Clinical Discussion and Review of the Management of Brain Metastases

Priscilla K. Brastianos, MD; William T. Curry, MD; and Kevin S. Oh, MD

Abstract
Brain metastases are common in patients with cancer and are associated with a poor prognosis. Optimal treatment requires an integrative multidisciplinary approach, and therapeutic options may include stereotactic radiosurgery, whole-brain radiation therapy, surgical resection, chemotherapy, and targeted agents. The goals of therapy are to prolong survival, preserve neurologic function, and palliate symptoms. This article outlines the various therapeutic modalities, factors that guide treatment decisions, and medical management of frequently encountered complications of brain metastases. (JNCCN 2013;11:1153–1164)

Background
An estimated 8% to 10% of patients with cancer will develop symptomatic brain metastases. The geographic distribution of metastases reflects the volume of brain parenchyma and vascular flow: approximately 80% within cerebral hemispheres, 15% within cerebellar hemispheres, and 5% within the brainstem. The overall survival of patients with brain metastases is historically poor in the range of 2 to 4 months, but this may be improving with more effective systemic therapies. The RTOG subjected a dataset of 1200 patients from 3 consecutive trials to a recursive partitioning analyses (RPA) and concluded that Karnofsky performance status (KPS) of 70 or greater, age younger than 65 years, controlled primary tumor, and lack of extracranial metastases were favorable prognostic factors that could classify patients into 3 groups with median survival estimates ranging from 2.3 to 7.1 months. More recently, Sperduto et al developed the Graded Prognostic Assessment (GPA), which broadened the RTOG dataset to 1960 patients and included the number of brain metastases as an index. The GPA categorized patients into 4 groups with median survivals ranging from 2.6 to 11.0 months. This was felt to be equally prognostic compared with the RPA, but more objective and user friendly. Since then, diagnosis-specific GPAs have been developed, including the Breast-GPA, which also accounts for genetic subtype in addition to KPS and age.

Radiation Therapy
Whole-Brain Radiation Therapy
For many decades, whole-brain radiation therapy (WBRT) has been an important component in the management of brain metastases. The goal of WBRT is to irradiate all brain parenchyma and include both grossly visible and occult micrometastatic disease. The benefits of WBRT include its simplicity, speed, cost-effectiveness, and ability to maximize total intracranial control of disease. WBRT is typically delivered using opposed lateral beams via a linear accelerator. Custom cerrobend blocks or multileaf collimators are used to block the orbits, nasal cavity, and oral cavity. Because of the large volume treated, small fraction sizes (eg, 2–3 Gy/d) are required to minimize acute and late sequelae. Common fractionation schedules include 2.5 Gy given in 14 to 15 fractions, 3 Gy given in 10 fractions, and 4 Gy given in 5 fractions. However, the RTOG conducted randomized trials comparing the effectiveness of multiple fractionation schedules and found no differences in survival, neurologic improvement, or palliative index, although poor perfor-
formance was seen when radiation was delivered in ultra-hypofractionated regimens (10 Gy in 1 fraction or 6 Gy in 2 fractions).8,9

WBRT is associated with acute side effects and late neurocognitive deficits, which has led to a trend toward avoiding WBRT when possible. Common acute side effects include fatigue, skin irritation, and hair loss. Chang et al10 conducted a randomized trial of stereotactic radiosurgery (SRS) with or without WBRT in patients with 1 to 3 brain metastases in which the primary end point was neurocognitive function measured as a 5-point drop from baseline at 4 months in the Hopkins Verbal Learning Test-Revised (HVLT-R) total recall. After 58 patients were enrolled, the trial was terminated early because of the high likelihood of significant deterioration in the WBRT arm (52% vs 24%). Similar trends were measured in HVLT-R delayed recall (22% vs 6%) and delayed recognition (11% vs 0%). However, the association between WBRT and neurocognitive decline must be made cautiously. Most patients with brain metastases have measurable impairments at baseline.11,12 Moreover, prospective data suggest that tumor control is a critically important factor in neurocognitive function,13 and that tumor response after WBRT is correlated with preservation or improvement in neurocognitive function in long-term survivors.13,14 Therefore, in select patients, WBRT may be viewed as an important strategy to protect neurocognitive function through maximizing intracranial tumor control.

Stereotactic Radiosurgery

SRS is the delivery of a high dose of radiation in a single treatment to a small target using a fixed, accurate, and reproducible system (Figures 1 and 2). Several technologies are available for SRS, including linear-accelerated based systems, proton-based systems, Gamma Knife (Elekta, Stockholm, Sweden), and CyberKnife (Accuray, Sunnyvale, CA). Doses used for SRS range from 15 to 24 Gy depending on size and location of the metastases. RTOG 90-05 was a dose-escalation study of SRS that concluded maximum tolerated doses (MTDs) of 24, 18, and 15 Gy for tumors 2 cm or less, 2.1 to 3.0 cm, and 3.1 to 4.0 cm, respectively, in patients who were previously irradiated. Dose-escalation in the cohort with tumors 2 cm or less was terminated prematurely because of investigators’ reluctance to further escalate. Patients treated at or below the MTDs in RTOG 90-05 developed grade 3 to 5 central nervous system toxicity at crude rates of 10%, 17%, and 12%, respectively.15 Therefore, many centers use lower doses or hypofractionate to minimize the risk of symptomatic radionecrosis. Toxicities of SRS are location-specific and often manifest as worsening of preexisting symptoms. Prospective data suggest that SRS alone is associated with a 10% to 15% risk of symptomatic acute neurologic toxicity often associated with either radionecrosis or leukoencephalopathy.16 Seizure is a risk for cortically based metastasis, and prospective data suggest an overall risk of 6%.16 Based on prospectively gathered data from EORTC 22952-26001, the local control rate at 2 years after SRS is 70% when used alone and 80% when used in combination with WBRT.17 Similar success has been noted in the salvage setting after WBRT.18,19

Roles of Surgical Resection, SRS, and WBRT

In the setting of a single brain metastasis, including surgical resection or SRS in the treatment of gross disease has been associated with a survival benefit in randomized trials. Patchell et al19 published the results of a landmark trial in which 48 patients with a single brain metastasis were randomized to receive WBRT with or without an upfront attempt at gross total resection. The inclusion of surgical resection was associated with benefits in overall survival (median duration, 40 vs 15 weeks; \( P < .01 \)) and length of functional independence (median duration, 38 vs 8 weeks; \( P < .005 \)). A similar trial found no survival benefit with the use of surgical resection, but included several patients with poor performance status or extensive extracranial disease.21

Similar to findings reported in the neurosurgical literature, the inclusion of SRS in the treatment of patients with a low burden of disease has been associated with benefits in functional preservation and perhaps survival. RTOG 95-08 was a multicenter randomized trial of 333 patients with 1 to 3 newly diagnosed brain metastases who received WBRT with or without an SRS boost.22 The addition of an SRS boost was associated with a survival benefit in patients with a single brain metastasis (median duration, 6.5 vs 4.9 months; \( P < .04 \)) on univariate analysis. On multivariate analysis, survival benefits were associated only with RPA class I and favorable histology. Functional independence was better preserved in patients who received an SRS boost. A
single-institution study from the University of Pittsburgh randomized 27 patients with 2 to 4 brain metastases of 2.5 cm or less to receive WBRT with or without SRS. Accrual was terminated early because a significant improvement was seen in the 1-year local failure rate with the inclusion of SRS (100% vs 8% failure; \( P < .002 \)). No significant difference was seen in overall survival.²³

In summary, these data suggest that an SRS boost after WBRT may be considered for select patients with 1 to 4 brain metastases to improve local control and functional preservation, and that SRS may confer a survival benefit in those with a single brain metastasis. Several randomized trials have evaluated the role of WBRT when added to either surgery or SRS for 1 to 4 brain metastases, and all have shown that WBRT improves local and total intracranial control, but not overall survival.¹⁶,¹⁷,²⁴ Notably, no randomized trials address the roles of WBRT and SRS in patients with greater than 4 brain metastases. These conclusions are consistent with those of the evidence-based review²⁵ and guidelines²⁶ published by the American Society for Radiation Oncology (ASTRO).

A recent trend after surgical resection is the delivery of postoperative SRS to the surgical cavity. By first principles, this strategy would maximize local control while avoiding WBRT and its late neurocognitive effects. Retrospective reports suggest local control rates of 80% to 90% and avoidance of WBRT in most cases that are appropriately selected and planned.²⁷,²⁸ NCCTG-N107C is a currently open randomized trial comparing SRS to the cavity versus WBRT in patients with 1 to 4 brain metastases after craniotomy.

No completed randomized trial has directly compared surgical resection and SRS in their ability to achieve local control. Although Roos et al²⁹ published the results of a randomized noninferiority trial of WBRT plus radiosurgery versus surgery, the trial was closed early because of poor accrual (only 21 evaluable patients). Several case-controlled ret-
rospective studies have suggested that SRS offers superior local control. The highest quality prospective data was generated by EORTC 22952-26001, in which 359 patients with 1 to 3 brain metastases underwent surgery or SRS and then were randomized to receive WBRT or observation. At 2 years, the local failure rates after SRS or surgery alone were 31% and 59%, respectively. The addition of WBRT reduced local failure rates to 19% and 27%, respectively. All of these data must be viewed cautiously because of a strong selection bias wherein bulky symptomatic metastases were surgically resected.

**Neurosurgery**

In the setting of multiple brain metastases, surgical resection can be used as a means of diagnosis, symptomatic palliation and corticosteroid reduction, local control of selected lesions, and salvage therapy in patients with stable systemic disease.

**Surgery for Diagnosis:** Surgical biopsy or resection may be appropriate in several contexts to establish a pathologic diagnosis. Although stereotactic biopsy may render a diagnosis, resection via craniotomy provides more tissue for more extensive histologic and molecular characterization. First, tissue may be required at diagnosis of either disease in the setting of an unknown primary or systemic disease that is otherwise poorly accessible. Second, confirmation may be required in the recurrent setting if it is the first instance of metastatic disease. Third, resection may be needed after SRS to differentiate true progression from radionecrosis, because no imaging technique or biomarker is more sensitive or specific than acquisition of tissue.

**Surgery as Palliation:** Multiple scenarios exist in which resection of a brain metastasis reduces mass effect, either before or after other therapies have been delivered. The resection of a large (≥3 cm) tumor in the posterior fossa will stave off symptoms of herniation and/or hydrocephalus, which might be exacerbated by radiation-associated inflammation. Hemorrhagic or large cystic tumors, regardless of location, may be symptomatic or challenging to target with SRS, and resection of one or more of these lesions can yield improvement of symptoms and achieve local control. Likewise, the impact of progressive radionecrosis with symptomatic mass effect and corticosteroid dependency can be successfully palliated with craniotomy for resection.

**Surgery for Local Control and Recurrence:** Randomized data support a survival benefit with metastasectomy of a single brain metastasis. However, no class I evidence exists regarding surgery in patients with 2 or more lesions. The historical mainstay of treatment for patients with multiple intracranial metastases has been WBRT. In the context of both single or multiple brain metastases, the use of local therapies such as surgery or SRS has been advocated as an approach to delay WBRT, thereby improving quality of life, particularly as more effective systemic therapies allow longer survival and uncover the late neurocognitive effects of WBRT.

The alternative therapeutic approach is to treat multiple tumors with local therapies (either SRS or resection) as deemed appropriate on a per-lesion basis. Most retrospective analyses of patients undergoing surgery for 2 or more metastases conclude that relatively long-term survival is associated with KPS and RPA status, with patients in class I or II benefitting most. The strongest conclusion that can be made is that patients presenting with multiple brain metastases may be candidates for resection of one or more foci if they are large and symptomatic as a strategy to avoid WBRT, and if a reasonable chance exists to control systemic disease. Because the local failure rate after resection alone is as high as 60%, postoperative therapy involving SRS to the cavity, WBRT, or emerging systemic agents is recommended. Lastly, patients with recurrent brain metastases may be candidates for surgery. Resection may be the only option for a given lesion that is progressing after treatment with SRS and WBRT. This scenario may become especially salient, because novel targeted therapies may effectively control systemic disease but may not impact the intracranial compartment. Interstitial brachytherapy, with implantation of radioactive seeds in the resection cavity, may also be considered in these instances of salvage.

**Systemic Therapy for Brain Metastases**

**General Concepts**

Traditionally, the major role of chemotherapy in managing brain metastases is in the recurrent setting for patients in whom other modalities have failed, or in the primary treatment of chemosensitive tumors, such as germ cell tumors. Unfortunately, a relative paucity of randomized studies have explored the role of chemotherapy in these patients, and most clinical trials in the United States exclude patients with brain...
metastases. Many of the trials in brain metastases have heterogeneous patient populations and variable endpoints, and are underpowered. Furthermore, systemic therapy for brain metastases has several challenges. Patients with brain metastases are often heavily pretreated and have a decreased response to second- and third-line agents. Although the blood–brain barrier (BBB) limits the delivery of large and hydrophilic molecules into normal brain, significant controversy surrounds the degree to which the BBB prevents drug delivery in brain metastases, although studies have shown that drugs likely do reach brain metastases in the setting of BBB breakdown. Intracerebral tumor concentrations of several known chemotherapeutics, such as doxorubicin and vinblastine, are similar to extracerebral tumor concentrations, although variable delivery likely occurs within the tumor. Also, discussed in a later section, studies have shown equivalent extracranial and intracranial clinical responses of chemotherapies not traditionally thought to cross the BBB, especially in the upfront setting. Therefore, the choice of chemotherapy should be more heavily influenced by its activity in the primary tumor than its potential to cross the BBB.

Upfront chemotherapy in newly diagnosed brain metastases has been explored in a limited number of studies. In a prospective trial of 48 patients with synchronous clinically silent brain metastases randomized to chemotherapy first versus WBRT first, response rates and survival outcomes were the same (Table 1). These results must be interpreted cautiously, because this was a small study and was limited to clinically asymptomatic patients. Robinet et al reported that response rates and survival rates in patients receiving cisplatin and vinorelbine along with delayed WBRT were similar when compared with those receiving early WBRT. Several other single-arm prospective studies have shown promising results for systemic regimens in newly diagnosed brain metastases (Table 2). In the absence of more definitive randomized trials, the data are too sparse to offer definitive conclusions. The role of primary upfront chemotherapy must be further evaluated. Radiosurgery and/or WBRT in the upfront setting based on the number of brain metastases and clinical status remains standard of care.

Limited data exist for the addition of chemotherapy to WBRT in patients with newly diagnosed brain metastases. Concurrent chemotherapy can improve response rates compared with WBRT alone (Table 1), but no survival benefit has been shown. Likewise, multiple studies investigating the use of radiation-sensitizing agents during WBRT have failed to demonstrate a benefit. Given the potential to increase acute and late sequelae of WBRT, the use of concurrent nontargeted chemotherapy is discouraged.

**Non–Small Cell Lung Cancer**

Platinum-based regimens have activity in brain metastases from non–small cell lung cancer (NSCLC), particularly in the upfront setting. Cisplatin as a single agent has a response rate of 30%, with response rates ranging from 28% to 45% when combined with etoposide, teniposide, fotemustine, paclitaxel, and vinorelbine/gemcitabine (carboplatin in lieu of cisplatin). In the recurrent heavily pretreated setting, temozolomide has modest activity, both as a single agent and when combined with vinorelbine. Pemetrexed, a multitarget antifolate, showed a response rate of 38% in recurrent brain metastases from NSCLC. Barlesi et al reported a response rate of 42% and median survival of 7.4 months in a phase II study of pemetrexed and cisplatin in the upfront setting before radiation. Intracranial and extracranial responses were similar.

Targeted therapies are promising in brain metastases from NSCLC. Several recent prospective trials have shown that the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have antitumor activity both in newly diagnosed and recurrent brain metastases from NSCLC (Table 2). A recent phase II trial of erlotinib given concurrently with WBRT showed an overall response rate of 86% and a well-tolerated toxicity profile. Responses, as expected, correlate with the presence of activating mutations in EGFR. However, in a phase III trial in patients with 1 to 3 brain metastases, the addition of erlotinib or temozolomide to SRS and WBRT in combination did not show a survival benefit and was associated with increased toxicities. Vascular endothelial growth factor inhibitors such as bevacizumab have been shown to be safe and may have activity in nonhemorrhagic brain metastases from NSCLC.

**Breast Cancer**

Traditional cytotoxic regimens have activity in brain metastases from breast cancer. Rosner et al reported response rates of 52% in patients treated with cyclophosphamide (C), fluorouracil (F), and prednisone (P); 54% in those treated with CFP-methotrexate
(M) and vincristine (V); 43% in those treated with MVP; and 17% in those treated with cyclophosphamide and doxorubicin (A). Notably, the intracranial response rates were equivalent to the extracranial rates. Oral CMF or CAF in a small study of 22 patients produced responses in 59% of patients. Two phase II studies of patients with brain metastases from breast cancer treated with the combination of cisplatin and etoposide showed response rates ranging from 38% to 55%. Topotecan also has activity in the brain. Notably, however, these trials enrolled patients with newly diagnosed brain metastasis, and response rates in the recurrent population are likely much lower.

Temozolomide has minimal activity as a single agent in recurrent brain metastases from breast cancer, with modest responses observed when combined

Table 1
Select Randomized Studies in Newly Diagnosed Brain Metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Histology (n)</th>
<th>Median Overall Survival</th>
<th>Cerebral Response Rate</th>
<th>Medial TTP/ Medial PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinet et al</td>
<td>Cisplatin + vinorelbine + delayed WBRT (Arm A; n=86) Cisplatin + vinorelbine + early WBRT (Arm B; n=85)</td>
<td>Squamous cell (44); adenocarcinoma (95); other NSCLC (32)</td>
<td>24 wk (Arm A) 21 wk (Arm B)</td>
<td>27.0% (Arm A) 33.0% (Arm B)</td>
<td>P=NS  P=NS</td>
</tr>
<tr>
<td>Guerrieri et al</td>
<td>WBRT (Arm A; n=21) WBRT + carboplatin (Arm B; n=21)</td>
<td>Squamous cell (11); adenocarcinoma (16); large cell (11); other (4)</td>
<td>4.4 mo (Arm A) 3.7 mo (Arm B)</td>
<td>10.0% (Arm A) 29.0% (Arm B)</td>
<td>P=NS  P=NS</td>
</tr>
<tr>
<td>Ushio et al</td>
<td>WBRT (Arm A; n=25) WBRT + CNU (Arm B; n=34) WBRT + CNU + tegafur (Arm C; n=29)</td>
<td>Adenocarcinoma (40); squamous cell (17); small cell (10); large cell (9); others (12)</td>
<td>27.0 wk (Arm A) 30.5 wk (Arm B) 29.0 wk (Arm C)</td>
<td>36.0% (Arm A) 69.0% (Arm B) 74.0% (Arm C)</td>
<td>P=NS  P=NS  P=NS</td>
</tr>
<tr>
<td>Postmus et al</td>
<td>Teniposide (Arm A; n=60) Teniposide + WBRT (Arm B; n=60)</td>
<td>Small cell (120)</td>
<td>3.2 mo (Arm A) 3.5 mo (Arm B)</td>
<td>22.0% (Arm A) 57.0% (Arm B)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Chemotherapy followed by WBRT (Arm A; n=25) WBRT followed by chemotherapy (Arm B; n=23)</td>
<td>Adenocarcinoma (40); squamous cell carcinoma (4); large cell carcinoma (1); NSCLC NOS (3)</td>
<td>9.1 mo (Arm A) 9.9 mo (Arm B)</td>
<td>28.0% (Arm A) 39.1% (Arm B)</td>
<td>P=NS  P=NS</td>
</tr>
<tr>
<td>Sperduto et al</td>
<td>WBRT + SRS (Arm A; n=44) WBRT + SRS + TMZ (Arm B; n=40) WBRT + SRS + ETN (Arm C; n=41)</td>
<td>NSCLC (125)</td>
<td>13.4 mo (Arm A) 6.3 mo (Arm B) 6.1 mo (Arm C)</td>
<td>NR</td>
<td>Median PFS: 8.1 mo (Arm A) 4.6 mo (Arm B) 4.8 mo (Arm C)</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mornex et al</td>
<td>Fotemustine (Arm A; n=39) Fotemustine + WBRT (Arm B; n=37)</td>
<td>Melanoma (76)</td>
<td>86 d (Arm A) 105 d (Arm B)</td>
<td>5.1% (Arm A) 8.1% (Arm B)</td>
<td>P=NS  P=NS</td>
</tr>
<tr>
<td><strong>All Histologies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antonadou et al</td>
<td>WBRT + TMZ (Arm A; n=25) WBRT (Arm B; n=23)</td>
<td>NSCLC (31); SCLC (9); breast (5); unknown (3)</td>
<td>8.6 mo (Arm A) 7.0 mo (Arm B)</td>
<td>96.0% (Arm A) 67.0% (Arm B)</td>
<td>P=0.017  P=0.017</td>
</tr>
<tr>
<td>Verger et al</td>
<td>WBRT (Arm A; n=41) WBRT + TMZ (Arm B; n=41)</td>
<td>Lung (42); breast (13); other (27)</td>
<td>3.1 mo (Arm A) 4.5 mo (Arm B)</td>
<td>At 90 days: 5.0% (Arm A) 15.0% (Arm B)</td>
<td>P=NS  P=NS</td>
</tr>
</tbody>
</table>

Abbreviations: CNU, chloroethylnitrosourea; ETN, erlotinib; NOS, not otherwise specified; NR, not reported; NS, nonsignificant; NSCLC, non–small cell lung cancer; PFS, progression-free survival; SCLC, small cell lung cancer; SRS, stereotactic radiosurgery; TMZ, temozolomide; TTP, time to progression; WBRT, whole-brain radiation therapy.
with cisplatin\textsuperscript{75} or capecitabine.\textsuperscript{76} Case reports have reported that capecitabine as a single agent may have efficacy in the upfront and recurrent settings,\textsuperscript{77–79} but this must be explored in larger studies. Similarly, a retrospective study showed efficacy of high-dose methotrexate in leptomeningeal or parenchymal metastases, which must be further investigated.\textsuperscript{80} The role of bevacizumab is also being explored. In a small case series of 4 patients with central nervous system metastases from breast cancer, all patients experienced a response to treatment with bevacizumab and paclitaxel.\textsuperscript{81} A study of carboplatin and bevacizumab is underway (ClinicalTrials.gov identifier: NCT01004172). Case reports and small series have

### Table 2 Prospective Trials of Targeted Agents in Brain Metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>New or Recurrent</th>
<th>Intervention</th>
<th>Histology (n)</th>
<th>Median Overall Survival</th>
<th>Cerebral Response Rate</th>
<th>mTTP/mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachelot et al\textsuperscript{86}</td>
<td>New</td>
<td>Lapatinib + capecitabine</td>
<td>HER2\textsuperscript{+} breast (45)</td>
<td>17.0 mo</td>
<td>66.0%</td>
<td>mTTP: 5.5 mo</td>
</tr>
<tr>
<td>Lin et al\textsuperscript{85}</td>
<td>Recurrent</td>
<td>Lapatinib</td>
<td>HER2\textsuperscript{+} breast (242)</td>
<td>6.4 mo</td>
<td>6.0%</td>
<td>mPFS: 2.4 mo</td>
</tr>
<tr>
<td>Wu et al\textsuperscript{87}</td>
<td>Recurrent</td>
<td>Gefitinib</td>
<td>Lung adenocarcinoma (40)</td>
<td>15.0 mo</td>
<td>38.0%</td>
<td>mPFS: 9.0 mo</td>
</tr>
<tr>
<td>Kim et al\textsuperscript{86}</td>
<td>New</td>
<td>Gefitinib or erlotinib</td>
<td>Lung adenocarcinoma (23)</td>
<td>18.8 mo</td>
<td>73.9%</td>
<td>mPFS: 7.1 mo</td>
</tr>
<tr>
<td>Ma et al\textsuperscript{115}</td>
<td>New</td>
<td>Gefitinib + WBRT</td>
<td>NSCLC (21): squamous cell (3); adenocarcinoma (18)</td>
<td>13.0 mo</td>
<td>81.0%</td>
<td>mPFS: 10.0 mo</td>
</tr>
<tr>
<td>Ceresoli et al\textsuperscript{116}</td>
<td>Recurrent</td>
<td>Gefitinib</td>
<td>NSCLC (41): adenocarcinoma (23); BAC (4); squamous cell (2); large cell (3); sarcomatoid (1); NOS (8)</td>
<td>5.0 mo</td>
<td>10.0%</td>
<td>mPFS: 3.0 mo</td>
</tr>
<tr>
<td>Chiu et al\textsuperscript{85}</td>
<td>Both</td>
<td>Gefitinib</td>
<td>NSCLC (76): adenocarcinoma (53); squamous cell (10); large cell (1); NOS (12)</td>
<td>9.9 mo</td>
<td>50.0%</td>
<td>mPFS: 5.0 mo</td>
</tr>
<tr>
<td>Welsh et al\textsuperscript{88}</td>
<td>New</td>
<td>Erlotinib + WBRT</td>
<td>NSCLC (40): adenocarcinoma (30); squamous (2); large cell (8)</td>
<td>11.8 mo</td>
<td>86.0%</td>
<td>mPFS: 8.0 mo</td>
</tr>
<tr>
<td>Long et al\textsuperscript{89}</td>
<td>Both</td>
<td>Dabrafenib</td>
<td>BRAF-mutant melanoma (172): no prior treatment (Group A; n=89) prior treatment (Group B; n=83)</td>
<td>33.1 wk (Group A V600E) 16.3 wk (Group A V600K) 31.4 wk (Group B V600E) 21.9 wk (Group B V600K)</td>
<td>39.2% (Group A) 30.8% (Group B)</td>
<td>mPFS: 16.1 wk (Group A V600E) 8.1 wk (Group A V600K) 16.6 wk (Group B V600E) 15.9 wk (Group B V600K)</td>
</tr>
<tr>
<td>Margolin et al\textsuperscript{88}</td>
<td>Both</td>
<td>Ipilimumab</td>
<td>Melanoma (72): asymptomatic (Group A; n=51) symptomatic (Group B; n=21)</td>
<td>7.0 mo (Group A) 3.7 mo (Group B)</td>
<td>16.0% (Group A) 5.0% (Group B)</td>
<td>mPFS: 1.4 mo (Group A) 1.2 mo (Group B)</td>
</tr>
</tbody>
</table>

Abbreviations: BAC, bronchoalveolar carcinoma; mPFS, median progression-free survival; mTTP, median time to progression; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; WBRT, whole-brain radiation therapy.
documented a response to hormonal agents, and these can be considered in progressive brain metastases in the setting of hormone receptor–positive breast cancer.\textsuperscript{82–84}

In HER2\textsuperscript{+} breast cancer, lapatinib, a small-molecule tyrosine kinase inhibitor of EGFR and HER2, has modest activity as a single agent in recurrent brain metastases, with higher responses observed with the combination of lapatinib and capecitabine.\textsuperscript{85} A recent study of upfront lapatinib and capecitabine in 44 patients with newly diagnosed brain metastases showed an intracranial response rate of 66\% and a median overall survival of 17 months, which is comparable to the responses seen with radiotherapy.\textsuperscript{86} In the absence of a randomized trial comparing WBRT, these results must be cautiously interpreted. Furthermore, more than 40\% of the patients in this study were neurologically asymptomatic, and therefore the results may not extrapolate to symptomatic patients.

**Melanoma**

Targeted agents and immunotherapy have recently emerged as playing an important role in the treatment of brain metastases from melanoma (Table 2). In a phase II study of the BRAF inhibitor dabrafenib in 172 patients with brain metastases from BRAF-mutant melanoma, response rates were 39\% in treatment-naive patients harboring the V600E mutation, and 31\% in previously treated patients with the mutation.\textsuperscript{87} Case reports have also shown promising results for the BRAF inhibitor vemurafenib in brain metastases.\textsuperscript{88} Ipilimumab, an anti-CTLA4 monoclonal antibody, also has activity in brain metastases,\textsuperscript{89,90} as does adoptive cell therapy (ACT) using autologous antitumor lymphocytes plus interleukin.\textsuperscript{91} Cytotoxic chemotherapy has limited activity in brain metastases from melanoma. Temozolomide and fotemustine have both been investigated in this setting, with modest responses.\textsuperscript{92,91}

**Supportive Care**

Critical to the treatment of brain metastases is effective supportive care to manage and palliate symptoms. Patients presenting with seizures should be treated with standard antiepileptic drugs (AEDs). Enzyme-inducing AEDs (EIAED) such as phenytoin and carbamazepine should be avoided if possible, given their potential interaction with traditional chemotherapeutic agents and newer targeted agents.\textsuperscript{94–96} Furthermore, patients receiving phenytoin and intracranial radiation therapy have a documented, albeit low, risk of developing erythema multiforme major (Stevens-Johnson syndrome).\textsuperscript{97,98} The non-EIAEDs such as levetiracetam, gabapentin, and the newer agent, lacosamide, have fewer drug–drug interactions and are preferred.\textsuperscript{99,100} In the absence of seizures, the American Association of Neurology published practice guidelines recommending against the use of prophylactic agents based on multiple studies that failed to demonstrate a substantial benefit.\textsuperscript{101} Prophylactic AEDs are used routinely in the perioperative setting,\textsuperscript{102,103} although the benefit of this is unclear in the absence of seizures, and tapering after the first postoperative week is recommended.\textsuperscript{101}

Corticosteroids are used for symptomatic peritumoral edema, with dexamethasone being the most commonly used steroid because it has a relatively low mineralocorticoid activity and a decreased risk of cognitive impairment.\textsuperscript{104} The recommended starting dose depends on the severity of symptoms. For severe symptoms related to increased intracranial pressure, a starting dose of 16 mg/d or more should be considered.\textsuperscript{105} Doses of 4 to 8 mg/d usually suffice for milder symptoms. For neurologic symptoms that are secondary to vasogenic edema, improvement is typically observed within 24 to 48 hours. For neurologic symptoms that are secondary to vasogenic edema, improvement is typically observed within 24 to 48 hours. Despite their beneficial effects, steroids should be tapered as quickly as possible given the risks of systemic complications associated with prolonged use. To avoid rebound symptoms, a taper over at least a 2-week period should be considered, and in some cases, longer tapers may be necessary. Steroid-associated complications include myopathy, Cushingoid features, osteoporosis, catastrophic, psychosis, peptic ulcer disease, and pneumocystis jiroveci pneumonia (PJP).\textsuperscript{96} With prolonged steroids use, prophylaxis against PJP should be considered with trimethoprim-sulfamethoxazole (TMP-SMZ) or, if the patient is allergic to TMP-SMZ, dapsone, aero-osolized pentamidine, or atovaquone.\textsuperscript{106}

Cognitive slowing and fatigue are common in patients with brain metastases, and can significantly impact quality of life.\textsuperscript{107} A phase III trial of the N-methyl-D-aspartate receptor antagonist, memantine, in patients undergoing WBRT recently showed that memantine delays cognitive decline compared with placebo.\textsuperscript{108} Psychostimulants may be considered in patients exhibiting symptoms of cognitive impair-
ment. Smaller studies have reported improvements in cancer-related fatigue, attention and concentration, executive function, and quality of life in patients with brain tumors taking methylphenidate.\textsuperscript{109,110} Prophylactic use of methylphenidate did not improve quality of life in a phase III trial of patients with brain tumors undergoing radiation therapy.\textsuperscript{111} To that effect, treatment should be reserved for symptomatic patients.

### Treatment Recommendations

Appropriate management of brain metastases requires a multidisciplinary approach. In patients with a single brain metastasis and favorable prognosis, sufficient evidence supports the need for either surgery or SRS for improving overall survival. Surgical resection is favored over SRS for lesions that are large, causing mass effect, symptomatic, or in need of tissue confirmation. WBRT alone in the setting of a single brain metastasis is not appropriate except in patients with poor prognosis. In patients with 2 to 4 metastases, options include either WBRT alone, surgery/SRS, or the combination of WBRT and surgery/SRS. In patients with 1 to 4 brain metastases, WBRT after surgery/SRS improves local and total intracranial control but does not confer a survival benefit. However, no prospective data are available comparing WBRT alone versus surgery/SRS alone in the setting of multiple metastases. For all patients with extremely poor prognosis, palliative care alone is a consideration. These recommendations are consistent with the recently published ASTRO evidence-based guidelines.\textsuperscript{20}

The management of patients with more than 4 metastases is an area of controversy, because no randomized data exist to guide decision-making. The NCCN currently recommends WBRT for all patients with more than 3 brain metastases.\textsuperscript{112} WBRT should be more heavily considered for patients suspected of having a high burden of gross and micrometastatic disease. Because tumor progression is the single most important influence on neurocognitive function, the benefits of upfront WBRT in maximizing tumor control may outweigh its toxicities. However, modern MRI sequences are able to discern extremely minute foci. Some SRS technology is able to treat far greater than 4 foci in a single session, and this strategy is commonly used at institutions with these capabilities. When SRS alone is used, close surveillance with MRI brain scans more frequently than every 3 months is recommended.

Although some data, albeit limited, support the use of upfront chemotherapy in select asymptomatic patients, the role of chemotherapy in treating newly diagnosed brain metastases must be further investigated in large randomized studies. Systemic chemotherapy is typically reserved for progression of brain metastases after failure of other treatment modalities. The choice of systemic chemotherapy should depend on the inherent activity of that agent in the primary tumor. Targeted agents are playing increasingly important roles in the treatment of brain metastases.

### References

45. Coccooni G, Lottici R, Bisagni G, et al. Combination therapy with platinum and etoposide of brain metastases from breast carcino-
Management of Brain Metastases