

Long-term Survival after Cerebellar Metastasis Resection from Her2 3+ Locally Advanced Breast Cancer

Zorica I Tomasevic,¹ Zoran M Tomasevic,¹ Zeljko Kovac,² Zorka Milovanovic,³ Dana Grujicic⁴ and Radan Dzodic⁵

1. Medical Oncologist, Institute for Oncology and Radiology of Serbia, Daily Chemotherapy Hospital, Belgrade, Serbia; 2. Radiotherapist, Department of Radiotherapy, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; 3. Director of Pathology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; 4. Professor of Neurosurgery, Medicine Faculty, Belgrade University, and Head of Neuro-Oncology Department, Institute for Neurosurgery, Serbian Clinical Center, Belgrade, Serbia; 5. Professor of Surgery, Medicine Faculty, Belgrade University and Director of Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Abstract

We present a patient who first developed a distant metastatic site in the cerebellum during treatment for Her2 3+ locally advanced breast cancer (LABC). LABC was in complete remission at that time and isolated cerebellar metastasis was resected. The patient is still alive more than 135 months after LABC diagnosis, and more than 99 months after neurosurgery, and is still receiving trastuzumab without further progression or any toxicity. To the best of our knowledge, this is first report of such exceptional disease course for a patient with a predicted grave prognosis according to all prognostic parameters.

Keywords

Breast cancer brain metastases, cerebellar metastases, locally advanced Her2 3+ breast cancer, long-term survival

Disclosure: Zorica I Tomasevic, Zoran M Tomasevic, Zeljko Kovac, Zorka Milovanovic, Dana Grujicic and Radan Dzodica have no conflicts of interest to declare. No funding was received in the publication of this article.

Compliance with Ethics Guidelines: All procedures were followed in accordance with the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and subsequent revisions, and informed consent was received from the patient involved in the study.

Open Access: This article is published under the Creative Commons Attribution Noncommercial License, which permits any non-commercial use, distribution, adaptation and reproduction provided the original author(s) and source are given appropriate credit.

Received: 15 April 2015 **Accepted:** 28 April 2015 **Citation:** *European Oncology & Haematology*, 2015;11(1):36–8 DOI: 10.17925/EOH.2015.11.01.36

Correspondence: Zorica I Tomasevic, Director of Daily Chemotherapy Hospital, Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Serbia. E: zoricant@ncrc.ac.rs; zoricant@gmail.com

Breast cancer brain metastases (BCBM) represent a devastating event with limited survival upon diagnosis of approximately 6 months. Incidence of symptomatic BCBM ranges from 10 to 46 % during metastatic BC course and in 3–6 % of patients who are treated for early BC.^{1–7} Although BM cannot be predicted, risk varies according to BC molecular subtype and is highest for triple negative and Her2+ BC.^{2,5,8–10}

However, there are reports suggesting more favourable prognosis for patients with Her2 3+ BM than for patients with other BC subtypes, but only if trastuzumab is continued beyond BM diagnosis and if there is no progression in other metastatic sites.^{11–13} In a large study with 598 patients with BCBM, survival of patients who continued with trastuzumab after BM diagnosis was a median 11.6 months compared with a median 6.1 months if trastuzumab was not continued and a median 6.3 months for patients with Her2- BC.¹¹

Whether that favourable outcome can also be applied for Her2 3+ cerebellar metastases has not been widely explored because of their rarity.

According to our previous research, Her2 3+ BC seemingly has a special predilection to the cerebellum compared with other BC molecular types.¹⁴

Here, we present a patient with Her2 3+ locally advanced breast cancer (LABC) and first distant metastatic site in cerebellum. LABC was in

complete remission at that time and isolated cerebellar metastasis was resected. The patient is alive for more than 135 months after LABC diagnosis, and more than 99 months after neurosurgery, and continues to receive trastuzumab without further progression or any toxicity.

Case Report

In January 2004, a 43-year-old pre-menopausal patient noticed a lump in the left breast. Mammography confirmed 6 x 7 cm tumour at the outer upper quadrant of the left breast. Clinically, the tumour was locally advanced with axillary involvement and small supraclavicular lymph node. Symptoms suggestive of metastatic disease were absent, all imaging were negative (chest/bones radiography, abdomen ultrasonography); therefore, the initial stage was determined as T3, N3, M0.

Tumour of the left breast was histologically confirmed as ductal invasive carcinoma grade 2. Also, biopsy of the supraclavicular node confirmed breast cancer metastases.

Immunohistochemistry performed on the primary BC confirmed Her2 3+ (≥30 % of cells), low oestrogen receptor (OR score 2; quick score 0–8) and negative progesterone receptor (PR score 0; quick score 0–8).

Treatment was initiated with FAC (5-fluorouracil/adriablastin/cyclophosphamide) as neo-adjuvant chemotherapy. After four cycles,

partial regression was achieved and the patient underwent irradiation of the left breast and regional nodes, according to standard treatment for LABC at that time. After irradiation, treatment was continued with four more cycles of FAC. Complete response was achieved in the breast, axillary and supraclavicle node, chemotherapy was stopped and treatment was continued with tamoxifen. Two months after tamoxifen initiation (in March 2005), local relapse was confirmed by extirpation of 6 mm skin nodule from the skin of the left breast. Histopathology confirmed BC metastasis with lymphangiosis. No other metastatic sites were detected, skin lesion was completely extirpated, breast re-irradiation was conducted and systemic treatment continued with paclitaxel (80 mg/m²) plus trastuzumab (2 mg/kg) in a weekly regimen. After 18 weekly doses of paclitaxel, chemotherapy was stopped and standard dose trastuzumab was continued in a 3-week regimen.

In December 2006, the patient complained of discrete gait disturbance and occasional mild headache, without nausea, vomiting or any other symptom. Brain magnetic resonance imaging (MRI) revealed solitary cerebellar lesion of approximately 25 mm (see *Figure 1*).

The patient was referred to neurosurgery and the metastasis was completely removed without any intra- or post-operative complication. Histology of the BM was identical to primary BC with almost the same molecular characteristics (Her2 3+ in 100 % of cells; OR score 0, PR score 0). Complete evaluation was performed, no other metastatic sites were detected and treatment continued with post-operative whole brain irradiation (WBRT), completed at the end of January 2007. Systemic treatment was continued with thrice-weekly trastuzumab. The first trastuzumab dose was a loading 8 mg/kg and other doses were 6 mg/kg.

Treatment with trastuzumab has been ongoing for 10 years (142 cycles), the patient is still metastases free, more than 8 years after cerebellar BM removal and more than 11 years after Her2 3+, OR weekly positive/PR negative LABC diagnosis.

Regular follow up consists of physical examination before each trastuzumab cycle, brain MRI in 6-month intervals and mammography and chest/ bone radiography annually. Until now (April 2015), no relapse in the brain or any other sites has been detected.

All procedures were followed in accordance with the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and subsequent revisions, and informed consent was received from the patient involved in the study.

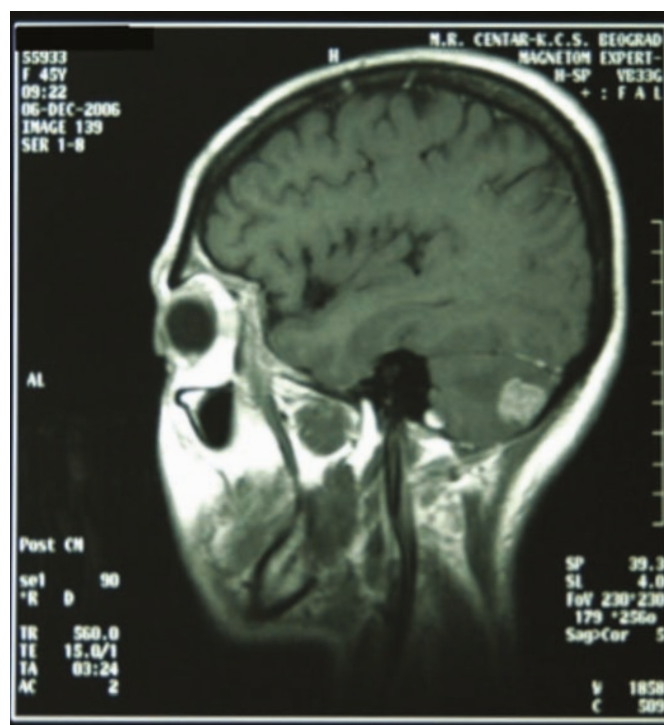
Discussion

The prognosis of patients with BM is always considered to be the worst compared with other metastatic sites, with median survival of approximately 6 months, 1-year survival rate of approximately 20 % and 2-year survival rate less than 2 %.^{15,16}

However, in the last decade it has been recognised that BC molecular characteristics, which reflects tumour biology and selects for targeted treatment, significantly influence prognosis upon BM development. Her2 3+ BC became more treatable once trastuzumab became available and improved prognosis is also associated with BM, with longer median survival compared with Her2- BMs.¹¹⁻¹³

Incidence of BC cerebellar metastases is low, and incidence of cerebellar metastases according to BC molecular subtype has not been

Figure 1: Magnetic Resonance Imaging Solitary Brain Metastasis in the Left Cerebellar Hemisphere



Cerebellar metastasis developed during trastuzumab treatment as the only site of progression.

widely explored. Therefore, whether the same favourable outcome can be achieved for Her2 3+ cerebellar metastases is actually unknown.

According to a publication from 1987, approximately 10–15 % of all BC metastasise to the cerebellum.¹⁷ However, details about patient characteristics, time to metastases development or molecular subtypes of BC that metastasise to this part of brain were not available at that time.

In a large study of 420 patients with BCBM, survival after BM was in a range of 7 to 95.9 months, median 6.8.¹⁸ Eighteen patients (4.2 %) survived for at least 60 months after BM diagnosis, but more detailed characterisation of this particularly interesting subgroup was not provided. Also, details about metastases localisation within the brain in long-term survivors were not provided and the incidence of cerebellar metastases is unknown.

In another publication, 83 patients with BCBM were presented with a special focus on survival according to Her2 3+ status.¹⁹ The authors concluded that Her2 3+ status, confirmed in 36 % of patients, was a strong positive predictor for survival after brain metastasis diagnosis. Median survival in that subgroup was 17.1 months compared with 5.2 months in the Her2- subgroup. Cerebellar metastases as isolated BM were recorded in 13 % of patients, while cerebellar combined with supratentorial metastases were found in an additional 45 % of patients. The authors noticed that cerebellar metastases were slightly more common in Her2 3+ than in Her2- patients, but without statistical significance.

Why some BCBM colonise only the cerebellum, without spreading to the other brain sites, is unknown. Also it is not known whether brain metastasis localisation only in the cerebellum carries a different prognosis compared with brain metastasis localisation in other brain regions.

Our previous results suggests that Her2 3+ BC seems to have a predilection to the cerebellum, hence 72.2 % of patients with cerebellar metastases had Her2 3+ BC.¹⁴ Interestingly none of the patients with cerebellar metastases had triple negative BC. Median survival of patients with cerebellar metastases was 13 months (range 2 to >99). However, the patient discussed in this case report is alive more than 8 years after the cerebellar metastasis was removed, and is still receiving trastuzumab without further brain relapse or progression in any other site.

By all means, this particular patient had negative prognostic factors from the beginning: Her2 3+ LABC, low oestrogen levels, early local relapse with lymphangiosis and, finally, cerebellar metastasis. Trastuzumab was ongoing for LABC at the time of cerebellar metastases development. Hence, LABC

was in complete remission and cerebellar metastasis was completely resected, trastuzumab was continued. Despite treatment being optimal, favourable disease course might not be related to treatment only. It could be speculated that this particular patient might possess some characteristics/properties important for such a favourable outcome. However, there are no specific tests that could be recommended to explore this theory.

Still, we are confident that presentation of this case contributes to the knowledge about BC cerebellar metastases. An international database along with a tumour bank for primary BC and resected metastases, whenever available, is probably the best way to gather information about such exceptionally rare patients who successfully resist a grave prognosis. ■

1. Lassman A, DeAngelis L, Brain metastases, *Neurol Clin*, 2003;21:1–23.
2. Bendell JC, Domchek SM, Burstein HJ, et al., Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma, *Cancer*, 2003;97:2972–7.
3. Shmuel E, Wigler N, Inbar M., Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment, *Eur J Cancer*, 2004;40:379–82.
4. Lower EE, Drosick DR, Blau R, et al., Increased rate of brain metastases with trastuzumab therapy does not associated with impaired survival, *Clin Breast Cancer*, 2003;4:114–9.
5. Clayton AJ, Danson S, Jolly S, et al., Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer, *Br J Cancer*, 2004;91:639–43.
6. Lin NU, Winer EP, Brain Metastases: The HER2 Paradigm, *Clin Cancer Res*, 2007;13:1648.
7. Lin NU, Bellon J, Winer E, CNS metastases in breast cancer, *J Clin Oncol*, 2004;22:3608–17.
8. Dawood S, Broglio K, Esteva FJ, et al., Survival among women with triple receptor-negative breast cancer and brain metastases, *Ann Oncol*, 2009;20:621–7.
9. Heitz F, Harter P, Traut A, et al., Cerebral metastases (CM) in breast cancer (BC) with focus on triple-negative tumors, *J Clin Oncol*, 2008;26:Abstract 1010.
10. Lin NU, Claus E, Sohl J, et al., Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases, *Cancer*, 2008;113:2638–45.
11. Dawood S, Broglio K, Esteva FJ, et al., Defining prognosis for women with breast cancer and CNS metastases by HER2 status, *Ann Oncol*, 2008;19:1242–8.
12. Clayton AJ, Danson S, Jolly S, et al., Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer, *Br J Cancer*, 2004;91:639–43.
13. Bendell JC, Domchek SM, Burstein HJ, et al., Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma, *Cancer*, 2003;97:2972–7.
14. Tomasevic Z, Tomasevic MZ, Kovac Z, et al., Breast cancer metastases to cerebellum, *J Clin Oncol*, 32, 2014;32(Suppl. 1):Abstract e11600.
15. DiStefano A, Yong Yap Y, Hortobagyi GN, et al., The natural history of breast cancer patients with brain metastases, *Cancer*, 1979;44:1913–8.
16. Zimm S, Wampler GL, Stablein D, et al., Intracerebral metastases in solid tumor patients: natural history and results of treatment, *Cancer*, 1981;48:384–94.
17. Fadul C, Misulis KE, Wiley RG, Cerebellar Metastases: Diagnostic and Management Considerations, *J Clin Oncol*, 1987;5:1107–15.
18. Altundag K, Bondy ML, Mirza QM, et al., Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis, *Cancer*, 2007;110:2640–7.
19. Eichler AF, Kuter I, Ryan P, et al., Survival in patients with brain metastases from breast cancer, the importance of HER-2 status, *Cancer*, 2008;112:2359–67.