Brain metastases in HER2 positive breast cancer: the next hurdle

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Advances in our understanding of the biological subtypes of breast cancer have revolutionized its treatment landscape and prognosis. This is particularly so in the field of HER2 positive tumours, where targeted therapy with anti-HER2 agents such as trastuzumab and lapatinib, are now approved options. Since the introduction of trastuzumab, patients with HER2 positive breast cancers are experiencing longer disease- and progression-free intervals as well as better overall survival. Paralleling the problems with an ageing population, the increasing life expectancy of such patients have resulted in a new set of medical issues that oncologists and palliative physicians have to grapple with, such as brain metastases.

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2, approved by the United States Food and Drug Administration (FDA) for use in the adjuvant and palliative treatment of HER2 positive breast cancer. It is well established that despite its anti-tumour efficacy, it does not penetrate the blood-brain barrier well, with one study showing serum to cerebrospinal fluid trastuzumab level being 420:1 (1). As such, the brain becomes an important sanctuary site for breast cancer cells to seek refuge in and replicate. Retrospective studies have also shown an increase in the incidence of brain metastases in patients treated with trastuzumab (2,3). Biological factors, in addition to treatment factors, contribute to the predisposition of HER2 positive tumours to disseminate to the brain compared to other subtypes (4). In an analysis of 10 adjuvant trials examining the sites of metastases in 9524 patients with early stage breast cancers treated without anthracyclines, taxanes or trastuzumab in the pre-trastuzumab era (5), the 10-year incidence of central nervous system (CNS) relapse at any time was almost double in patients with HER2 positive disease compared to those with HER2 negative breast cancer (6.8% versus 3.5%; $P<0.01$), supporting the hypothesis that HER2 positive breast cancer is biologically inclined to develop brain metastases. Furthermore, the improved prognosis of HER2 positive breast cancer patients with trastuzumab treatment 'unmasks' brain metastases which may not have been detected had the patients succumb to the disease earlier.

Brain metastases pose a great challenge clinically due to their associated morbidity and significant impact on patients' quality of life. Interestingly, anti-HER2 agents continue to show efficacy in controlling the extra-cranial tumour burden in patients with brain metastases, which may account for the longer time from brain metastases to death observed in HER2 positive metastatic breast cancer patients treated with trastuzumab compared to those who did not receive treatment or have HER2 negative disease (6,7). However, overall survival is still compromised as half of them will eventually die from CNS disease progression (2). Current treatment options for brain metastases in breast cancer include steroids, neurosurgery, stereotactic radiosurgery and whole brain radiotherapy (WBRT), depending on the size and number of lesions (8). WBRT, probably the most commonly employed palliative treatment for brain metastases, is associated with radio-induced neurocognitive impairment that can occur early, or present late with irreversible decline (9). These potentially debilitating side effects are a constant reminder that development of alternative therapies with lower morbidity is still required.

Although trastuzumab, a monoclonal antibody, is unable to permeate the CNS, numerous studies have shown that

lapatinib, a small dual tyrosine-kinase inhibitor of HER1 and HER2, has activity against brain metastases in HER2 positive breast cancer patients. In the landmark study by Geyer *et al.* which proved the superiority of lapatinib and capecitabine over capecitabine alone in patients with advanced HER2 positive breast cancer who had progressed on trastuzumab, a smaller albeit non-significant number of patients developed brain metastases in the combination arm, providing hints that lapatinib could prevent or delay the onset of CNS involvement (10). Since then, lapatinib has been studied prospectively in phase 2 trials in HER2 positive breast cancer patients with brain metastases, as monotherapy (11,12) and in combination with capecitabine (12-14). However, most of these trials were small and involved patients who have previously received WBRT. Objective CNS responses were heterogeneous, ranging from 3% with lapatinib alone to up to 38% for combination therapy. In a small number of patients who had CNS progression on lapatinib monotherapy, 20% experienced partial CNS response when capecitabine was added, suggesting that combination therapy has a role to play even if patients had previous treatment with lapatinib (12). Subgroup analysis of two trials showed that capecitabine-naïve patients had better response than those who had prior exposure to capecitabine (14,15).

The recent online publication by Bachelot *et al.* in Lancet Oncology describes the LANDSCAPE study, a prospective single-arm phase 2, open label, multicentre study in which HER2 positive breast cancer patients with brain metastases without prior exposure to whole brain irradiation, capecitabine or lapatinib, were treated with lapatinib (1,250 mg daily) combined with capecitabine (2,000 mg/m^2 daily from day 1 to day 14) in 21-day cycles (16). The primary endpoint was the proportion of patients with an objective CNS response, which was defined as a 50% or greater volumetric reduction of CNS lesions in the absence of increased steroid use, progressive neurological symptoms and progressive extra-CNS disease. Of the 45 patients enrolled, 44 were assessable for efficacy with a median follow-up of 21.2 months (range, 2.2-27.6 months). 29 patients had an objective CNS response (65.9%, 95% CI, 50.1-79.5), all of which were partial responses.

LANDSCAPE is the first prospective study examining the combination of lapatinib and capecitabine in HER2 positive breast cancer patients with brain metastases who were WBRT-naïve. The study results are encouraging, with a high CNS response rate and fairly short median time to first documented response of 1.8 months (95% CI, 1.1-5.8 months). As expected, the regimen resulted in the additional benefit of extra-CNS disease control, with 44.1% of evaluable patients having an objective extra-CNS response. The importance of CNS control in the overall prognosis of patients with brain metastases was further substantiated in subgroup analysis showing significant improved time to progression in responders (6.0 months; 95% CI, 5.5-7.4 months) compared to non-responders (2.8 months; 95% CI, 1.4-4.2 months; P<0.0001). Median time to WBRT was a meaningful 8.3 months (95% CI, 5.4-9.1 months) in the study population whose median overall survival was reported to be 17 months (95% CI, 13.7-24.9 months). Amongst the patients who progressed on treatment, four-fifths relapsed first in the CNS alone, and almost all ultimately received WBRT as a palliative measure.

These data provide strong evidence that combination of lapatinib and capecitabine is a feasible alternative to delay whole brain radiotherapy and its associated side effects. The combination is especially relevant for patients with significant extra-cranial disease and who also require systemic therapy. Convenience of oral administration makes this an appealing option compared to WBRT which could be a logistical challenge in patients with limited mobility or poor performance status. However, there are still limitations and many questions left unanswered. The applicability of LANDSCAPE is constrained by its phase 2 design and small sample size. In addition, 43% had asymptomatic brain metastases and all had good Graded Prognostic Assessment scores. Patients with ECOG status of 2 made up less than 5% of study participants, implying that patients may have been naturally self-selected to account for the good outcome observed in the trial. This is in contrast with real life situation where patients often present with seizures and other neurological disability and may not have good performance status that would be required for trial entry.

Although the authors concluded that the regimen was tolerable, almost half the patients (49%) actually experienced grade 3 or 4 adverse events, with diarrhoea and hand-foot syndrome being most common. One-third of patients required dose reduction for lapatinib, and slightly more than half had dose reductions for capecitabine, while treatment was discontinued in 9%, suggesting that toxicities must be clinically significant in these patients. Lapatinib is also not readily available in many less developed healthcare systems, compared to facilities for palliative radiation, making these findings irrelevant in certain countries. Importantly, barring resource restriction issues, the cost of lapatinib and capecitabine for an average woman in the

United States is USD$2,919 per cycle (17), or USD$21,406 for 5.5 months, the median progression-free interval seen in LANDSCAPE, which is more than three-fold the USD$6,500 for WBRT reported in a cost-effectiveness analysis (18). However, one may argue that systemic treatment with an anti-HER2 agent such as lapatinib would still be warranted post-WBRT, thereby negating the cost difference in developed countries where both options are readily available.

In the LANDSCAPE study, 78% of the 41 patients with available data had CNS disease alone as the first site of progression, underscoring the fact that many patients may require several lines of brain metastases-specific treatments as overall survival rates improve. One pertinent question is the optimal sequence of treatment for brain metastases in HER2 positive breast cancer, i.e. lapatinib and capecitabine before WBRT, or vice versa, which needs to be addressed in a phase 3 clinical trial, now being planned by the LANDSCAPE investigators.

Brain metastases are now an important site of disease progression and a major cause that limits quality of life and survival in HER2 positive breast cancer. We are now entering an era where anti-HER2 treatment is no longer limited to trastuzumab and lapatinib. Pertuzumab, a monoclonal antibody against HER2, has recently received FDA approval (19) while T-DM1, a trastuzumab-cytotoxic conjugate, is seeking approval, for metastatic HER2 positive breast cancer (20). These large molecules, while unlikely to be active against brain metastases, are expected to further prolong survival, making treatment of brain metastases an ever more pertinent issue. Other anti-HER2 agents in active development in breast cancer include afatinib, a small molecule tyrosine kinase inhibitor that has promising activity against brain metastases (21), and may further expand the treatment options in these patients.

Once a domain which was largely excluded from major therapeutic trials, brain metastases are increasingly being acknowledged by clinicians and scientists as the next major hurdle to prolonging survival in HER2 positive breast cancer. The results from the LANDSCAPE study brings home the point that good clinical outcome is achievable in selected patients with brain metastases with systemic therapy. Beyond solely targeting the HER2 receptor, research into therapies blocking novel pathways such as bevacizumab, phosphoinositide-3-kinase inhibitors, and poly (ADP ribose) polymerase (PARP) inhibitors in brain metastases in breast cancers is on-going. It is hopeful that in the near future, oncologists will be equipped with an armamentarium of different agents which can be deployed in succession to treat patients with HER2 positive breast cancer with brain metastases. The days where local therapies such as WBRT are these patients' only option are over.

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