Challenges of Brain Metastasis in ErbB2 (HER-2-positive) Breast Cancer and the Potential of Small Molecules

a report by

Alexandra dos Santos Zimmer[1] *and* **David Cameron**[2]

1. Breast Group Fellowship, European Organisation for Research and Treatment of Cancer; 2. University of Leeds

DOI: 10.17925/EOH.2007.0.1.14

Brain Metastasis in Breast Cancer

The incidence of central nervous system (CNS) metastatic disease in breast cancer patients depends on the stage at initial diagnosis. Approximately 2.5% of those patients who initially presented with localised disease, 7.6% of those with regional disease at presentation and 13.4% of patients presenting with stage IV disease are suffering from CNS metastatic disease.[1–3] However, there are no prospective screening studies of serial computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the rate of occult CNS metastasis in patients with breast cancer over time.[4] Where more extensive studies have been performed, higher rates have been reported. For example, Miller et al. reported an incidence of 14.8% of occult CNS involvement in heavily pre-treated breast cancer patients,[5] and autopsy studies have found clinically unsuspected brain metastasis in 30% of patients with advanced breast cancer.[6,7]

The median time to diagnosis of CNS metastatic disease is two years after the initial diagnosis of breast cancer, and it is unusual for it to be the only site of metastatic disease.[8,9] Systemic disease used to be the leading cause of morbidity and mortality in these patients.[2] There is only limited knowledge of the factors that predict for the development of CNS metastasis, but the main ones reported include young age, African ethnicity, oestrogen receptor (OR)-negativity, HER2-positivity, high tumour grade and BRCA1 phenotype.[1,2,5,9–12]

Clinical Presentation and Consequences of Brain Metastasis

Headache is the most common manifestation of parenchymal brain metastasis, occurring in between quarter and half of all patients. In addition, changes in mental status and cognitive function occur in a similar number of patients. Other manifestations that can also occur are motor deficits, seizures, ataxia and nausea or vomiting. The presence of hemiparesis, hemisensory loss and aphasia are not common, but are usually related to parenchymal metastasis.[2]

Leptomeningeal metastasis can present with the same clinical picture as parenchymal lesions, but more frequently the symptoms involve pain or headache. Cranial neuropathies may occur, with cranial nerves 3, 4, 6, 7 and 8 the most often affected.[2]

The negative impact of brain metastasis on the quality of life for both patients and their families is clear. There will be obvious limitations in daily tasks and activities and, even for those without any functional loss, in many countries there is an immediate prohibition on driving a vehicle.

Brain Metastasis in HER-2-positive Breast Cancer

HER-2 (ErbB2) is a 185-kDa transmembrane tyrosine kinase with extensive homology to the epidermal growth factor receptor (EGFR). The amplification of the HER-2 oncogene occurs in ~25% of breast cancer patients and is associated with diminished disease-free and overall survival.[13,14]

While it has been recognised for some time that overexpression of HER-2 is a poor prognostic factor in breast cancer, it was the advent of trastuzumab, a humanised monoclonal antibody directed against the extracellular domain of HER-2, that has allowed clinicians to better understand the natural history of HER-2-positive metastatic breast cancer. The use of trastuzumab when given with chemotherapy improves response rates and progression-free and overall survival of patients with HER-2-positive metastatic breast cancer.[15]

It soon became clear that patients with HER-2-overexpressing metastatic breast cancer were at high risk of developing CNS involvement. After the introduction of trastuzumab, an apparent increase in the incidence of CNS metastasis was observed in comparison with historical estimates. Several retrospective series have documented an incidence of ~25–40% of CNS metastasis in patients who had been treated with trastuzumab in the setting of metastatic breast cancer (see *Table 1*).[2,12,16–18]

More than one-third of HER-2-positive patients presented with CNS metastasis at a time when the systemic disease remained either stable or responsive to trastuzumab.[19] It seems that improvements in systemic control have led to an 'unmasking' of brain metastasis that would otherwise have remained clinically silent prior to a death from other sites

Alexandra dos Santos Zimmer is a Clinical Oncologist. She had completed her medical training in Porto Alegre, Brazil, and is currently working as a Fellow at Breast Cancer Group at the European Organisation for Research and Treatment of Cancer.

David Cameron is the Director of the UK National Cancer Research Network and Professor of Medical Oncology at the University of Leeds. Professor Cameron received his medical degree in 1986 from St George's Hospital Medical School, London. After completing a fellowship and an MSc in clinical oncology at the University of Edinburgh, he received an MD with distinction in 1997. He is active in a number of clinical trials in breast cancer and his major clinical interests are breast cancer, with an ongoing clinical and translational research programme. Professor Cameron is a member of several professional societies, including the American Society of Clinical Oncology and the European Society for Medical Oncology, and is Secretary of the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Group, as well as Chairman of the EORTC New Drugs Advisory Group.

of disease.[16] In addition, it would seem that for monoclonal antibodies such as trastuzumab that are unable to cross the blood–brain barrier, the brain behaves as a sanctuary site.[20] Thus, in women with HER-2-positive breast cancer, we have a combination of a tumour type with a high potential for CNS spread and a key therapy that does not penetrate the CNS[21] but is effective outside the CNS. Therefore, in this group of patients, the CNS disease becomes a major clinical problem as a potential site of progression, morbidity and mortality.[4] In addition, it is now becoming clear that, although the rate is lower, CNS metastatic disease is also a problem for patients with early HER-2-positive breast cancer. This can be seen from the data presented from some recent studies pre-dating the adjuvant use of transtuzumab, as well as the adjuvant trastuzumab trials (see *Table 2*).[2,12,16–18]

Table 1: Incidence of Central Nervous System Metastasis in Patients Treated with Trastuzumab

Metastatic	Brain Mets/ HER-2 Status		Brain Mets/ TrastuzumabUse	
	Positive	Negative	Yes	No
Bendell [22] Dana-Farber 1998–2000	42/122 (34%)	–	42/122 (34%)	–
Miller[5] EUA 1998–2001	9/35 (25%)	11/89 (12%)	–	–
Lai[23] MSKCC 1997–2000	Mixture	Mixture	123/264 (46%)	38/79 (48%)
Burstein[24]	31/342 (9%)	6/104 (5.8%)	21/342 (6.1%)	11/342 (3.2%)

Table 2: Incidence of Central Nervous System Metastatic Disease in Patients with Early HER-2-positive Breast Cancer

Adjuvant	Brain Mets/ HER2 Status		Brain Mets/ Trastuzumabuse	
	Positive	Negative	Yes	No
Gabos[25] 1998–2003	27/301 (9%)	7/363 (1.9%)	–	–
Hera trial[26]	48/3,401 (1.4%)	–	26/1703 (2%)	22/1,698 (1%)
B-31+[27]	1,736	–	21/864 (2.4%)	11/872 (1.2%)
N9831[27]	1,615		12/808 (1.2%)	04/807 (0.5%)
Pestalozzi[21] IBCSG 1979–99	6.8% 2.7%	3.5% 1.0%	– –	– –

Brain Metastasis Treatment Overview

Standard Treatment and Results

The standard treatment for disease metastatic to the brain is whole-brain radiation therapy (WBRT) with palliative intent. This treatment is associated with clinical improvement and stabilisation in most patients, but the median survival is less than six months, with fewer than 20% of patients surviving to one year. However, depending on the clinical presentation and the site and number of metastatic sites present, there are other therapeutic approaches to CNS disease.[4,28] Surgical excision or radio surgery are options for suitable cases, according to the number and localisation of lesions, with better control achieved when WBRT is added post-resection.[28]

The role of cytotoxic chemotherapy in the treatment of CNS disease remains uncertain. Most cytotoxic agents do not appear to cross the blood–brain barrier. However, there are anecdotal reports of tumour response with many agents, including anthracyclines and platinum.[29–31] One drug in particular – temozolamide – does have activity in primary brain cancer and good CNS penetration, although limited activity has been reported in the treatment of breast cancer metastatic to the brain.[32] This may because of an old lesson: a treatment must be active against the primary tumour to be active in its metastatic lesion.

Carcinomatous meningitis occurs in approximately 2–5% of breast cancer patients.[33] The clinical presentation can involve cranial nerve palsies, metabolic dysfunction or even generalised encephalopathy, and increased intracranial pressure. The treatment usually involves focal irradiation of symptomatic sites with bulky disease and/or intrathecal chemotherapy to suppress the disease in neuraxis. Methotrexate and cytarabine are the agents generally used in the intrathecal route.[34] High doses of intravenous methotrexate were also demonstrated to achieve cytotoxic concentrations in cerebrospinal fluid, but systemic toxicity often limits its use.[35] Regardless of the route, the results with chemotherapy are poor, extending survival for one to three months in some patients, with controversial results in the relief of clinical symptoms.[36,37]

Problems

We are currently facing a changing scenario. Continued improvements in cancer treatments are achieving better control of systemic disease, not only in breast cancer but also in other neoplasms such as lung, kidney, colon and melanoma. The development of better imaging studies is permitting detection of subclinical disease and better control of systemic disease. These and other factors are leading to more patients being diagnosed with brain and other CNS metastatic disease.

Nowhere does this seem more true than for patients with HER-2-positive breast cancer receiving trastuzumab treatment, as CNS metastases are becoming the most important site of progression and limitation of quality of life and survival.[38]

Nevertheless, for many patients standard treatments only offer a median six months' survival with few prospective trials conducted for the treatment of brain metastasis of breast cancer. Most studies of novel agents excluded women with known brain metastasis, and the majority of published trials of brain metastasis treatment have grouped different histological types of tumours together as one.[4,38]

Perspectives

There is a clear, unmet need to improve the therapeutic option for patients with CNS metastatic disease, specifically for patients with HER-2-positive breast cancer. The advent of active targeted therapies and antiangiogenesic agents has the potential to bring a new perspective to the treatment of CNS disease.

Small Molecules

Dual Kinase Inhibitors

The epidermal growth factor (EGF) or ErbB receptors are members of the receptor tyrosine kinase superfamily. There are four ErbB receptor family members: ErbB1 (EGFR, HER-1), ErbB2 (HER-2/neu), ErbB3 (HER3) and ErbB4 (HER-4).[39] These receptors are situated at the cell membrane and

have an extracellular ligand-binding region, a transmembrane region and a cytoplasmic tyrosine kinase domain. Ligand binding to the receptors results in receptor homo- and/or hetero-dimerisation, activating the intrinsic kinase domain and leading to phosphorylation of specific tyrosine residues within the cytoplasmic tail and, finally, to the activation of a variety of intracellular signalling pathways that promote cell growth, proliferation, differentiation and migration.[39] Interactions between ErbB receptors allows ErbB2 – which has no kinase activity but is the preferred dimerisation partner for all the other ErbB receptors – to participate in effective signalling.[40]

Amplification of HER-2 is seen in 25–30% of breast cancers and is associated with a statistically significant shortening in disease-free and overall survival.[13] Overexpression of ErbB1 occurs in a similar proportion of breast cancers, although it is less clear in what proportion expression confers biological activity (and thus the potential for therapeutic intervention).[19]

A number of agents directed against individual ErbB receptors have been approved for clinical use in human cancer and can broadly be separated into two main groups. Humanised monoclonal antibodies are directed against the extracellular domain of the receptor, such as trastuzumab, and small-molecule tyrosine kinase inhibitors, such as gefitinib, bind to the ATP-binding site of the intracellular tyrosine kinase domain of the receptor.[40]

Molecular pathways can be both adaptable and redundant. It is thus unlikely that therapy focusing on a single target will achieve durable disease control for most patients. The ErbB receptor family members follow this paradigm, in that they are known to be interdependent, preferentially functioning as dimmers to induce signal transduction and malignant transformation.[41] This is supported by the clinical observation that cancers concomitantly overexpressing EGFR and HER-2 have a worse outcome than those that overexpress either receptor alone.[42,43] There is therefore increasing evidence in support of developing effective therapies that concurrently inhibit two or more receptors.

HER-2 overexpression has been shown to activate and potentiate EGFR signalling, and combined inhibition of EGFR and HER-2 results in greater tumour growth inhibition. Pre-clinical data with breast cancer cell lines and animal models resulted in superior antitumour activity utilising a dual ErbB approach rather than single-receptor targeting, suggesting that the addition of EGFR blocking could overcome trastuzumab resistance.[19] In these studies, the combined use of trastuzumab with gefitinib, erlotinib or lapatinib was compared with the activity of trastuzumab alone. A phase II study with gefitinib and trastuzumab was unfortunately terminated early with no effect seen.[19]

Most interest has been centred on agents that produce dual inhibition from one molecule such as lapatinib, but there is still room for developing combinations of single agents in order to attain full blockade of both receptors, which might not be efficiently obtained from a single molecule since the toxicity of blocking one receptor may hinder dose escalation to achieve complete blockade of the combined receptor.[19]

Lapatinib

Lapatinib is a potent, reversible, selective dual inhibitor of EGFR and HER-2 kinases, and has demonstrated growth inhibition in both *in vitro* and *in vivo* models overexpressing these receptors.[44] Toxicology studies supported the clinical development of the oral use of lapatinib with minimal side effects.[45] Lapatinib acts intracellularly and directly targets the tyrosine kinase domain, preventing downstream signalling events.[19]

Early clinical studies have reported significant activity, with phase II studies in advanced or metastatic breast cancer showing a response rate of 22% in trastuzumab-refractory patients[46] and 24% in patients treated with lapatinib in first line.[47]

Clinical trials have been carried out with lapatinib for the treatment of brain metastasis because it is a small molecule able to penetrate the blood–brain barrier.[19] At the American Society of Clinical Oncology Annual Meeting in 2006, Winer and colleagues presented a phase II study involving lapatinib in the treatment of breast cancer patients with progressive brain metastasis despite prior treatment with radiotherapy and/or surgery. These patients were evaluated for objective response according to Response Evaluation Criteria In Solid Tumours (RECIST), with MRI and positron emission tomography (PET) as imaging studies. The study goal was to observe four objective responses – only two, however, were observed in their sample of 39 patients, and overall the median time to progression (TTP) was three months (95% confidence interval (CI) 2.04–3.68) with a median overall survival time of 6.6 months.[48] However, anecdotal evidence suggests that more patients than just these two benefited from the intervention, which has led to larger studies to more precisely determine the activity of this agent for these patients, including the multicentre phase II study, NCT00263588. This study has closed to accrual and the results are eagerly awaited. With a similar design, the study registered as NCT00098605 and sponsored by Dana Farber Institute is also presently closed to accrual (see www.clinicaltrials.gov).[49]

A pivotal phase III study with lapatinib was conducted in patients with metastatic HER-2-positive breast cancer already treated with trastuzumab, anthracyclines and taxanes. The goal was to compare the use of the combination lapatinib and capecitabine with capecitabine alone. It is interesting to observe that in the first report of this study, the number of women presenting CNS metastasis as first-site progression during this treatment was only four in the combined treatment group compared with 11 in the monotherapy group. While this difference did not reach statistical significance by Fisher's exact test ($p=0.10$), it suggests that lapatinib might be able to help prevent this devastating complication of HER-2-positive breast cancer.[50] Updated clinical data are expected soon.

The Tykerb® Evaluation After Chemotherapy trial is enrolling patients. The objective of this trial is to determine whether adjuvant therapy with lapatinib for one year will improve disease-free survival in women with early-stage ErbB2-overexpressing breast cancer that has not previously received trastuzumab. Results for lapatinib use versus placebo will also be compared for the rate of CNS recurrence.[19] In a similar way, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation trial will explore the relative efficacy of adjuvant trastuzumab and lapatinib, as well as their use in sequence and concomitantly. The incidence of brain metastasis and, consequently, the possible efficacy of these drugs in its prevention will also be evaluated.

The concurrent use of lapatinib and radiation has not previously been evaluated in humans, but the experience with gefitinib (ErbB1 inhibitor) in patients with non-small-cell lung cancer suggested that this agent could be useful in the treatment of brain metastasis.[51] The results of the use of lapatinib in this group of patients remain to be proved. A real need exists for drugs capable of crossing the blood–brain barrier with significant activity against brain metastasis, and other agents can also fit this requirement.

Other Agents

Other agents with dual-targeting irreversible activity – such as BIBW-2992[52] and HKI-272[53] – have been evaluated in initial studies in solid tumours, but no data reports of its specific activity in brain metastasis are available. Canertinib (or CI-103354) is an irreversible pan-ErbB tyrosine kinase inhibitor. Targeting all four ErbB receptors has the theoretical advantage of blocking redundant signalling that might be used to bypass more specific ErbB tyrosine kinase inhibitors. However, there have been no reports of their activity in brain metastasis to date.

Other Small-molecule Agents

Sunitinib

Sunitinib is a novel, orally bio-available, multitargeted tyrosine kinase inhibitor with high binding affinity for VEGFR (types 1–3) and PDGFR (α and β), showing antitumour and antiangiogenic activities. It also inhibits FLT3, Kit (stem cell factor-receptor), colony-stimulating factor type 1 (CSF-1R) and glial cell line-derived neurotrophic factor receptor (RET) in biochemical and cellular assays.[55]

Sunitinib has already been approved by the US Food and Drug Administration and the European Medicines Agency for treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours in patients resistant to imatinib. Pre-clinical evaluation of its use in animal models of breast cancer provided encouraging results, showing potent antiproliferative activity either alone or in combination with 5-FU/doxorubicin/docetaxel[56] and capacity for inhibiting associated osteolysis.[57]

In an open-label, single-arm, phase II trial of 64 patients with heavily pre-treated metastatic disease, previously resistant to anthracyclines and taxane, sunitinib treatment resulted in an objective response rate of ~11%. Three patients (5%) had stable disease for more than six months and the overall clinical benefit was evaluated to be 16%.[58]

Pre-clinical studies show that sunitinib and its metabolite penetrate the CNS with rapid clearance in mice, rats and monkeys, without any apparent accumulation. This suggests a favourable potential for antitumour activity in the brain. However, optimal target drug concentrations still have to be determined in the clinical setting.[59]

Ample evidence suggests that radiation could induce tumours to produce angiogenic growth factors, which could be a mechanism of the tumour's paracrine regulation of endothelial resistance to radiation.[60] Conversely, human cells evaluated *in vitro* can show activation of PI3K/Akt in the absence of a growth factor stimulus, suggesting an alternative method of this pathway's activation.[61,62] Apparently, increased doses of ionised radiation treatment of endothelial cells leads to increased phosphorylation of Akt, which plateaus at around 3Gy per dose.[63] The exact mechanism of how radiation activates the PI3K/Akt pathway in the absence of growth factors in endothelial cells remains to be elucidated. These cells are, however, susceptible to apoptosis in higher doses of radiation.

Tyrosine kinase receptor signalling of tumour endothelium may contribute to angiogenesis, maintenance of tumour vascular supply and, ultimately, to tumour survival and resistance to cytotoxic therapy. Because radiation therapy activates PI3/Akt signalling, the use of RTK inhibitors to block the radiation-induced activation of this pathway in the tumour vasculature has been studied.

Sunitinib has been reported to enhance radiation-induced endothelial cytotoxicity.[61] Part of the response to treatment was due to increased apoptosis in endothelial cells treated with that combination, reflected by destruction of tumour vasculature in a tumour vascular window model. However, it was also noted in this study that, although the combination of treatments leads to improved tumour control, the tumours rapidly resumed growth in test animals when the therapy was discontinued.

Persistent tumour control was achieved only by adjuvant or maintenance therapy with sunitinib. One potential advantage of maintenance therapy with antiangiogenic agents is that resistance to this form of therapy does not seem to develop, perhaps because these agents target normal rather than malignant cells.[64] If tumour regrowth is seen, salvage therapy by use of these agents may still be an option, because the endothelium is unlikely to develop resistance to these compounds.[65]

Preliminary data from Kim and colleagues, working with mice treated with sunitinib and radiation therapy, demonstrate that even within the same animal that received systemic sunitinib, increased binding occurs only in the presence of radiotherapy. This result strongly suggests that combination therapy is important for this response.[65] Currently, ongoing clinical trials are evaluating the role of sunitinib in advanced breast cancer. Related to brain metastatic disease, a phase II clinical trial (NCT00372775) is continuing in the US and Europe, evaluating the safety and effectiveness of sunitinib associated with WBRT in non-small-cell lung-cancer patients.

Conclusions and Perspectives

The role of small molecules in the treatment of CNS metastatic disease remains to be established. There are difficulties in the evaluation of objective response by current imaging methods, which is the normal procedure to confirm activity. For patients, tumour response may be less important than restoration or preservation of neurocognitive function or quality of life, both of which are equally challenging to measure accurately and reproducibly in clinical trials.

Distinguishing tumour progression from radiation necrosis is a unique problem in CNS disease because of the difficulty in accessing tissue for definitive diagnosis.[4] Ultimately, we may need to turn to novel imaging techniques, which could include metabolic imaging with PET, MRI etc.,[66] which is probably also the case with the targeted therapy agents.

Finally, much needs to be learned about the pathophysiology of CNS metastasis at a molecular level, and current models still have limitations, particularly related to the difficulty in accessing tissue for translational research. ■

Acknowledgements

This research project was supported in part by a grant from the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Co-operative Group to the EORTC Charitable Trust. This publication was supported by grant number 5U10 CA11488-37 from the National Cancer Institute (Bethesda, Maryland, US). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

1. Barnholtz-Sloan JS, et al., Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System, *J Clin Oncol*, 2004;22:2865–72.
2. Lin NU, Bellon JR, Winer, EP, CNS metastases in breast cancer, *J Clin Oncol*, 2004;22:3608–17.
3. Tsukada Y, Fouad A, Pickren JW, Lane WW, Central nervous system metastasis from breast carcinoma. Autopsy study, *Cancer*, 1983;52:2349–54.
4. Lin NU, Winer EP, Brain metastases: the HER2 paradigm, *Clin Cancer Res*, 2007;13:1648–55.
5. Miller KD, *et al*., Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival, *Ann Oncol*, 2003;14: 1072–7.
6. Cho SY, Choi HY, Causes of death and metastatic patterns in patients with mammary cancer. Ten-year autopsy study, *Am J Clin Pathol*, 1980;73:232–4.
7. Lee YT, Breast carcinoma: pattern of metastasis at autopsy, *J Surg Oncol*, 1983;23:175–80.
8. Carey LA, et al., Central nervous system metastases in women after multimodality therapy for high risk breast cancer, *Breast Cancer Res Treat*, 2004;88:273–80.
9. Gonzalez-Angulo AM, et al., Central nervous system metastases in patients with high-risk breast carcinoma after multimodality treatment, *Cancer*, 2004;101:1760–66.
10. Hicks DG, *et al*., Breast cancers with brain metastases are more likely to be estrogen receptor negative, express the basal cytokeratin CK5/6, and overexpress HER2 or EGFR, *Am J Surg Pathol*, 2006;30:1097–1104.
11. Ryberg M, et al., Predictors of central nervous system metastasis in patients with metastatic breast cancer. A competing risk analysis of 579 patients treated with epirubicin-based chemotherapy, *Breast Cancer Res Treat*, 2005;91:217–25.
12. Souglakos J, et al., Central nervous system relapse in patients with breast cancer is associated with advanced stages, with the presence of circulating occult tumour cells and with the HER2/neu status, *Breast Cancer Res*, 2006;8:R36.
13. Slamon DJ, et al., Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene, *Science,* 1987;235:177–82.
14. Slamon DJ, et al., Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer, *Science,* 1989;244:707–12.
15. Slamon DJ, et al., Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2, *N Engl J Med*, 2001;344:783–92.
16. Clayton AJ, et al., Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer, *Br J Cancer*, 2004;91:639–43.
17. Stemmler HJ, et al., Characteristics of patients with brain metastases receiving trastuzumab for HER2 overexpressing metastatic breast cancer, *Breast,* 2006;15:219–25.
18. Yau T, et al., Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab, *Acta Oncol*, 2006;45:196–201.
19. Moy B, Goss PE, Lapatinib: current status and future directions in breast cancer, *Oncologist,* 2006;11:1047–57.
20. Doolittle ND, et al., Delivery of chemotherapy and antibodies across the blood-brain barrier and the role of chemoprotection, in primary and metastatic brain tumours: report of the Eleventh Annual Blood-Brain Barrier Consortium meeting, *J Neurooncol*, 2007;81:81–91.
21. Pestalozzi BC, 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;17:935–44.
22. Bendell JC, et al., Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma, *Cancer,* 2003;97:2972–7.
23. Lai R, Dang CT, Malkin MG, Abrey LE, The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma, *Cancer,* 2004;101:810–16.
24. Burstein HJ, Lieberman G, Slamon DJ, et al., Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy, *Ann Oncol*, 2005;16:1772–7.
25. Gabos Z, et al., Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer, *J Clin Oncol*, 2006;24:5658–63.
26. Smith I, et al., 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial, *Lancet*, 2007;369:29–36.
27. Romond EH, et al., Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer, *N Engl J Med*, 2005;353:1673–84.
28. Patel RR, Mehta MP, Targeted therapy for brain metastases: improving the therapeutic ratio, *Clin Cancer Res*, 2007;13: 1675–83.
29. Boogerd W, Dalesio O, Bais EM, van der Sande JJ, Response of brain metastases from breast cancer to systemic chemotherapy, *Cancer,* 1992;69:972–80.
30. Rosner D, Nemoto T, Lane WW, Chemotherapy induces regression of brain metastases in breast carcinoma, *Cancer,* 1986;58:832–9.
31. Fleming DR, Goldsmith GC, Stevens DA, Herzig RH, Dose-intensive chemotherapy for breast cancer with brain metastases: a case series, Am *J Clin Oncol*, 1999;22:371–4.
32. Rivera E, 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: 1348–54.
33. Jayson GC, Howell A, Carcinomatous meningitis in solid tumours, *Ann Oncol*, 1996;7:773–86.
34. Grossman SA, Krabak MJ, Leptomeningeal carcinomatosis, *Cancer Treat Rev*, 1999;25:103–19.
35. Tetef ML, et al., Pharmacokinetics and toxicity of high-dose intravenous methotrexate in the treatment of leptomeningeal carcinomatosis, *Cancer Chemother Pharmacol*, 2006;46:19–26.
36. Chamberlain MC, Kormanik PR, Carcinomatous meningitis secondary to breast cancer: predictors of response to combined modality therapy, *J Neurooncol*, 1997;35:55–64.
37. Orlando L, et al., Intrathecal chemotherapy in carcinomatous meningitis from breast cancer, *Anticancer Res*, 2002;22: 3057–9.
38. Aragon-Ching JB, Zujewski JA, CNS metastasis: an old problem in a new guise, *Clin Cancer Res*, 2007;13:1644–7.
39. Reid A, Vidal L, Shaw H, de Bono J, Dual inhibition of ErbB1 (EGFR/HER1) and ErbB2 (HER2/neu), *Eur J Cancer*, 2007;43: 481–9.
40. Baselga J, Arteaga CL, Critical update and emerging trends in epidermal growth factor receptor targeting in cancer, *J Clin Oncol*, 2005;23:2445–59.
41. Britten CD, Targeting ErbB receptor signalling: a pan-ErbB approach to cancer, *Mol Cancer Ther*, 2004;3:1335–42.
42. Xia W, et al., Combination of EGFR, HER-2/neu, and HER-3 is a stronger predictor for the outcome of oral squamous cell carcinoma than any individual family members, *Clin Cancer Res*, 1999;5:4164–74.
43. Tateishi M, et al., Prognostic influence of the co-expression of epidermal growth factor receptor and c-erbB-2 protein in human lung adenocarcinoma, *Surg Oncol*, 1994;3:109–13.
44. Rusnak DW, et al., The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumour-derived cell lines *in vitro* and *in vivo*, *Mol Cancer Ther*, 2001;1:85–94.
45. Burris HA 3rd, et al., Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pre-treated patients with metastatic carcinomas, *J Clin Oncol*, 2005;23:5305–13.
46. Blackwell KL, Burstein H, Pegram M, et al., Determining relevant biomarkers from tissue and serum that may predict response to single agent lapatinib in trastuzumab refractory metastatic breast cancer, in *ASCO* Vol. 23 3004 (*J Clin Oncol*, 2005).
47. Gomez HL, Chavez MA, Doval DC, Randomised study of lapatinib as first-line treatment for patients with HER2-amplified advanced or metastatic breast cancer, in San Antonio Breast Cancer Symposium (San Antonio-USA, 2006).
48. Lin NUC, Lin LA, Younger J, et al., Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer, in *ASCO* Vol. 24 503 (*J Clin Oncol*, 2006).
49. www.clinicaltrials.gov. Clinical Trials. Vol. 2007.
50. Geyer CE, et al., Lapatinib plus capecitabine for HER2-positive advanced breast cancer, *N Engl J Med*, 2006;355:2733–43.
51. Namba Y, et al., Gefitinib in patients with brain metastases from non-small-cell lung cancer: review of 15 clinical cases, *Clin Lung Cancer*, 2004;6:123–8.
52. Shaw H, A phase I dose escalation study of BIBW 2992, an irreversible dual EGFR/HER2 receptor tyrosine kinase inhibitor, in patients with advanced solid tumours, in *ASCO* Vol. 18S (*J Clin Oncol*, 2006).
53. Rabindran SK, et al., Antitumour activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase, *Cancer Res*, 2004;64:3958–65.
54. Allen LF, Eiseman IA, Fry DW, Lenehan PF, CI-1033, an irreversible pan-erbB receptor inhibitor and its potential application for the treatment of breast cancer, *Semin Oncol*, 2003;30:65–78.
55. Izzedine H, Buhaescu I, Rixe O, Deray G, Sunitinib malate, *Cancer Chemother Pharmacol*, 2006.
56. Abrams TJ, et al., Pre-clinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with 'standard of care' therapeutic agents for the treatment of breast cancer, *Mol Cancer Ther*, 2003;2:1011–21.
57. Murray LJ, et al., SU11248 inhibits tumour growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model, *Clin Exp Metastasis*, 2003;20:757–66.
58. Miller KDB, Rugo AD, et al., Phase II study of SU11248, a multitargeted receptor tyrosine kinase inhibitor (TKI), in patients with previously treated metastatic breast cancer, in *ASCO* Vol. 23 563, 2005.
59. Patyna SP, Distribution of sunitinib and its active metabolite in brain and spinal cord tissue following oral or intravenous administrations in rodents and monkeys, in ENA Vol. 4 21 (*Eur J Cancer*, Prague, 2006).
60. Wachsberger P, Burd R, Dicker AP, Improving tumour response to radiotherapy by targeting angiogenesis signalling pathways, *Hematol Oncol Clin North Am*, 2004;18:1039–57, viii.
61. Schueneman AJ, et al., SU11248 maintenance therapy prevents tumour regrowth after fractionated irradiation of murine tumour models, *Cancer Res*, 2003;63:4009–16.
62. Zingg D, et al., Differential activation of the phosphatidylinositol 3'-kinase/Akt survival pathway by ionising radiation in tumour and primary endothelial cells, *Cancer Res*, 2004;64:5398–5406.
63. Tan J, Hallahan DE, Growth factor-independent activation of protein kinase B contributes to the inherent resistance of vascular endothelium to radiation-induced apoptotic response, *Cancer Res*, 2003;63:7663–7.
64. Boehm T, Folkman J, Browder T, O'Reilly MS, Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance, *Nature*, 1997;390:404–7.
65. Kim DW, Huamani J, Fu A, Hallahan DE, Molecular strategies targeting the host component of cancer to enhance tumour response to radiation therapy, *Int J Radiat Oncol Biol Phys*, 2006;64:38–46.
66. Wong TZ, van der Westhuizen GJ, Coleman RE, Positron emission tomography imaging of brain tumours, *Neuroimaging Clin N Am*, 2002;12:615–26.