

Lapatinib as a therapeutic option in brain metastases from HER2+ breast cancer

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The treatment of brain metastases is one of the most challenging management issues in solid tumor oncology. In addition to the well-recognized problem with the adequacy of drug delivery to the central nervous system, even moderate increases in tumor size in this closed space can result in devastating symptoms and substantially shorten survival.

The major treatment modality for brain metastasis from solid tumors has been external beam radiation, although in some circumstances (e.g., single metastatic lesion in a patient with a good performance status) surgical resection is a reasonable option or even the favored strategy. Unfortunately, while radiation is frequently quite effective in providing short-term palliation of distressing symptoms, the modality can also result in neuro-cognitive dysfunction. In addition, the benefits from central nervous system radiation are generally only modest in duration with most patients progressing after a fairly limited period of stabilization of the disease process.

The development of brain metastases in patients with advanced breast cancer is a relatively common event. In particular, as many as one-half of women with HER2 positive metastatic disease will be found to have developed brain metastases during the course of their illness.

It is uncertain whether this high substantial risk of metastatic disease in the brain is due to the relative lack of activity of the available anti-neoplastic agents against breast cancer within the brain (including cytotoxic chemotherapy and trastuzumab), the relatively poor penetration of such agents into brain tissue, or may actually be somewhat of an artifact of the longer survival being experienced by patients due to the increasing effectiveness of therapy in non-brain sites. As a result, patients with HER2 positive metastatic

breast cancer will have a greater opportunity to develop both symptomatic and asymptomatic brain metastases.

Limited prior experience had revealed modest activity for lapatinib against metastatic breast cancer within the brain in a setting where radiation had been previously delivered to this site. These data led to the initiation of a prospective phase 2 trial examining the combination of lapatinib with capecitabine in patients with HER2 positive breast cancer metastatic to the brain where brain radiation had not been previously delivered (1).

Patients received lapatinib (1,250 mg daily) and capecitabine (2,000 mg/m² day 1-14 in a 21 day cycle). An objective response was defined as at least a 50% reduction in the total volume of the central nervous system metastatic lesions. To be declared a response, steroid use was not permitted and there could be no deterioration in the neurological status. Further, the response had to last at least 4 weeks and there could be no evidence of progression outside the central nervous system.

A total of 44 patients were eligible for an evaluation of response to this treatment regimen, of which 66% (29 patients) achieved a partial response (no complete response observed). Overall, 84% of the patient population exhibited some reduction in their tumor volume within the brain compared to the baseline determination.

The median follow-up in this patient population was 21 months. The median time to disease progression for the entire population was 5.5 months, with the time to progression in the responding population (median: 6 months) being superior to the group who failed to respond (median: 2.8 months). As anticipated, the most common site of initial progression was the central nervous system (78% of

patients). The median survival for the treated population was 17 months, with 91% of patients surviving for at least 6 months. Finally, the median time to subsequent radiation was 8.3 months, with the majority of patients (82%) ultimately requiring brain radiation.

Side effects were common with this therapeutic program, particularly diarrhea and the “hand-foot syndrome”. Approximately one-third of the treated population experienced at least one serious adverse event. Fortunately, there were no deaths felt to be caused by the program of lapatinib and capecitabine.

As this was a non-randomized phase 2 trial it remains uncertain if the activity observed in this trial is superior to what would have been achieved if these patients had been treated with primary whole brain radiation, perhaps with the addition of chemotherapy or lapatinib. However, it is certainly fair to label these results as being quite interesting in that more than one-half of the treated population appeared to exhibit an element of genuine clinical benefit. In addition, the data certainly support the hypothesis

that the anti-cancer drug therapy achieved sufficient concentrations within the central nervous system to produce both a biologic and clinical effect.

A phase 3 trial is planned, comparing this strategy to whole brain radiation therapy, which will hopefully provide a definitive answer regarding the role of lapatinib as a primary strategy for the management of metastatic HER2 positive breast cancer within the brain.

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References

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