

Long-term Survival after Lapatinib Rechallenge in Isolated Brain Metastasis of HER2-positive Breast Cancer

HER2-pozitif Meme Kanserinin İzole Beyin Metastazında Yenilenen Lapatinib Kullanımı Sonrası Uzun Süreli Sağkalım

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ABSTRACT

Lapatinib is an effective drug in HER2-positive breast cancer. We present a case with successful treatment of lapatinib in brain metastasis of HER2+ breast cancer. Forty-eight years old woman was admitted our clinic with early breast cancer. In third years after adjuvant chemotherapy and trastuzumab, isolated and multiple brain metastasis were detected. After whole brain RT, lapatinib (with capecitabine for 10 months and with letrozole for 3 months) has been used. Volumetric reduction of lesions was achieved and symptoms disappeared. When lapatinib discontinued, brain metastasis relapses. Lapatinib plus capecitabine reinduction has been started. Totally, longer survival than 45 months was achieved after first brain metastasis detection. Because both combinations of lapatinib with capecitabine and letrozole were effective and reinduction treatment was successful, presented case has strongly supported activity of lapatinib treatment in brain metastasis of HER2+ breast cancer.

Keywords: Lapatinib rechallenge, isolated brain metastasis, HER2

ÖZ

Lapatinib HER2-pozitif meme kanserinin etkili bir ajandır. HER2-pozitif meme kanserinin beyin metastazında lapatinib ile başarılı tedavi sağlanan bir olgu sunulmaktadır. 48 yaşında kadın hasta erken evre meme kanseri tanısıyla kliniğimize kabul edildi. Adjuvan trastuzumab ve kemoterapi sonrası üçüncü yılda izole beyin metastazı saptandı. Tüm beyin radyoterapi sonrası lapatinib (10 ay kapesitabin ve 3 ay letrozol ile beraber) kullanıldı. Lezyonlarda volümetrik azalma görüldü. Lapatinib kesilince beyin metastazları nüksetti. Lapatinib ve kapesitabin reindüksiyonu başlandı. Toplamda beyin metastazının ilk tanısından sonra 45 ayın üzerinde bir sağkalım elde edildi. Lapatinibin hem kapesitabin hem de letrozol ile etkili olması ve reindüksiyon tedavisinin başarılı olması nedeniyle sunulan olgu lapatinibin HER2-pozitif meme kanserinin beyin metastazının tedavisindeki etkinliğini kuvvetle desteklemektedir.

Anahtar sözcükler: Yenilenen lapatinib kullanımı, izole beyin metastazı, HER2

Introduction

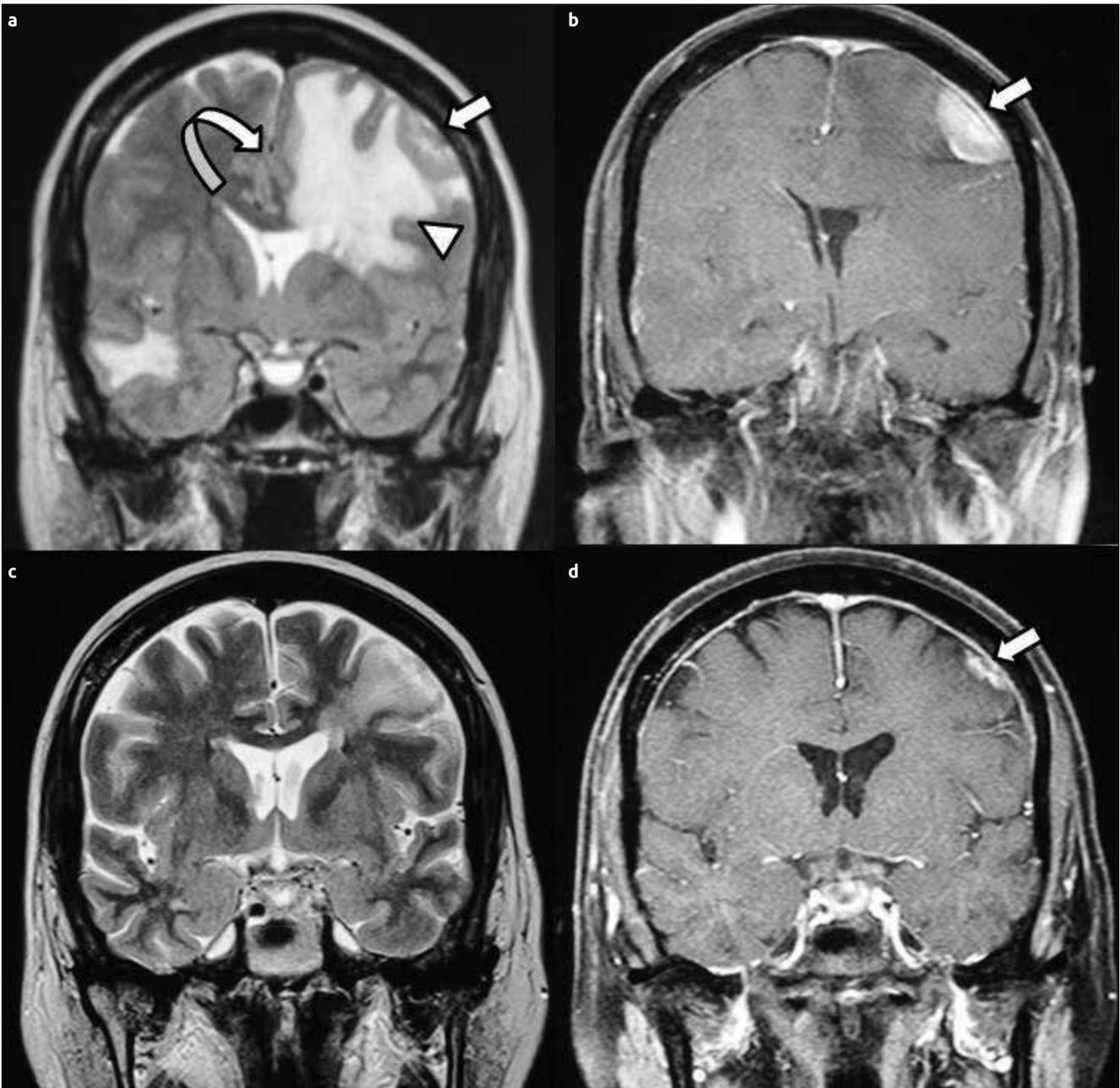
Metastasis to the central nervous system (CNS) is significant clinical situation of breast cancer. It is documented to occur in approximately 10%-16% of cases, and tend to occur in patients with larger tumors, aggressive histological subtypes, triple negative or HER2- positive tumors (1).

Brain metastasis of breast cancer is managed with local therapy, systemic therapy, and supportive therapy. Three local treatments are basically used, namely surgical resection, stereotactic radiotherapy (RT), and whole brain RT. The surgical resection is principle therapy. The stereotactic RT and/or whole brain RT may be replaced or added to surgery. Symptom control is important. It includes corticosteroid treatment of peritumoral edema and increased intracranial pressure, treatment and prevention of seizures and of venous thromboembolism.

The systemic therapy of breast cancer contains chemotherapy, hormonal therapy, and targeted therapy. Trastuzumab and lapatinib have been used for a long time in HER2+ breast cancer systemic treatment. Trastuzumab is very effective, but it cannot cross the blood-brain barrier. CNS metastases have been reported in 25%-50% in patients undergoing chemotherapy and trastuzumab (2). Lapatinib has been considered as effective treatment option in brain metastases from HER2-positive breast cancer (3, 4). We would like to also present a case strongly supported efficacy of lapatinib in brain metastasis of HER2+ breast cancer.

Case Presentation

Forty-eight years old woman was admitted our clinic with early breast cancer. Estrogen receptor was negative, progesterone receptor and HER2 were positive (>90 and (+++) respectively). Perimenopausal patient received adjuvant TAC (docetaxel, doxorubicin and cyclophosphamide) chemotherapy, adjuvant trastuzumab, adjuvant radiotherapy (RT) and tamoxifen. After 3 years, isolated and multiple brain metastasis were detected. T2-weighted MR images show dural metastases adjacent to the left frontal lobe and surrounding



Resim 1. a-d. Coronal T2-weighted MR image shows dural metastases (arrow) adjacent to the left frontal lobe and surrounding edema (arrow head). Note that the edema causes midline shift effect (curved arrow) (a). Contrast-enhanced coronal T1-weighted MR image shows homogeneously enhancing dural-based mass (arrow) (b). Coronal T2-weighted MR image obtained after radiotherapy and lapatinib based therapy show regression of the surrounding edema and normalization of the midline (c). Contrast-enhanced coronal T1-weighted MR image obtained after treatment shows regression in size of the dural-based mass (arrow) (d)

edema caused midline shift effect. Contrast-enhanced T1-weighted MR images showed homogeneously enhancing dural-based masses (Figure 1).

Whole brain RT was performed with a scheme of 36Gy, 300 cGy/ fx, 12 fx. Subsequently lapatinib plus capecitabine chemotherapy was started. After first course of therapy, symptoms disappeared. Because of hand and foot syndrome was occurred, dose of capecitabine was reduced by 20%, two weeks later.

Volumetric reduction of CNS lesions was achieved in interval radiologic evaluation. The T2-weighted MR images after the therapy showed regression of the surrounding edema and normalization of the

midline. Contrast-enhanced T1-weighted MR images showed regression in size of the dural-based masses (Figure 1).

In tenth month, complaints of hand and foot syndrome have intensified again. The treatment was switched to lapatinib plus letrozole for three months. The patient had been asymptomatic for thirteen months. She was feeling so good, but wanted to stop the therapy. Therefore, treatment was continued with letrozole alone.

In ninth month after stopping of lapatinib, symptomatic (convulsion and dizziness) new brain metastasis were detected. The radiosurgery treatment with Cyberknife (20 Gy/2fx) was performed. The reinduction with lapatinib plus capecitabine was started. The patient

has been symptomless and steroid free for two years with lapatinib reinduction.

Achieved survival was longer than 45 months after the diagnosis for brain metastasis, although lapatinib treatment has been interrupted. She is still asymptomatic and progression free.

Discussion and Conclusion

Brain metastasis of breast cancer has worst outcome. It occurs more often in the patients with HER2+ tumors than with hormone positive tumors (5). HER2+ tumors treated with trastuzumab based therapy have been associated with an increased risk of brain metastasis (6). Trastuzumab related increasing survival might allow occurrence of brain metastasis. Approximately half of the patients with HER2+ metastatic breast cancer die from CNS metastasis (7).

Lapatinib is a potent reversible and selective inhibitor of the tyrosine kinase domains of epidermal growth factor receptor and human epidermal growth factor receptor (HER)-2. It binds to the intracellular ATP-binding site of the receptor. This binding leads to blockage of mitogen-activated protein kinase (MAP kinase) and phosphatidylinositol 3-kinase (PI3K), Akt, and mammalian target of rapamycin (mTOR) dependent transduction pathways. Therefore, it causes growth arrest and induces apoptosis of tumor cells. Unlike trastuzumab, lapatinib can bind and inhibit p95HER-2. p95HER-2 is the truncated form of HER-2, has not an extracellular domain but possessing greater kinase activity than wild-type HER-2.

It is known that lapatinib can cross the blood-brain barrier. It is extensively used for treatment of metastatic HER2+ breast cancer. The addition of lapatinib to capecitabine resulted in an improvement survival of metastatic HER2+ breast cancer in phase 3 study. In retrospective exploratory analysis of this study, lower number of CNS metastases at first event have been reported in the patients received lapatinib plus capecitabine (8).

There are currently no studies as a head-on-head comparison of lapatinib based therapy with trastuzumab in this situation, but studies about efficacy of lapatinib have been investigated in CNS metastases of HER2-positive breast cancer. Iwata H et al. reported a subset analysis of a phase II study of lapatinib (4). Of six patients, two patients had shown volumetric reduction >20 % in their CNS lesions, one of whom had >50 % reduction. Three patients, including two of these patients, had shown >20 % volumetric reduction in non-CNS lesions.

A multicentric phase 2 study evaluated the CNS activity of lapatinib (9). CNS objective responses to lapatinib were observed in 6% of 242 patients. In 21% of patients, 20% and more volumetric reduction was detected. It was associated with improvement of progression-free survival. These results suggested the modest CNS activity of lapatinib.

The LANDSCAPE phase 2 study investigated lapatinib plus capecitabine for previously untreated brain metastases from HER2+ breast cancer (3). 38 out of 45 enrolled patients had extra-CNS metastases at baseline. Of forty-two evaluable patients, 2 patients had a complete response, 22 patients had a partial response, and 15 patients had stable disease for CNS lesions. Only 7% of patients had progressive disease. Median time to CNS progression was 5.5 months. Median overall survival was 17 months.

Herein, our presented case has long time survival more than 45 months after first detection of brain metastasis. In pre-lapatinib era,

median survival was 13 months in breast cancer patients with brain metastasis as a first recurrence site and 24 months in patients achieved complete response (10). Because both combinations of lapatinib with capecitabine and letrozole were effective and reinduction treatment was successful, presented case has strongly supported activity of lapatinib treatment in brain metastasis of HER2+ breast cancer.

Lapatinib might be considered as a good option in treatment of brain metastasis from HER2+ breast cancer until reports of new efficient therapy options (pertuzumab, TDM1 etc.).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.K.; Design - A.Ö., L.E.; Supervision - O.B., B.K.; Funding - S.Ç., K.K.; Materials - L.E., T.T.; Data Collection and/or Processing - L.E., T.T.; Analysis and/or Interpretation - A.Ö., L.E.; Literature Review - A.Ö., L.E., S.Ç.; Writer - B.K., A.Ö.; Critical Review - B.K., O.B.

Financial Disclosure: The authors declared that this study has received no financial support.

Conflict of Interest: No conflict of interest was declared by the authors.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - B.K.; Tasarım - A.Ö., L.E.; Denetleme - O.B., B.K.; Kaynaklar - S.Ç., K.K.; Malzemeler - L.E., T.T.; Veri toplanması ve/veya işlemesi - L.E., T.T.; Analiz ve/veya yorum - A.Ö., L.E.; Literatür taraması - A.Ö., L.E., S.Ç.; Yazıyı yazan - B.K., A.Ö.; Eleştirel İnceleme - B.K., O.B.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

References

1. Dawood S, Gonzalez-Angulo AM. Progress in the biological understanding and management of breast cancer-associated central nervous system metastases. *Oncologist* 2013; 18:675-684. (PMID: 23740934) [\[CrossRef\]](#)
2. Gori S, Rimondini S, De Angelis V, Colozza M, Bisagni G, Moretti G, Sidoni A, Basurto C, Aristei C, Anastasi P, Crino L. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: incidence, survival, and risk factors. *Oncologist* 2007; 12:766-773. (PMID: 17673608) [\[CrossRef\]](#)
3. Bachelot T, Romieu G, Campone M, Dieras V, Cropet C, Dalenc F, Jimenez M, Le RE, Pierga JY, Goncalves A, Leheurteur M, Domont J, Gutierrez M, Cure H, Ferrero JM, Labbe-Devilliers C. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol* 2012; 14:64-71. (PMID: 23122784) [\[CrossRef\]](#)
4. Iwata H, Narabayashi M, Ito Y, Saji S, Fujiwara Y, Usami S, Katsura K, Sasaki Y. A phase II study of lapatinib for brain metastases in patients with HER2-overexpressing breast cancer following trastuzumab based systemic therapy and cranial radiotherapy: subset analysis of Japanese patients. *Int J Clin Oncol* 2012; 18:621-8. (PMID: 23011099) [\[CrossRef\]](#)

5. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. *J Clin Oncol* 2009; 27:5278-5286. (PMID:19770385) [\[CrossRef\]](#)
6. Musolino A, Cicolallo L, Panebianco M, Fontana E, Zannoni D, Bozzetti C, Michiara M, Silini EM, Ardizzoni A. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. *Cancer* 2011; 117:1837-1846. (PMID: 21509760) [\[CrossRef\]](#)
7. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R, Winer E. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer* 2003; 97:2972-2977. (PMID:12784331) [\[CrossRef\]](#)
8. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, Jagiello-Gruszfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; 355:2733-2743. (PMID: 17192538) [\[CrossRef\]](#)
9. Lin NU, Dieras V, Paul D, Lossignol D, Christodoulou C, Stemmler HJ, Roche H, Liu MC, Greil R, Ciruelos E, Loibl S, Gori S, Wardley A, Yardley D, Brufsky A, Blum JL, Rubin SD, Dharan B, Steplewski K, Zembryki D, Oliva C, Roychowdhury D, Paoletti P, Winer EP. Multi-center phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; 15:1452-1459. (PMID: 19228746) [\[CrossRef\]](#)
10. Saip P, Cicin I, Eralp Y, Kucucuk S, Tuzlali S, Karagol H, Aslay I, Topuz E. Factors affecting the prognosis of breast cancer patients with brain metastases. *Breast* 2008; 17:451-458. (PMID: 18455400)