

Lapatinib? or Radiotherapy? In Cranial Metastasis of Breast Cancer

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Dear Editor,

During the last two decades, significant advances in molecular oncology have led to the introduction of targeted therapies into clinical use. Many drugs that are being used in targeted therapy interfere with the proliferation of tumor cells by interacting with cell receptors and intracellular signaling molecules. Monoclonal antibodies and oral small molecule kinase inhibitors, which have recently been used in cancer treatment, are molecular agents that have been developed with the understanding of specific signaling pathways (1-3).

Lapatinib ditosylate (Tykerb[®], GW 572016) is a tyrosine kinase inhibitor that acts reversibly to human epidermal growth factor receptor 1 (EGFR/HER1) and human epidermal growth factor receptor 2 (HER2/ErbB2) tyrosine kinase by inhibiting the phosphorylation and activation of the receptor. Inhibition of phosphorylation and activation of the receptor results in inhibition of the PI3K/Akt and MAPK pathways activated by HER2, thereby stopping cellular growth and proliferation, resulting in increased apoptosis. Lapatinib's activity against several types of tumors were investigated in phase trials and their effect was tested especially in breast cancer. It has been approved for use in patients with HER2-positive metastatic breast cancer after progressive, regimens including taxanes, anthracyclines and trastuzumab. With the introduction of this drug, it has been possible to prolong survival in the treatment of metastases in HER2 positive breast cancer and in adjuvant therapy. Although it was moderately effective as monotherapy in first-line treatment in metastatic breast cancer, its main effect was obtained by its combination with cytotoxic agents. Lapatinib is generally well tolerated and most of its side effects are mild (grade 1 or 2). Diarrhea, nausea, vomiting and cutaneous toxicity are frequently observed in the early stages of treatment (1-6).

Lapatinib crosses the blood-brain barrier due to its small molecule structure. Lapatinib has been shown to prevent the development of brain metastases in breast cancer when combined or alone. Cameron et al. (1) reported a lower incidence of brain metastasis in the lapatinib group in the phase III study in which lapatinib-capecitabine was compared with the combination of lapatinib-capecitabine in HER2 (+) metastatic breast cancer (2% in lapatinib-capecitabine arm, 6% in capecitabine arm, $p=0.045$). Lin et al. (3) looked at the efficacy of monotherapy lapatinib in patients who had previously been treated with trastuzumab and developed brain metastasis. A 20% response to brain metastases has been reported. Metro et al. (4) reported a 31.8% partial response with a combination of lapatinib - capecitabine and a stabilization of 27.3% in HER2 (+), metastatic breast cancer patients who had been treated with brain metastasis under the treatment of trastuzumab. The overall survival was 27.9 months in patients treated with lapatinib - capecitabine and 16.7 months in patients who were treated with trastuzumab alone ($p=0.01$) (4). These results led to the demonstration of the efficacy of lapatinib in breast cancer brain metastases and led scientists to compare other treatment options applied. Miller et al. (6) looked at the response in radiotherapy in patients with HER2/epidermal growth factor receptor tyrosine kinase inhibitor (TKI) and untreated breast cancer brain metastasis. The incidence of 12-month cumulative poor response decreased from 15.1% to 5.7% in patients with concurrent TKI with stereotactic radiosurgery ($p<.001$). In conclusion, in the HER2 positive patient group, radiosurgery with TKIs was suggested to prevent neurocognitive disorder and all brain radiotherapy should be considered in salvage treatment (6). Studies have shown that lapatinib treatment after whole brain radiation therapy can improve survival in patients with HER2-positive breast cancer with multiple brain metastasis with significant neurological symptoms (7). In another study, it has been suggested that lapatinib as a consecutive treatment because of the limited

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effect of cranial radiotherapy in patients with HER2 positive cranial metastases (8). In the phase II study of patients with brain metastasis, the efficacy of lapatinib monotherapy was evaluated in patients who had previously received local treatments such as trastuzumab or cranial radiotherapy. The partial response in 8% of the patients and the stable response in 16% of the patients indicated that the treatment alternative seemed to be an important option in a very limited group of patients. However, it has been reported that it can prolong survival by preventing the development of brain metastasis (5).

As a result, lapatinib is a double-acting selective inhibitor that inhibits signal transduction by inhibiting EGFR/HER1 and HER2/ErbB2 tyrosine kinase. In addition, the results of the treatment of brain metastases, which is an important problem in HER2 overexpressing breast cancers, are promising because of the first small molecule TKI that crosses the blood brain barrier. However, in order to achieve better control of cranial metastasis and a longer overall survival, new treatment strategies should be developed with radiotherapy. Studies on this subject are needed.

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