain metastases [42]. However, T-DXd may be preferred in some instances, particularly among patients with stable/treated brain metastases, if extracranial progression is the most significant clinical issue. (See 'Tucatinib, capecitabine, and trastuzumab' below and 'Fam-trastuzumab deruxtecan' below.)

  Because of the substantial progression-free survival (PFS) benefit observed in patients with stable brain metastases comparing T-DXd versus T-DM1, and preliminary evidence of CNS activity of T-DXd in patients with active brain metastases, we would generally sequence T-DXd prior to T-DM1 unless there is a contraindication to its use. (See 'Trastuzumab-emtansine' below and 'Fam-trastuzumab deruxtecan' below.)

- If these options are not available, neratinib and capecitabine or lapatinib plus capecitabine are appropriate alternatives, both of which have supporting data from single-arm, phase II studies [43]. (See 'Alternatives or later-line options' below.)

Tucatinib, capecitabine, and trastuzumab — Tucatinib is an oral TKI that is selective for the kinase domain of HER2, with minimal inhibition of epidermal growth factor receptor (EGFR) [44]. For patients with treated brain metastases, we often use this combination after progression on T-DM1. This combination may also be an appropriate alternative to RT in a select group of patients, who have progressed previously on trastuzumab, pertuzumab, and T-DM1. (See 'Choosing between options' above.)

In a randomized trial (HER2CLIMB) including patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1 (and with a median of four prior lines of therapy), tucatinib, capecitabine, and trastuzumab improved both PFS and overall

survival (OS) relative to capecitabine and trastuzumab [44]. In this trial, 291 patients had brain metastases at study entry, 174 of whom had active brain metastases (including both untreated and treated, progressing brain metastases). At a median follow-up of approximately 30 months [45]:

- Among all patients with brain metastases, the tucatinib arm experienced improved median OS (22 versus 13 months; hazard ratio [HR] 0.60, 95% CI 0.44-0.81). Previously reported, the CNS PFS was also improved (9.9 versus 4.2 months; HR 0.32, 95% CI 0.22-0.48) [42].

- In the subset of patients with active brain metastases, the tucatinib group also experienced improvements in both median OS (21 versus 12 months; HR 0.52, 95% CI 0.36-0.77) [45]. In earlier reporting, the CNS PFS was 9.5 versus 4.1 months (HR 0.36, 95% CI 0.22-0.57) and among those with measurable disease, the confirmed intracranial ORR was 47 percent in the tucatinib arm versus 20 percent in the control arm.

- In the subset of patients who had treated stable brain metastases, OS was 22 months for those who received tucatinib and 16 months for those who did not (HR 0.70, 95% CI 0.42-1.16) [45]. Previously reported CNS PFS was 8.1 versus 3.1 months, and intracranial ORR was 47 versus 17 percent, respectively.

This trial was unique in that it allowed enrollment of patients with active brain metastases, supporting the use of this regimen rather than RT in select patients with brain metastases from HER2-positive breast cancer. Appropriate candidates for this option are discussed above. (See 'Choosing between options' above.)

However, the trial did not include patients with leptomeningeal disease, and the activity of tucatinib in this setting is under investigation. In preliminary results of a single arm trial in patients with leptomeningeal disease from HER2-positive metastatic breast cancer, tucatinib, trastuzumab, and capecitabine was associated with a median overall survival time of 10 months, which compares favorably with a historical control of 4 to 5 months [46].

The US Food and Drug Administration (FDA) has approved tucatinib in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting [47].

Fam-trastuzumab deruxtecan — Fam-trastuzumab deruxtecan is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor [48]. It is approved by the FDA for use in adult patients with

unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen in the metastatic setting, or in the (neo)adjuvant setting for those who developed progression during or within six months of completing therapy [49,50]. At this time, there are only limited data regarding its use in patients with brain metastases, but available evidence suggests intracranial activity both for treated brain metastases and untreated brain metastases.

- **Treated brain metastases** – The phase III Destiny-Breast03 trial compared T-DM1 versus T-DXd among patients with HER2-positive metastatic breast cancer with progression on a trastuzumab- and taxane-containing regimen [51]. Patients with brain metastases were eligible if they had clinically stable, previously treated brain metastases. Among the 114 patients with stable brain metastases, the hazard ratio for disease progression or death was 0.38, favoring T-DXd (95% CI 0.23-0.64).

  Additionally, fam-trastuzumab deruxtecan was evaluated in a single-arm, phase II study, in 112 patients with a median of six prior lines of treatment [48]. The median duration of PFS was 16.4 months (95% CI 12.7-not reached) among all patients and 18.1 months (95% CI 6.7-18.1) among the 24 patients who were enrolled with treated and asymptomatic brain metastases. Reassuringly, isolated CNS progression in the face of controlled extracranial disease was uncommon [52].The most common grade ≥3 adverse events included decreased neutrophil count (21 percent), anemia (9 percent), and nausea (8 percent). Fam-trastuzumab deruxtecan was associated with interstitial lung disease in 14 percent of patients, including one patient who died from this complication. Full details of this trial are found elsewhere. (See "Systemic treatment for HER2-positive metastatic breast cancer", section on 'Fam-trastuzumab deruxtecan'.)

- **Active brain metastases** – In preliminary data from a single-arm phase II trial including 15 patients with HER2-positive breast cancer and newly diagnosed untreated brain metastases or brain metastases progressing after local therapy, with prior exposure to trastuzumab and pertuzumab, and no indication for immediate local therapy, T-DXd was associated with an intracranial response rate of 73 percent (11 of 15 patients) [53]. Median PFS was four months. Main nonhematologic toxicities consisted of grade 1/2 fatigue (87 percent), nausea (47 percent), and diarrhea. Grade 2 interstitial lung disease and a symptomatic drop of left ventricular ejection fraction were observed in one patient each. In a separate phase II study including 13 patients with active brain metastases from HER2-positive breast cancer, the intracranial response rate was 50 percent among those with asymptomatic, untreated brain metastases (n = 4) and 44 percent among those with

progressive brain metastases after local therapy (n = 9) [54]. Toxicities were similar to previous reports.

Accumulating, though limited, evidence therefore supports a role for T-DXd in patients whose brain metastases have progressed despite prior local therapy. The number of patients with newly diagnosed brain metastases treated to date with T-DXd in lieu of radiotherapy is very small and further data is required before this is employed in routine clinical practice. Although we do not recommend routine CNS surveillance of asymptomatic patients with CT or MRI scans, we have a low threshold to pursue CNS imaging in those with symptoms, given the high incidence of brain metastases in patients with HER2-positive breast cancer.

Trastuzumab-emtansine — Trastuzumab-emtansine (T-DM1) is an option in patients who progress after trastuzumab and a taxane (with or without pertuzumab), including for those with treated, stable brain metastases [55]. Prospective trials of T-DM1 that led to its development and eventual regulatory approval specifically excluded patients with active brain metastases. Postapproval, multiple case series and a prospective post-marketing trial experience have emerged, reporting CNS ORRs of between 20 and 44 percent in human epidermal growth factor receptor 2 (HER2)-positive breast cancer [56-59].

For example, in a study including over 2000 patients with prior chemotherapy and anti-HER2-directed therapy for advanced HER2-positive disease, among 126 patients with measurable brain metastases, the best overall response rate and clinical benefit rate with T-DM1 were 21 percent and 43 percent, respectively [59]. In the 398 patients with baseline brain metastases, median PFS and OS were 5.5 and 18.9 months, respectively. A reduction in the sum of the major diameters of brain metastases by at least 30 percent occurred in 43 percent of all patients, and in 49 percent of the 67 patients without prior RT to the brain metastases. Use of this agent as an alternative to RT in very select patients is discussed above. (See 'Choosing between options' above.)

Case reports also suggest that the agent T-DM1 may occasionally result in clinically significant increases in brain edema following treatment with stereotactic radiosurgery (SRS) [60]. In one series of four patients, all received SRS a median of 8.5 days (range, 3 to 449 days) prior to the start of T-DM1, and the onset of symptoms (eg, headache, nausea, vomiting, speech impairment) varied between them. All four patients were treated with steroids, with eventual clinical resolution of symptoms. Of note, one of four continued on T-DM1 and had worsening of symptoms. Ultimately, that patient had surgery for resection of a posterior fossa metastasis, and pathology revealed severe radionecrosis without viable tumor. These data suggest that

worsening of CNS symptoms may be due to complications of treatment rather than disease progression.

Alternatives or later-line options — The options below are acceptable for those with brain metastases, although we typically prefer those discussed above as initial strategies if available, given higher likelihood of benefit or stronger supporting evidence. In addition, the activity of neratinib or lapatinib in patients with CNS progression on prior tucatinib is not well described at this time.

- **Lapatinib plus capecitabine** – Lapatinib with capecitabine represents another orally available later-line option for those with metastatic HER2-positive breast cancer, including those with brain metastases.

  - **Untreated brain metastases** – The LANDSCAPE trial was a small, single-arm, phase II study that enrolled 45 patients with previously untreated brain metastases from HER2-positive metastatic disease with lapatinib (1250 mg daily) plus capecitabine (2000 mg/m^2 on days 1 to 14 of a 21-day cycle) [43]. Over 90 percent of patients had previously been exposed to trastuzumab. With a median follow-up of 21 months, 29 of 44 evaluable patients (66 percent) had a partial response. The median time to progression was 5.5 months, and in 32 patients, the first site of progression was in the CNS. OS at six months was 91 percent. Serious (grade 3/4) toxicity was recorded in 22 (49 percent) patients, including diarrhea (n = 9), hand-foot syndrome (n = 9), fatigue (n = 6), and rash (n = 2).

  - **Refractory brain metastases** – Two prospective, single-arm clinical trials have evaluated the use of lapatinib, an orally active small molecule inhibitor of EGFR and HER2, in patients with refractory CNS metastases from HER2-positive metastatic breast cancer [61,62]. The ORR to lapatinib monotherapy in these trials was modest, though a few patients achieved prolonged clinical benefit. In the larger of these trials, a subset of 50 patients went on to receive the combination of lapatinib and capecitabine at the time of progression [62]. Of these, 10 (20 percent) achieved an objective response in the CNS while maintaining stable or responsive disease in extracranial sites.

    The combination of lapatinib plus capecitabine has been subsequently evaluated in several phase II and retrospective studies. A systematic review of the literature and pooled analysis included data on 799 patients with brain metastases in 12 studies treated with either lapatinib plus capecitabine or lapatinib alone (661 and 138 patients, respectively) [63]. In all of the studies, patients were pretreated with trastuzumab, and, in 11 of the studies, with local therapy at study entry or previously. The pooled overall

response was 21 percent, and the response rate for those treated with the combination was 29 percent. The median PFS and OS were 4.1 and 11.2 months, respectively.

- **Neratinib plus capecitabine** – Neratinib with capecitabine is an orally available later-line option for those with metastatic HER2-positive breast cancer, and has demonstrated intracranial activity.

  In a phase II trial of 49 patients with measurable, progressive, HER2-positive brain metastases (92 percent having received CNS surgery and/or RT), neratinib (240 mg daily) plus capecitabine (750 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle) resulted in an ORR of 49 percent among lapatinib-naïve patients, and 33 percent among those with prior lapatinib treatment [64]. Median PFS and OS among lapatinib-naïve patients was 5.5 and 13.3 months, and 3.1 and 15.1 months among those with prior lapatinib treatment. However, grade 3 diarrhea occurred in 29 percent of patients, overall. Thus, if considering this option for patients, significant attention must be paid to toxicity avoidance and management, and toxicity must be considered in the risk-benefit assessment of the regimen.

PROGNOSIS

Retrospective analyses suggest that the prognosis of brain metastases in patients with breast cancer is improving, and this appears to be primarily a result of advances in systemic therapy, which have led to better control of disease (typically reported as systemic control or overall survival benefit) outside the central nervous system (CNS).

In historic series, the median survival for patients with brain metastases treated with whole-brain radiation therapy (WBRT) was less than six months [65,66]. By contrast, a more recent retrospective study of 112 breast cancer patients diagnosed with brain metastases between 1997 and 2007 showed a median survival of 14.4 months (for the entire cohort); among patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, it was 23.1 months. This markedly exceeds median survival estimates from patients treated prior to the widespread use of trastuzumab for metastatic, HER2-positive breast cancer (approximately three months), and therefore likely represents the effect of improved systemic control on breast cancer mortality [6,67]. Other investigators have noted similar results (table 3) [7,8,12,68-71]. Unfortunately, the prognosis for patients with brain metastases with triple-negative breast cancer remains poor (table 4) [17,71-73].

Prognostic classification systems can aid in defining favorable versus poor-prognosis patients to help guide subsequent treatment. These systems include the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) and the disease-specific graded prognostic assessment (GPA). The use of these systems specifically in breast cancer patients is covered below. A general discussion of these classification systems is covered separately. (See "Overview of the treatment of brain metastases", section on 'Prognostic assessment'.)

- The RPA is based on performance status, age, primary tumor site, and the presence of extracranial metastases (table 5). It was validated in 117 breast cancer patients who were treated with WBRT [74]. Only two patients met criteria for RPA Class I, leaving roughly 50 percent of patients in each of RPA Class II and III. RPA Class II patients had a longer median survival compared with those with RPA Class III (eight versus three months, respectively).

- Studies have indicated that prognostic factors for patients with brain metastases vary by primary histology [75].

  - The breast cancer-specific GPA takes into account Karnofsky Performance Status, age, breast cancer subtype (defined by estrogen receptor, progesterone receptor, and HER2 status), number of brain metastases, and extracranial metastases (table 6) [76].

SPECIAL CONSIDERATIONS

Leptomeningeal metastases — Increasingly, we use systemic therapy and radiation therapy (RT) in management of leptomeningeal disease, but rarely attempt intrathecal treatment given the historic difficulties and limited efficacy of this approach. The treatment of leptomeningeal metastases, including RT, intrathecal, and systemic treatments, is covered in more detail separately. (See "Treatment of leptomeningeal disease from solid tumors".)

Despite improvements in the prognosis of some patients with parenchymal brain metastases from breast cancer, the prognosis of patients with leptomeningeal metastases (LM, otherwise called carcinomatous meningitis) has not markedly changed in the last decade. As an example, in a retrospective series of 68 women with metastatic breast cancer who had evidence of LM, median overall survival was four months and the one-year survival rate was 13 percent [77]. On multivariate analysis, independent factors associated with survival were: conversion to negative cytology (hazard ratio [HR] for death 0.42, 95% CI 0.20-0.89), absence of systemic metastases (ie, metastasis limited to LM with or without brain metastases; HR 0.42, 95% CI 0.19-0.91), and combined-modality treatment (HR 0.24, 95% CI 0.09-0.63).

Leptomeningeal disease is relatively more common in patients with estrogen receptor-positive lobular breast cancer.

Considerations during the COVID-19 pandemic — The COVID-19 pandemic has increased the complexity of cancer care. Important issues in areas where viral transmission rates are high include balancing the risk from treatment delay versus harm from COVID-19, ways to minimize negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources. These and recommendations for cancer care during active phases of the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Because of the prevalence of breast cancer in the United States, it is the second most common cancer associated with brain metastases in the United States. As patients with advanced breast cancer live longer, the incidence of brain metastases appears to be increasing. (See 'Introduction' above.)

- **Local control of intracranial disease** – For patients who have progressed on systemic therapies, particularly if they are neurologically symptomatic, local therapies, rather than systemic therapy alone, is the mainstay for CNS treatment. Exceptions may be made for very select patients with HER2-positive disease, with appropriate counseling. (See 'Choosing between options' above.)

  The choice between surgery, whole-brain radiation therapy, and stereotactic radiosurgery as local treatment, as well as supporting data, are discussed in detail elsewhere. (See "Overview of the treatment of brain metastases", section on 'Recurrent disease' and 'HER2-positive disease' above.)

- **Systemic therapy** – For patients with responding extracranial disease, their current line of systemic therapy may be continued after local treatment of brain metastases. **However,** for those with **progressive extracranial disease,** next-line therapy is appropriate.

- **HER2-negative disease** – For patients with HER2-negative disease, next-line therapy is chosen based on multiple factors including prior therapies, hormone receptor status, and other molecular features of the tumor. (See "ER/PR negative, HER2-negative (triple-negative) breast cancer", section on 'Metastatic disease' and "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

  - Although few of the commonly used chemotherapy agents for breast cancer penetrate the intact blood-brain barrier to a significant degree, many of the same agents (eg, capecitabine, platinums, doxorubicin) have been described to have activity against central nervous system (CNS) metastases, likely as a result of increased vessel permeability associated with tumor vasculature. (See 'Single-agent chemotherapy for most patients' above.)

- **HER2-positive disease** – For patients with HER2-positive disease, a number of agents have shown intracranial activity. Our approach to systemic therapy is as follows:

  - **Treated brain metastases** – For patients with treated brain metastases and extracranial progression, we suggest either T-DXd or tucatinib-capecitabine-trastuzumab rather than other systemic agents (**Grade 2C**). However, T-DM1 is an acceptable option, particularly for those who have experienced progression on these regimens. For those with treated brain metastases and stable or responding extracranial disease, a change in systemic therapy is not warranted, unless due to toxicity.

  - **Active brain metastases** – For patients with active brain metastases, we suggest initial treatment with local therapies (**Grade 2C**). However, systemic therapy alone is an alternative option for a select subset of patients with asymptomatic disease and a limited disease burden. In such patients, we suggest tucatinib, capecitabine, and trastuzumab, rather than other systemic therapies (**Grade 2C**). T-DXd is an acceptable alternative or later line option, although data are limited in those with active brain metastases. (See 'Choosing between options' above.)

- **Prognosis** – Retrospective analyses suggest that the prognosis of brain metastases in patients with breast cancer is improving, and this appears to be primarily a result of advances in systemic therapy, which have led to better control of disease outside the CNS. (See 'Prognosis' above.)

- **Leptomeningeal disease** – The treatment of leptomeningeal metastases, including RT, intrathecal, and systemic treatments, is covered separately. (See "Treatment of leptomeningeal disease from solid tumors".)

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REFERENCES

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004; 22:2865.
2. Kuksis M, Gao Y, Tran W, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro Oncol 2021; 23:894.
3. Arvold ND, Oh KS, Niemierko A, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. Breast Cancer Res Treat 2012; 136:153.
4. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer 1983; 52:2349.
5. Yerushalmi R, Woods R, Kennecke H, et al. Patterns of relapse in breast cancer: changes over time. Breast Cancer Res Treat 2010; 120:753.
6. Park YH, Park MJ, Ji SH, et al. Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. Br J Cancer 2009; 100:894.
7. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97:2972.
8. Gori S, Rimondini S, De Angelis V, et al. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. Oncologist 2007; 12:766.
9. Kirsch DG, Ledezma CJ, Mathews CS, et al. Survival after brain metastases from breast cancer in the trastuzumab era. J Clin Oncol 2005; 23:2114.
10. Duchnowska R, Szczylik C. Central nervous system metastases in breast cancer patients administered trastuzumab. Cancer Treat Rev 2005; 31:312.
11. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. Clin Cancer Res 2007; 13:1648.
12. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011; 17:4834.

13. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 2004; 91:639.
14. Stemmler HJ, Heinemann V. Central nervous system metastases in HER-2-overexpressing metastatic breast cancer: a treatment challenge. Oncologist 2008; 13:739.
15. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010; 28:3271.
16. Dawood S, Lei X, Litton JK, et al. Incidence of brain metastases as a first site of recurrence among women with triple receptor-negative breast cancer. Cancer 2012; 118:4652.
17. Lin NU, Claus E, Sohl J, et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008; 113:2638.
18. Pestalozzi BC, Zahrieh D, Price KN, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol 2006; 17:935.
19. Yin W, Jiang Y, Shen Z, et al. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. PLoS One 2011; 6:e21030.
20. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 2013; 14:244.
21. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380:617.
22. Albiges L, André F, Balleyguier C, et al. Spectrum of breast cancer metastasis in BRCA1 mutation carriers: highly increased incidence of brain metastases. Ann Oncol 2005; 16:1846.
23. Song Y, Barry WT, Seah DS, et al. Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers. Cancer 2020; 126:271.
24. Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: identification of a high-risk group. Clin Oncol (R Coll Radiol) 2004; 16:345.
25. Slimane K, Andre F, Delaloge S, et al. Risk factors for brain relapse in patients with metastatic breast cancer. Ann Oncol 2004; 15:1640.
26. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004; 22:3608.
27. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. Cancer 1992; 69:972.

28. Rivera E, Meyers C, Groves M, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. Cancer 2006; 107:1348.
29. Franciosi V, Cocconi G, Michiara M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. Cancer 1999; 85:1599.
30. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. Cancer 1986; 58:832.
31. Friedman HS, Evans B, Reardon DA. Phase II trial of temozolomide for patients with progressive brain metastases (abstract #408). Proc Am Soc Clin Oncol 2003; 22:102.
32. Siena S, Landonio G, Beaietta E. Multicenter phase II study of temozolomide therapy for brain metastasis in patients with malignant melanoma, breast cancer, and non-small cell lung cancer (abstract #407). Proc Am Soc Clin Oncol 2003; 22:407.
33. Trudeau ME, Crump M, Charpentier D, et al. Temozolomide in metastatic breast cancer (MBC): a phase II trial of the National Cancer Institute of Canada - Clinical Trials Group (NCIC-CTG). Ann Oncol 2006; 17:952.
34. Christodoulou C, Bafaloukos D, Linardou H, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II study. J Neurooncol 2005; 71:61.
35. Stewart DJ, Dahrouge S. Response of brain metastases from breast cancer to megestrol acetate: a case report. J Neurooncol 1995; 24:299.
36. Salvati M, Cervoni L, Innocenzi G, Bardella L. Prolonged stabilization of multiple and single brain metastases from breast cancer with tamoxifen. Report of three cases. Tumori 1993; 79:359.
37. Madhup R, Kirti S, Bhatt ML, et al. Letrozole for brain and scalp metastases from breast cancer--a case report. Breast 2006; 15:440.
38. O'Sullivan CC, Davarpanah NN, Abraham J, Bates SE. Current challenges in the management of breast cancer brain metastases. Semin Oncol 2017; 44:85.
39. Tolaney SM, Sahebjam S, Le Rhun E, et al. A Phase II Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor-Positive Breast Cancer. Clin Cancer Res 2020; 26:5310.
40. Brastianos PK, Kim AE, Wang N, et al. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. Nat Cancer 2021; 2:498.

41. Giordano SH, Franzoi MAB, Temin S, et al. Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Guideline Update. J Clin Oncol 2022; 40:2612.
42. Lin NU, Borges V, Anders C, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol 2020; 38:2610.
43. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013; 14:64.
44. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med 2020; 382:597.
45. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol 2023; 9:197.
46. Murthy RK, O'Brien BJ, Berry DA, et al. Safety and efficacy of a tucatinib-trastuzumab-capecitabine regimen for treatment of leptomeningeal metastasis (LM) in HER2-positive breast cancer: Results from TBCRC049, a phase 2 non-randomized study. Cancer Res 2021; 82S: SABCS 2021.
47. Tucatinib tablets. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213411s004lbl.pdf (Accessed on January 24, 2023).
48. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382:610.
49. ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. US Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s017s020lbl.pdf (Accessed on May 12, 2022).
50. Fam-trastuzumab deruxtecan-nxki injection. United States Prescribing Information. US National Library of Medicine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf (Accessed on December 31, 2019).
51. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022; 386:1143.
52. Modi S, Park H, Murthy RK, et al. Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib

Study. J Clin Oncol 2020; 38:1887.

53. Bartsch R, Berghoff AS, Furtner J, Marhold M et. Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain metastases: Primary outcome analysis from the TUXEDO-1 trial. Ann Oncol 2022; 33S3 S194-S223.
54. Pérez-García JM, Vaz Batista M, Cortez P, et al. Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial. Neuro Oncol 2023; 25:157.
55. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol 2015; 26:113.
56. Bartsch R, Berghoff AS, Preusser M. Breast cancer brain metastases responding to primary systemic therapy with T-DM1. J Neurooncol 2014; 116:205.
57. Jacot W, Pons E, Frenel JS, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. Breast Cancer Res Treat 2016; 157:307.
58. Fabi A, Alesini D, Valle E, et al. T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer. Breast 2018; 41:137.
59. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Ann Oncol 2020; 31:1350.
60. Carlson JA, Nooruddin Z, Rusthoven C, et al. Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema. Neuro Oncol 2014; 16:1006.
61. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2008; 26:1993.
62. Lin NU, Diéras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 2009; 15:1452.
63. Petrelli F, Ghidini M, Lonati V, et al. The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: A systematic review and pooled analysis. Eur J Cancer 2017; 84:141.

64. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. J Clin Oncol 2019; 37:1081.
65. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. Cancer 1979; 44:1913.
66. Mahmoud-Ahmed AS, Suh JH, Lee SY, et al. Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. Int J Radiat Oncol Biol Phys 2002; 54:810.
67. Dawood S, Broglio K, Esteva FJ, et al. Defining prognosis for women with breast cancer and CNS metastases by HER2 status. Ann Oncol 2008; 19:1242.
68. Melisko ME, Moore DH, Sneed PK, et al. Brain metastases in breast cancer: clinical and pathologic characteristics associated with improvements in survival. J Neurooncol 2008; 88:359.
69. Tham YL, Sexton K, Kramer R, et al. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer 2006; 107:696.
70. Stemmler HJ, Kahlert S, Siekiera W, et al. Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer. Breast 2006; 15:219.
71. Eichler AF, Kuter I, Ryan P, et al. Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. Cancer 2008; 112:2359.
72. Dawood S, Broglio K, Esteva FJ, et al. Survival among women with triple receptor-negative breast cancer and brain metastases. Ann Oncol 2009; 20:621.
73. Nam BH, Kim SY, Han HS, et al. Breast cancer subtypes and survival in patients with brain metastases. Breast Cancer Res 2008; 10:R20.
74. Le Scodan R, Massard C, Mouret-Fourme E, et al. Brain metastases from breast carcinoma: validation of the radiation therapy oncology group recursive partitioning analysis classification and proposition of a new prognostic score. Int J Radiat Oncol Biol Phys 2007; 69:839.
75. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012; 30:419.
76. Sperduto PW, Mesko S, Li J, et al. Survival in Patients With Brain Metastases: Summary Report on the Updated Diagnosis-Specific Graded Prognostic Assessment and Definition of the Eligibility Quotient. J Clin Oncol 2020; 38:3773.

77. Lee S, Ahn HK, Park YH, et al. Leptomeningeal metastases from breast cancer: intrinsic subtypes may affect unique clinical manifestations. Breast Cancer Res Treat 2011; 129:809.

Topic 775 Version 43.0

GRAPHICS

Karnofsky Performance Status scale

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Graphic 58785 Version 7.0

Selected studies of systemic therapy for brain metastases from breast cancer

Study	Regimen	Patient population	Total number of patients	Number of patients with breast cancer and brain metastases	Objective response rate (percent)
Rosner et al[1]	Various (CFP, CFPMV, MVP, CA)	Breast cancer	100	100	50
Boogerd et al[2]	Oral CMF (n=20), or CAF (n=2)	Breast cancer	22	22	54
Friedman et al[3]	Temozolomide 150 mg/m^2 days 1-7, 15-21, every 28 days	Solid tumors	52	15	6
Siena et al[4]	Temozolomide 150 mg/m^2 days 1-7, 15-21, every 28 days	Solid tumors	62	21	19 (in subset of patients with breast cancer)
Trudeau et al[5]	Temozolomide 150 mg/m^2 days 1-7, 15-21, every 28 days	Breast cancer	19	5	0
Rivera et al[6]	Escalating doses of capecitabine and temozolomide	Breast cancer	24	24	18
Franciosi et al[7]	Cisplatin 100 mg/m^2 day 1 Etoposide 100 mg/m^2 days 1, 3, and 5, every 21 days	Solid tumors	107	56	38 (in subset of patients with breast cancer)

Christodoulou et al[8]	Temozolomide 150 mg/m^2 days 1-5 Cisplatin 75 mg/m^2 day 1, every 21 days	Solid tumors	32	15	40 (in subset of patients with breast cancer)
Lin et al[9]	Lapatinib	HER2+ breast cancer	39	39	2.6
Lin et al[10]	Lapatinib	HER2+ breast cancer	237	237	6

TTP: time to tumor progression; PFS: progress-free survival; NR: not reported; CFP: cyclophosphamide, fluorouracil, and prednisone; CFPMV: cyclophosphamide, fluorouracil, and prednisone plus methotrexate and vincristine; MVP: methotrexate, vincristine, and prednisone; CA: cyclophosphamide and adriamycin; CMF: cyclophosphamide, methotrexate, and fluorouracil; CAF: cyclophosphamide, doxorubicin, and fluorouracil; HER2+: human epidermal growth factor receptor 2.

1. Rosner D, Nemoto T, Lane WW. Chemotherapy induces regression of brain metastases in breast carcinoma. Cancer 1986; 58:832.

2. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. Cancer 1992; 69:972.

3. Friedman HS, Evans, B and Reardon, DA. Phase II trial of temozolomide for patients with progressive brain metastases (abstract #408). Proc Am Soc Clin Oncol 2003; 22:102.

4. Siena S, Landonio G, Beaietta E. Multicenter phase II study of temozolomide therapy for brain metastasis in patients with malignant melanoma, breast cancer, and non-small cell lung cancer (abstract #407). Proc Am Soc Clin Oncol 2003; 22:407.

5. Trudeau ME, Crump M, Charpentier D, et al. Temozolomide in metastatic breast cancer (MBC): a phase II trial of the National Cancer Institute of Canada - Clinical Trials Group (NCIC-CTG). Ann Oncol 2006; 17:952.

6. Rivera E, Meyers C, Groves M, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. Cancer 2006; 107:1348.

7. Franciosi V, Cocconi G, Michiara M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. Cancer 1999; 85:1599.

8. Christodoulou C, Bafaloukos D, Linardou H, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II study. J Neurooncol 2005; 71:61.

9. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2008; 26:1993.

10. Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 2009; 15:1452.

Graphic 81191 Version 2.0

Prognosis of patients with brain metastases from HER2-positive breast cancer

Study	Time period	Number of patients	Median survival after CNS recurrence
Tham, et al[1]	1970-1999	21	~3 months
Bendell, et al[2]	1998-2000	42	13 months
Gori, et al[3]	1999-2005	43	23 months
Stemmler, et al[4]	2000-2004	42	13 months
Eichler, et al[5]	2001-2005	30	17 months
Melisko, et al[6]	1997-2007	35	23 months
Brufsky, et al [7]	2003-2009	377	20.3 months

Trastuzumab approved by the United States Food and Drug Administration (FDA) for treatment of HER2-positive, metastatic breast cancer in 1998.

CNS: central nervous system; HER2: human epidermal growth factor receptor 2.

References:

1. *Tham YL, Sexton K, Kramer R, et al. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer 2006; 107:696.*
2. *Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97:2972.*
3. *Gori S, Rimondini S, De Angelis V, et al. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. Oncologist 2007; 12:766.*
4. *Stemmler HJ, Kahlert S, Siekiera W, et al. Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer. Breast 2006; 15:219.*
5. *Eichler AF, Kuter I, Ryan P, et al. Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. Cancer 2008; 112:2359.*
6. *Melisko ME, Moore DH, Sneed PK, et al. Brain metastases in breast cancer: clinical and pathologic characteristics associated with improvements in survival. J Neurooncol 2008; 88:359.*
7. *Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011; 17:4834.*

Graphic 80803 Version 3.0

Prognosis of patients with brain metastases from triple-negative breast cancer

Study	Time period	Number of patients	Median survival after CNS recurrence
Dawood et al[1]	1980-2006	42	2.9 months
Lin et al[2]	2000-2006	53	4.9 months
Eichler et al[3]	2001-2005	21	4.0 months
Nam et al[4]	2001-2006	47	3.4 months

CNS: central nervous system.

1. Dawood S, Broglio K, Esteva FJ, et al. Survival among women with triple receptor-negative breast cancer and brain metastases. Ann Oncol 2009; 20:621.

2. Lin NU, Claus E, Sohl J, et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008; 113:2638.

3. Eichler AF, Kuter I, Ryan P, et al. Survival in patients with brain metastases from breast cancer: the importance of HER-2 status. Cancer 2008; 112:2359.

4. Nam BH, Kim SY, Han HS, et al. Breast cancer subtypes and survival in patients with brain metastases. Breast Cancer Res 2008; 10:R20.

Graphic 58556 Version 2.0

Prognostic groups for outcome after palliative treatment of brain metastases by recursive partitioning analysis

Class	Prognostic factors	Median survival (months)
I	KPS ≥70 percent	7.1
	Age <65 years	
	Controlled primary site	
	No extracranial metastases	
III	KPS <70	2.3
II	All others	4.2

KPS: Karnofsky performance status.

Gaspar L, et al. Int J Radiat Oncol Biol Phys 1997; 37:745.

Graphic 77561 Version 3.0

Worksheet for calculation of the breast cancer-specific GPA

Prognostic factor	GPA					Patient score
	0	0.5	1.0	1.5	2.0	
KPS	≤60	70-80	90-100			
Age, years	≥60	<60				
Number of BM	≥2	1				
ECM	Present	Absent				
Subtype	Basal	Luminal A		HER2 or luminal B		
						Sum = median survival by GPA: 0-1 = 6 months; 1.5-2.0 = 13 months; 2.5-3.0 = 24 months; 3.5-4.0 = 36 months

Breast cancer subtypes: basal = triple negative (ER/PR/HER2–); luminal A (ER/PR+, HER2–); luminal B (triple positive, ER/PR/HER2+); HER2 (HER2+, ER/PR–).

GPA: graded prognostic assessment; KPS: Karnofsky Performance Status; BM: brain metastases; ECM: extracranial metastases; HER2: human epidermal growth factor receptor 2.

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