Primary systemic treatment of HER2-positive metastatic brain disease: profaning the sanctuary

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The incorporation of anti-HER2 therapies has significantly altered the natural history of HER2-positive breast cancer, converting them from an aggressive tumor subtype to one with improved prognostic outcome (1). However, at the same time, it has been reported an apparent increase in the incidence of central nervous system (CNS) metastases, that can be explained by several factors including; (I) an intrinsinc biological predisposition of HER2-positive tumors to metastasize to CNS (2), (II) the extended survival of patients receiving trastuzumab that may actually heighten the risk of brain metastasis (3,4), and (III) the fact that trastuzumab does not penetrate well the bood-brain barrier (BBB), leading CNS to behaves as a sanctuary site (5).

Management of metastatic CNS disease depends on location (brain and/or leptomeningeal), number and size of metastases, presence of extra-cerebral disease, and ECOG status. Good prognostic patients can be treated with local treatment (surgery or stereotactic radiosurgery [either alone or with whole-brain radiotherapy (WBRT)] while worse prognostic cases (poor performance status or diffuse brain metastases) are treated with WBRT or just supportive care (6). In addition to radiotherapy, a key component in the management of CNS disease from HER2-positive breast cancer is the use of an adequate systemic treatment. Studies have shown that patients with HER2-positive brain metastases have improved outcome than other breast cancer subtypes (7), and that trastuzumab therapy, after brain metastases, improves survival compared with patients who have not received trastuzumab (1). This extended survival has led to a growing porportion of patients to die as a result of uncontrolled CNS progression, often at a time when their extra-CNS disease is under control. At the same time, patients surviving longer are at risk of experiencing delayed side-effects of radiotherapy (8,9).

The Landscape study, recently published in *Lancet Oncology* by Bachelot and collegues (10), offers a novel an interesting approach in the management of brain metastases from HER2-positive breast cancer. This is a phase II single arm study, that investigates the combination of lapatinib + capecitabine as first line treatment of previously untreated brain metastasis from HER2-positive breast cancer. The primary end-point of the study was CNS volumetric response by magnetic resonance. In this terms, capecitabine + lapatinib was shown to be very active and safe; 29 out of 44 patients (65%) achieved a reduction greater than 50% and only 6 evaluable patients (14%) had progressive disease, 1 extracranial progression and 5 CNS progression. Nearly half of the patients had at least one grade 3 or grade 4 adverse event, and dose reductions of lapatinib and capecitabine were necessary in 36% and 58% of patients, respectively. The median time to progression was 5.5 months (95% CI, 4.3-6.0 months). The authors report that at the time of the analysis, 36 (82%) patients had received radiotherapy to the brain, with median time to radiotherapy of 8.3 months (95% CI, 5.4-9.1 months).

The results of Landscape are consistent with previous studies showing that lapatinib + capecitabine is an active regimen after cranial RT progression. In this setting CNS overall response are about 20-38% and median time to progression 3 to 5 months (11-13). In previously untreated brain metastases, WBRT alone has a 2 dimensions overall response of 27% (14) and when combined with trastuzumab

or lapatinib in HER-2 positive disease, the volumetric CNS response reported are 83% and 74% respectively (15,16).

Landscape is the first study that evaluates capecitabine + laptinib as primary treatment of brain metastases. The response rates of the combination are surprisingly high, taking into account the absence of WBRT that is thought to disrupt the BBB increasing its permeability to systemic therapies (17). Landscape results challenges the timing of radiotherapy in the management of brain metastases from HER-2 positive breast cancer. Upfront treatment with capecitabine + lapatinib has the advantage of providing an adecuate therapy for both, systemic and CNS diseases, and could help to delay the need of WBRT and therefore its neurological side effects.

It is possible that these excellent results could be explained, in part, by the good prognognis chracterisitics of the study population: most patients (96%) have an ECOG 0-1, 19 (43%) patients had asymptomatic brain metastases, and all patients had a good Graded Prognostic Assessment score. In addition, patients included were less pretreated than usual, 30% hadn't received any treatment in the metastatic setting, and 47% have just received one previous line of treatment. Another issue is that patients included had a median number of brain metastases of 3 [1-25], which suggests that maybe some of them could have been treated with surgery or radiosurgery according to NCCN guidelines. All these facts make Landscape findings to be taken with caution; it is uncertain if capecitabine + lapatinib would be as effective in a general population of patients with multiple symptomatic brain metastases and a more resistant systemic disease.

Specific goals of treatment for patients with brain metastases should include to improve/maintain quality of life, by relieving symptoms, preventing symptomatic progression, minimizing treatment related toxicity and, when possible, to prolong survival. Although further evaluation in a phase III trial (with special attention to quality of life items) is needed, combined lapatinib and capecitabine certainly seems a valid treatment option that could replace in a near future WBRT as upfront treatment of difuse HER2-positive brain metastases.

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