[ISSN:2582-3663]

Canadian Journal of Biomedical Research and Technology

Can J Biomed Res & Tech

November 2020 Vol:3, Issue:4

Therapeutic Effect After Radiotherapy And Targeted Therapy For Leptomeningeal Metastases From HER 2 Positive Invasive Ductal Breast Carcinoma

Open Access **Case Report**

Lena Marinova[1*], Radoslav Georgiev[2]

[1]Department of Radiotherapy, Oncology Hospital, Russe, Bulgaria
[2]Department of Imaging, Radiation therapy and Nuclear medicine Medical University, Varna, Bulgaria

***Address for Correspondence**

Lena Mainova, Department of Radiotherapy, Oncology Hospital, Russe, Bulgaria

Submission: October 28, 2020
Published: November 09, 2020

Abstract

Summary

Leptomeningeal disease (LMD), also known as leptomeningeal carcinomatosis, is a rare solid cancer complication, in which malignant cells infiltrate the layers of the central nervous system (CNS), known as meninges. The presented clinical case is in a woman with HER 2 positive invasive breast cancer with manifestation of late leptomeningeal metastases, 10 years after long-term complex treatment. Whole-brain radiotherapy (WBRT) and CNS boost-RT of a linear accelerator with the Volume Modulated Arc Therapy (VMAT) method was conducted. During the radiotherapy, the patient continued her treatment with Kadcyla (transtuzumab emtansine) at a therapeutic dose of 3.6 mg/kg body weight, administered as an intravenous infusion every 3 weeks (21-day cycle). In this article, we present the significant reduction of CNS leptomeningeal metastatic cells in HER 2 positive breast cancer (BC) after whole-brain radiotherapy (WBRT) followed by boost-RT combined with Kadcyla targeted therapy (TT). For the first time in the world medical literature in English, MRI imaging presents the significant effect on leptomeningeal cells from BC, 4 months after WBRT combined with Herceptin and 3 months after self-conducted targeted therapy. In breast cancer LMD through the above RT combined with targeted therapy we achieved six months of asymptomatic survival with a very good quality of life.

Keywords:

Leptomeningeal disease, breast cancer, whole-brain radiotherapy, MRI imaging, targeted therapy, complex treatment

Introduction

Central nervous system (CNS) metastasis occur somewhat commonly in breast cancer (BC), and may present long after treatment of the primary cancer *[1]*. In BC, aggressive chemotherapy (Ch) has resulted in improved outcomes for individuals with advanced disease *[2]*. The majority of CNS metastasis is due to parenchymal brain metastases (BM), with leptomeningeal metastatic disease (LMD) comprising a much smaller number *[3]*. LMD is common in lung, breast, and renal cell cancers and melanomas, and is one of the most devastating metastatic disease scenarios *[4]*. There is currently no generally accepted standard of care in the treatment of breast cancer LMD *[3]*. In this article we present the treatment results after whole-brain radiotherapy (WBRT) combined with targeted therapy (TD) in leptomeningeal metastatic disease of HER 2 positive invasive ductal BC.

Clinical Case

It concerns a female patient of 48 years of age diagnosed with a 10-year-old invasive intraductal carcinoma of the right mammary gland/pT2N0M0, G2, positive estrogen and progesterone receptors, HER2/+++. Estrogen receptor (ER) and human epidermal growth factor receptor-2 (HER2) status were determined based on primary breast tumor samples; patients with $\geq 1\%$ of nuclear immunohistochemistry staining were considered ER positive and HER2 status was defined according to current American Society of Clinical Oncology criteria *[5]*. Surgery (quadrantectomy with axillary dissection), adjuvant chemotherapy (Ch), radiotherapy (RT) of right breast with operative scarring to total dose (TD) 50 Gy, endocrine therapy (ETh), targeted therapy (TT) with Herceptin was conducted. Two years after the diagnosis et treatment, local relapse is manifested, surgically removed by a simple mastectomy with subsequent systemic chemotherapy (SCh), Herceptin and ETh. In the next 8 years, a consistent solitary liver and pulmonary metastases are diagnosed and surgically removed. The patient continues SCh and TT. On the occasion of an epileptic seizure, after the CT of the brain with venous contrast, the infratentorial metastases in the cerebrum are established. In April 2020, MRI of the neuroaxis revealed leptomeningeal brain metastases, mainly infratentorial in the cerebellum and medulla oblongata, with mild compression of the brainstem. The spinal axis has no visible pathological changes *(Fig.1, Fig.2)*.

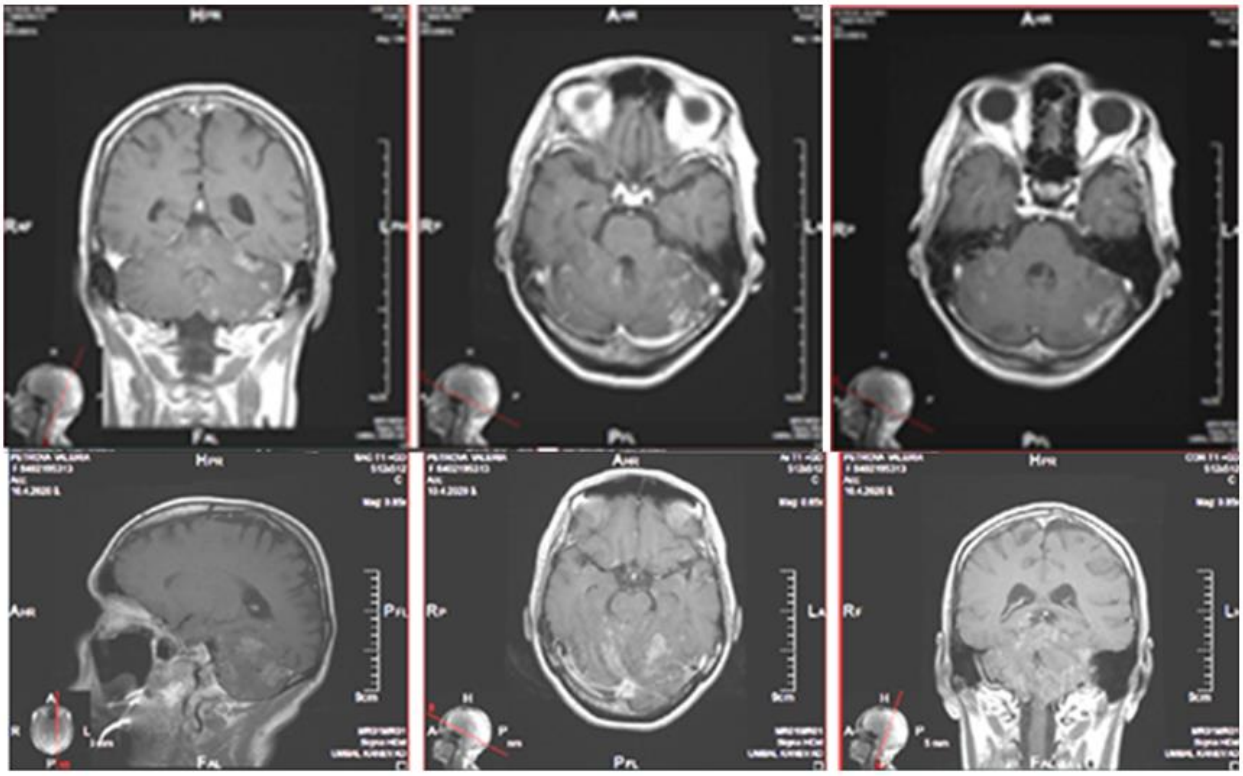

Figure 1: SAG T1 FLAIR+C, AX T1 FLAIR+C, COR T1 FLAIR+C MR postcontrast images showing hyperintense contrast-enhancing leptomeningeal brain lesions, mainly infratentorial in the cerebellum and medulla oblongata, with mild compression of the brainstem.

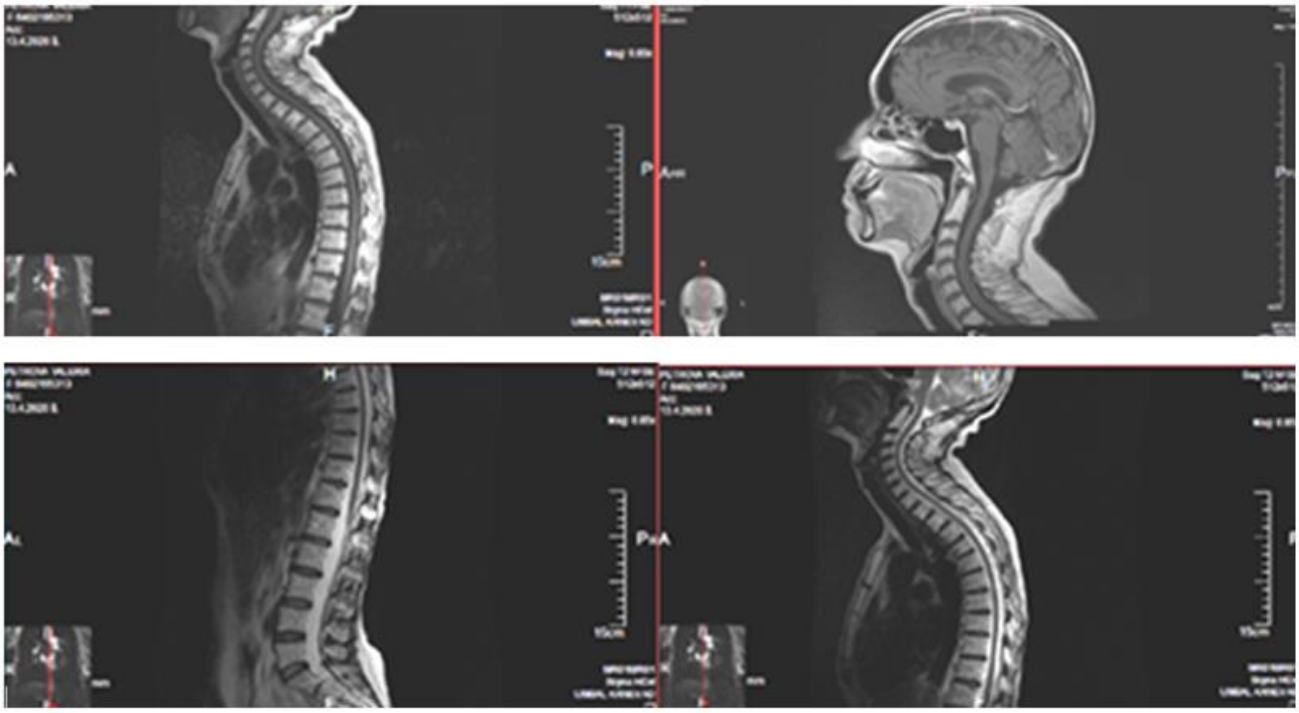

Figure 2: SAG T2 and SAG T1+C postcontrast MR images of the spinal column without leptomeningeal metastases in the spinal cord

Linear accelerator whole brain radiotherapy (WBRT) with the Volume Modulated Arc Therapy (VMAT) to total dose (TD) 40 Gy with daily dose (DD) 2 Gy, was conducted (Figure 3), after which CNS boost-RT in the cerebellum, medulla oblongata, cerebral ventricles and retrobulbar areas bilaterally up to TD 50 Gy with DD 2 Gy *(Figure 4)*. During the radiotherapy, the patient continued her treatment with Kadcyla (transtuzumab emtansine) at a therapeutic dose of 3.6 mg/kg body weight, administered as an intravenous infusion every 3 weeks (21-day cycle).

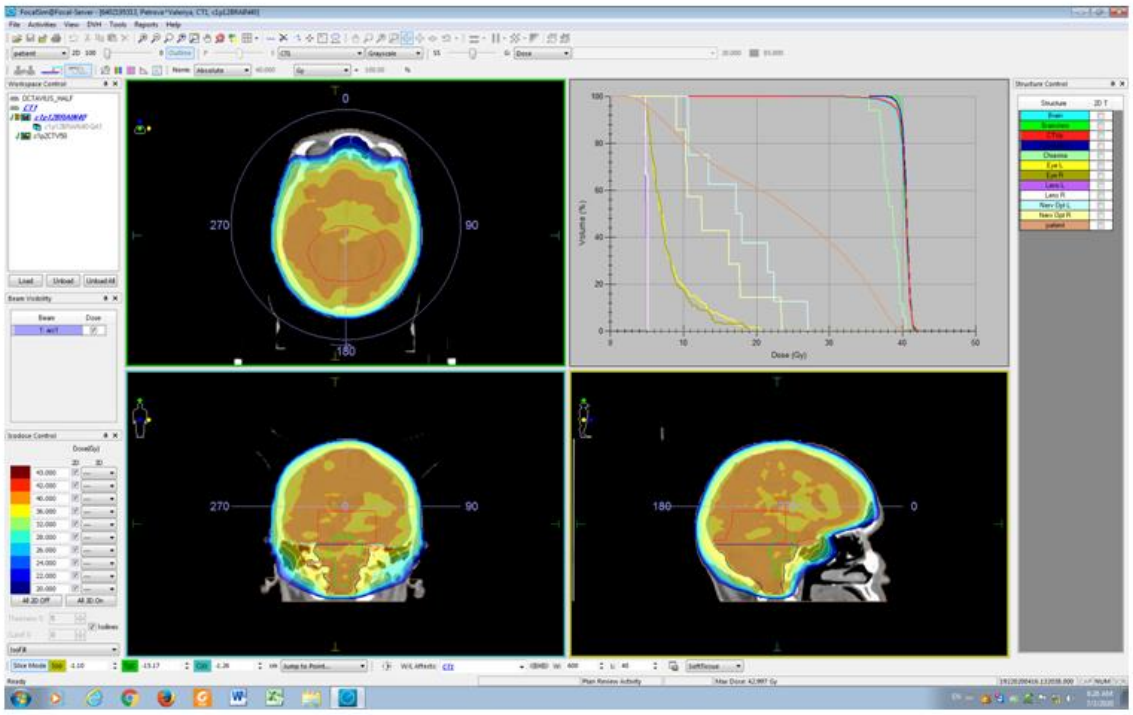

Figure 3: Linear accelerator whole brain radiotherapy with the VMAT method up to TD 40 Gy with DD 2 Gy

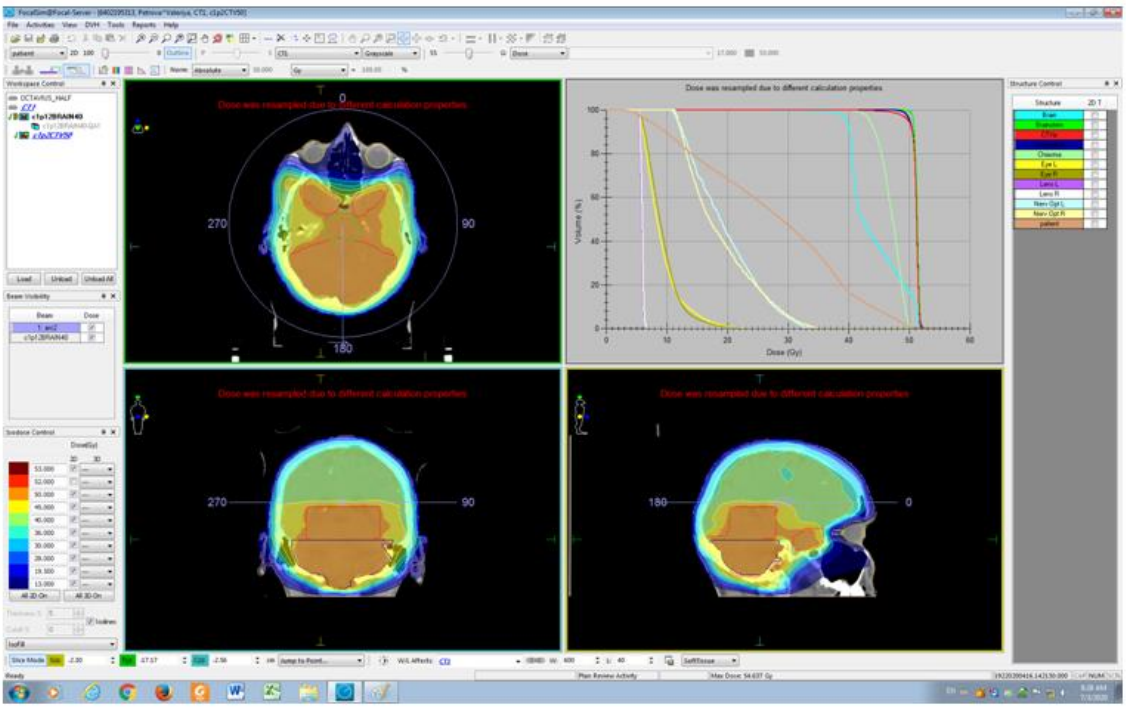

Figure 4: Linear accelerator CNS boost- RT with the VMAT method in the cerebellum, medulla oblongata, cerebral ventricles and retrobulbar areas bilaterally up to TD 50 Gy with DD 2 Gy

Citation Lena Marinova. Therapeutic Effect After Radiotherapy And Targeted Therapy For Leptomeningeal Metastases From Her 2 Positive Invasive Ductal Breast Carcinoma 2020;3(4): 10.

After the completion of the radiotherapy, the targeted therapy continues. After 2 months of RT in a month June 2020, a control MRI was performed, which revealed a significant reduction in leptomeningeal metastases. Residual lesions are predominantly in the cerebellum, but metastatic involvement of the spinal axis / cervical region is already reported. *(Figure 5, Figure 6).*

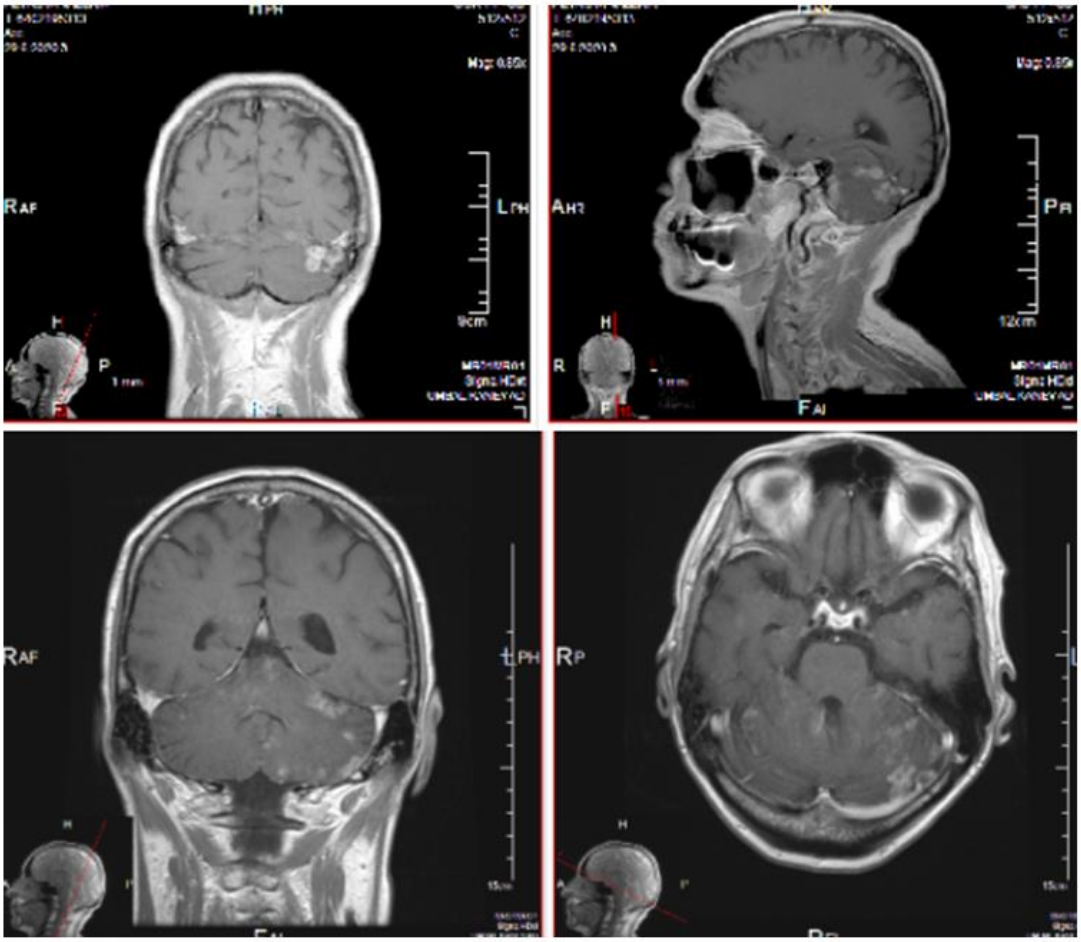

Figure 5: COR T1 FLAIR+C, SAG T1 FLAIR+C, AX T1 FLAIR+C MR postcontrast images after 2 months of RT

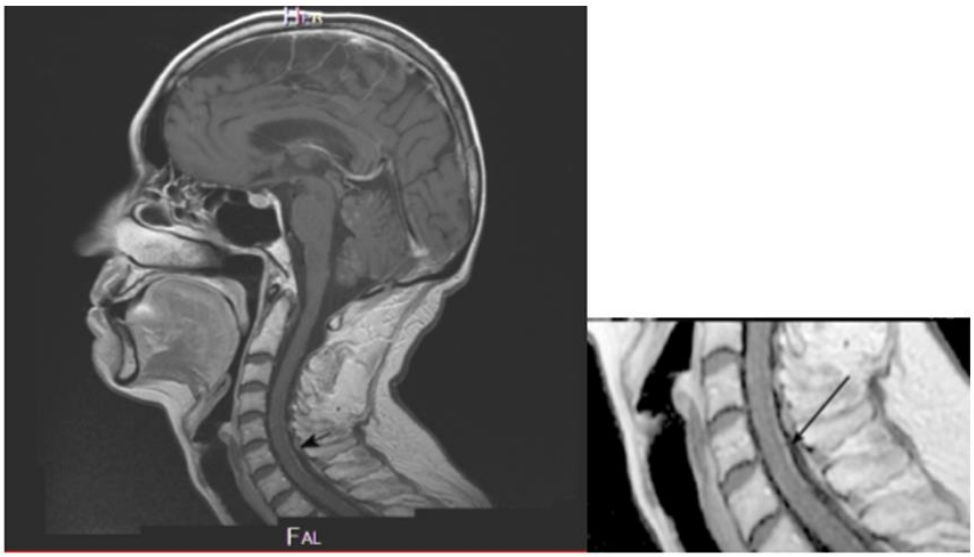

Figure 6: SAG T1 FLAIR+C MR postcontrast images of cervical spinal axis after 2 months of RT - leptomeningeal metastatic involvement of the spinal axis/cervical region

After 4 months of RT and 3 months of targeted therapy alone, a control MRI was performed, which showed a reduction in leptomeningeal metastases in the cerebellum with persistence of lesions in the cervical spinal cord *(Figure 7-Figure 11)*. To date, the patient continues targeted therapy and has a good quality of life. After the RT described above, combined with targeted therapy, we achieved a six-month survival in LMD of breast cancer.

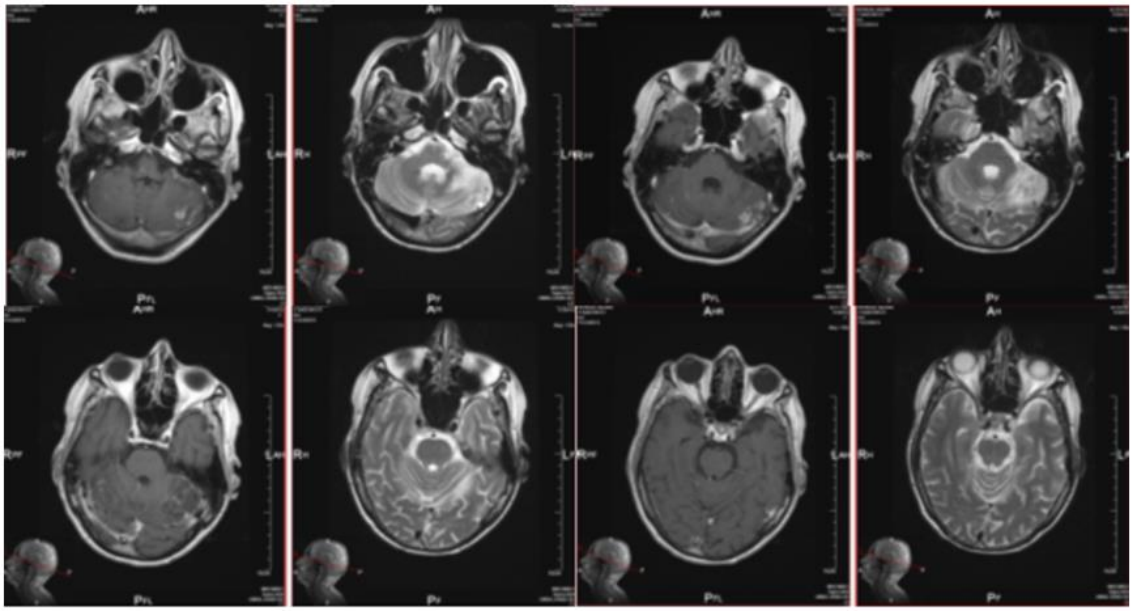

Figure 7: AX T1 FLAIR+C postcontrast and AX T2 MR images after 4 months of RT and after 3 months of targeted therapy alone

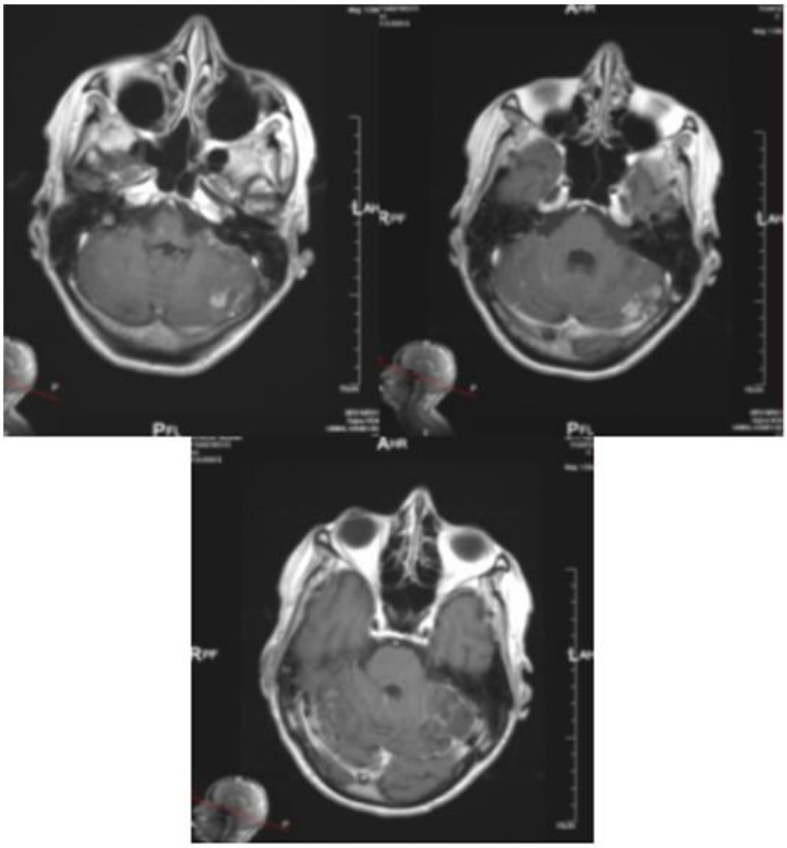

Figure 8: AX T1 FLAIR+C MR postcontrast images after 4 months of RT and after 3 months of targeted therapy alone

Citation Lena Marinova. Therapeutic Effect After Radiotherapy And Targeted Therapy For Leptomeningeal Metastases From Her 2 Positive Invasive Ductal Breast Carcinoma 2020;3(4): 10.

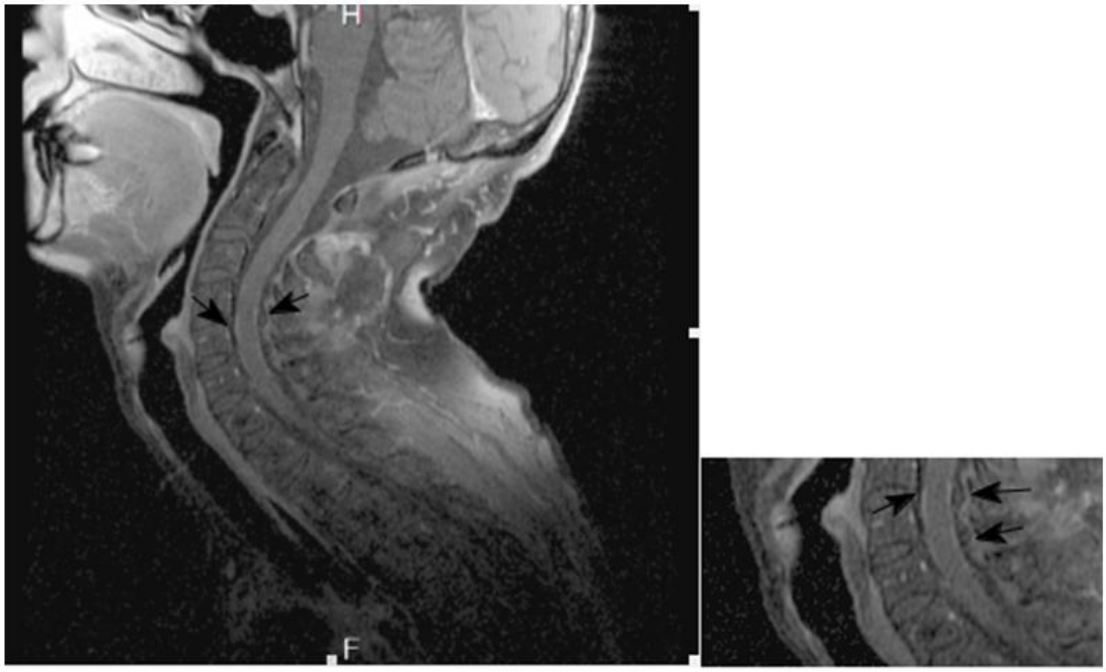

Figure 9: SAG T1 FLAIR Fat Sat +C MR postcontrast images of cervical spinal axis after 4 months of RT and after 3 months of targeted therapy alone

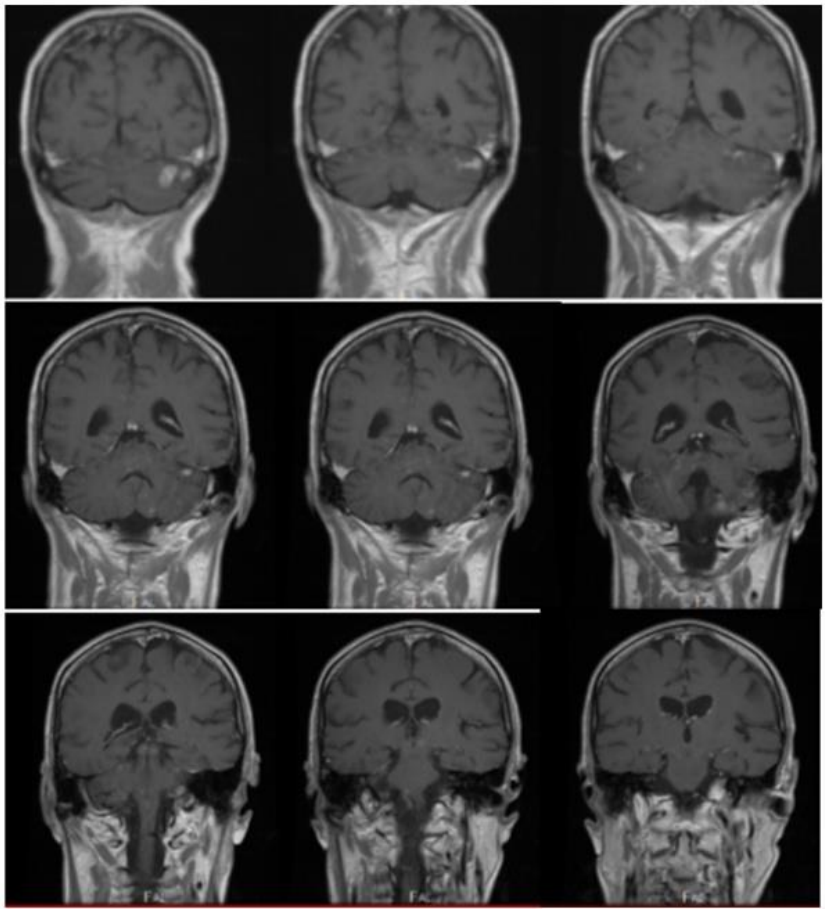

Figure 10: COR T1 FLAIR+C MR postcontrast images after 4 months of RT and after 3 months of targeted therapy alone

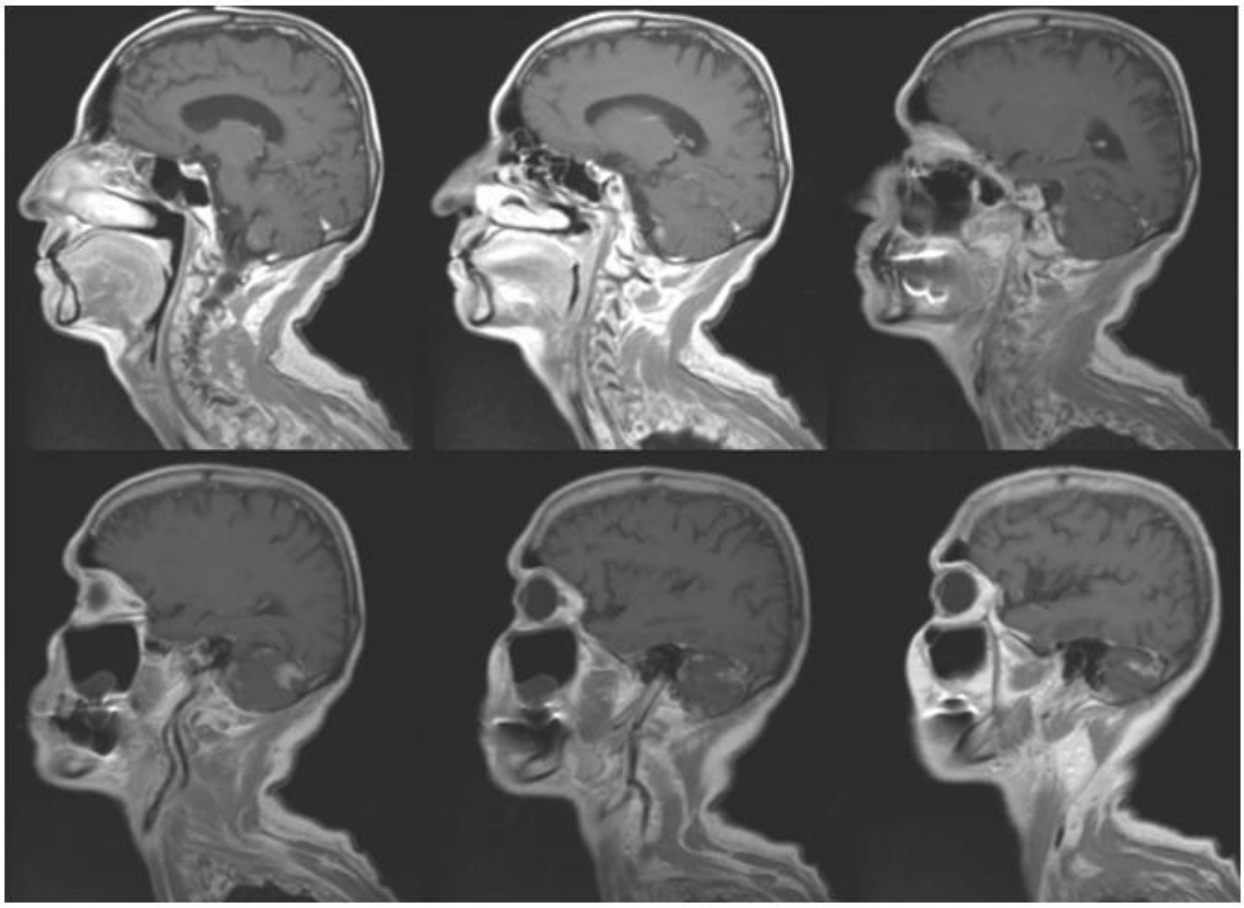

Figure 11: SAG T1 FLAIR+C MR postcontrast images after 4 months of RT and after 3 months of targeted therapy alone

Discussion

Leptomeningeal metastases (LM) result from metastatic infiltration of the leptomeninges by malignant cells originating from an extrameningeal primary tumor site that may be extraneural (most common) or intraneural (less common) *[6]*. Furthermore, there is evidence of increasing incidence rates of central nervous system (CNS) metastases, including brain parenchyma and possibly leptomeninges, in metastatic breast cancer *[7,8]*. Although any cancer can metastasize to the leptomeninges, breast cancer (12-35%), lung cancer (10-26%), melanoma (5-25%), gastrointestinal cancer (4-14%), and cancers of unknown primary (1-7%) are the most common causes of solid-tumor-related LM *[6]*. Overall, LMD likely comprises about 11-20% of CNS metastasis *[9,10]*. Today, it is known that LMD occurs in~5% of all cancer patients *[11-13]*. Pathophysiological mechanism of leptomeningeal metastasis in breast cancer -The hematogenous metastatic dissemination (HMD) of breast cancer cells applies to the choroidal plexus localized in the entire ventricular system of the brain, given the relatively high cerebral inflow of blood (5 times higher than that in the brain parenchyma) and the porous endothelium of its capillaries *[14,15]*. One of main reasons for HMD is that the blood brain barrier (BBB) makes the CNS a perfect sanctuary for tumor cells. The BBB consisting of endothelial cells, a basement membrane, and astrocyte foot processes, is a barrier that selectively chooses molecules to enter the CNS *[16]*. Multimodality treatment-There is currently no generally accepted standard of care in the treatment of breast cancer LM. Surgery (for hydrocephalus), radiation therapy (RT), and systemic or intra-cerebrospinal fluid (CSF) chemotherapy (Ch) may be considered *[3]*. With combined treatments, the median survival of patients with LM averages several months. Specific treatment of LM typically combines systemic and intrathecal (IT) chemotherapy and site-specific RT *[6]*. Molecular therapeutic strategies are likely to play an increasingly important role in the treatment of breast cancer LM. Although the OS of patients with HER 2-positive breast cancer has improved substantially in the trastuzumab (T-DM1) era *[17-19]*, in recent years the incidence of brain metastases among these patients has been increasing. Individual case reports and case series have shown that IT-trastuzumab may have some activity in HER-2 positive breast cancer LM, is potentially well-tolerated *[6, 20-23]* and is associated with significantly improved overall survival (OS) *[24]*. Although retrospective studies suggest that systemic treatment may improve the survival of BC with LM *[25,26]*, but a number of prospective trials of systemic treatments, such as temozolomide, have not demonstrated convincing clinical efficacy *[27]*. The BEEP regimen entailed a 21-day cycle of bevacizumab (15 mg/kg) on day 1, followed by cisplatin and etoposide (both 70 mg/m2) on day 2, then etoposide (70 mg/m2) only on days 3 and 4 *[28]*. A clearer understanding of the role of systemic regimens, especially BEEP, in LM is needed to improve the management

and prognosis of breast cancer with LM *[24]*. Radiotherapy (RT) is especially important to consider in cases with bulky leptomeningeal disease, as the penetration of IT-chemotherapy is poor in these instances *[29]*. Combination chemotherapy and RT may be considered in breast cancer LM, especially those without active systemic disease or concurrent brain metastasis *[3]*. RT has a positive impact on the quality of life due to the alleviation of neurological symptoms *[30]*. The eradication radiation doses required to achieve remission in LMD are different and depend on the histology of the tumor, the volume of leptomeningeal infiltration and the proximity to critical brain structures such as medulla oblongata, pons, chiasm and others. In the most common medulloblastoma leptomeningeal disease it is necessary to irradiate the entire craniospinal axis up to tolerant brain and spinal structures radiation doses, which is TD 36-40Gy. In adulthood medulloblastoma LMD, after re-craniospinal RT (in the spinal cord up to TD-24 Gy; cauda equina up to TD-28 Gy; in cerebellum up to TD-24 Gy; the two hemispheres up to TD-26 Gy and paraventricular up to TD-30 Gy with DD-1.8 Gy), we achieved complete remission due to the extreme radiation sensitivity of medulloblastoma cells *[31]*. In the presented clinical case the patient develops late LMD after 10 years of diagnosis and the complex treatment of invasive intraductal carcinoma/pT2N0M0, G2, positive estrogen and progesterone receptor status and positive HER2/+++/. The disease progresses with hematogenous metastasis in the lung and liver, despite repeated courses of SCh and TT. Patients with cerebral LMD involvement typically receive whole brain radiotherapy (WBRT), which is planned to involve all neural tissue from the retro-orbit to the upper cervical vertebrae *[32]*. Due to massive leptomeningeal metastases in the presented clinical case, whole-brain radiotherapy was performed up to TD 40 Gy, and in the places of concentrated amount of tumor cells up to TD 50 Gy. The radiation dose was overdose due to the higher radioresistance of invasive ductal breast carcinoma compared to medulloblastoma. During the radiotherapy, the patient continued her treatment with Kadcyla (transtuzumab emtansine) at a therapeutic dose of 3.6 mg/kg body weight, administered as an intravenous infusion every 3 weeks (21-day cycle). The unfavorable in the presented clinical case is the manifestation of LMD in the cervical part of the spinal cord after two months of WBRT and their progression after 4 months of RT, against the background of self-targeted therapy. This means that the initial hematogenous overcoming of BBB is followed by the spread of tumor cells along the CSF from the cerebral ventricles to the spinal axis. The patient needs to discuss spinal RT of the entire spinal axis up to 45 Gy. As a result of the combined treatment [whole-brain RT with Kadcyla (transtuzumab emtansine)], we achieved an asymptomatic six-month survival with a very good quality of life.

Conclusions

1. Brain and spinal cord MRI with contrast-enhancement is required in the diagnosis of late LMD in the case of extracranial solid neoplasms.
2. LMD breast cancer RT has a different target volume and necessary radiation doses, depending on the histological appearance of tumor cells, as well as on the volume and localization of leptomeningeal metastases.
3. For the first time in the world medical literature in English, MRI imaging presents the significant effect on leptomeningeal cells from BC, 4 months after WBRT combined with Kadcyla (transtuzumab emtansine) and 3 months after self-targeted therapy.
4. In breast cancer LMD through combined with targeted therapy the whole-brain radiotherapy up to 40 Gy and boost-RT in the places of concentrated amount of tumor cells up to 50 Gy, we achieved an asymptomatic six-month survival with a very good quality of life.

References

1. Kennecke H, Yerushalmi R, Woods R, Cheang MCU, Voducet D, et al., (2010) Metastatic behavior of breast cancer subtypes. J Clin Oncol 28: 3271-3277.
2. Mehta AI, Brufsky AM, Sampson JH (2013) Therapeutic approaches for HER2-positive brain metastases: Circumventing the blood-brain barrier. Cancer Treat Rev 39: 261-269.
3. Brian J Scott and Santosh Kesari (2013) Leptomeningeal metastases in breast cancer. Am J Cancer Res 3: 117-126.
4. E Le Rhun, Weller M, Brandsma D, M Van den Bent, E de Azambuja, et al., (2017) EANO Executive Board and ESMO Guidelines Committee EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. Ann Oncol 28: 84-99.
5. Wolff AC, Hammond ME, Hicks DG, Dowsett M, Lisa M, et al., (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31: 3997-4013.
6. Rhun EL, Taillibert S, Chamberlain MC (2013) Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int 4.
7. Frisk G, Svensson T, Backlund LM, Lidbrink E, Blomqvist, et al., (2012) Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden. Br J Cancer 106: 1850-1853.
8. Wang N, Bertalan MS, Brastianos PK (2018) Leptomeningeal metastasis from systemic cancer: Review and update on management. Cancer 124: 21-35.
9. Altundag K, Bondy ML, Mirza NQ, Shu-Wan Kau, Broglio K, et al., (2007) Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. Cancer 110: 2640-2647.
10. Kim HJ, Im SA, Keam B, Jung K, Han SW, et al., (2012) Clinical outcome of central nervous system metastases from breast cancer: Differences in survival depending on systemic treatment. J Neurooncol 106: 303-313.
11. Shapiro WR, Posner JB, Ushio Y, Chemik, Young DF, et al., (1977) Treatment of meningeal neoplasms. Cancer Treat Rep: 61: 733-743.
12. Aroney RS, Dalley DN, Chan WK, Bell DR, Levi JA, et

al., (1981) Meningeal carcinomatosis in small cell carcinoma of the lung. Am J Med 71: 26-32.
13. Glass JP, Melamed M, Chernik NL, Posner JB (1979) Malignant cells in cerebrospinal fluid (CSF): The meaning of a positive CSF cytology. Neurology 29: 1369-1375.
14. Levine S (1987) Choroid plexus: Target for systemic disease and pathway to the brain. Lab Invest 56: 231-233.
15. Al Anazi A, Shannon P, Guha A (2000) Solitary metastasis to the choroid plexus. Case illustration. J Neurosurg 92: 506.
16. Lena Marinova, Radoslav Georgiev and Nikolay Evgeniev (2020) Hypothesis on the distant spread of HER2-positive breast cancer brain metastasis via the human brain glymphatic system-Clinical and imaging data. Glob Imaging Insights 5: 1-8.
17. Lin NU, Winer EP (2007) Brain metastases: The HER2 paradigm. Clin Cancer Res 13: 1648-1655.
18. Pestalozzi BC, Holmes E, de Azambuja E, Metzger FO, Hogge L, et al., (2013) CNS relapses in patients with HER2 positive early breast cancer who have and have not received adjuvant trastuzumab: A retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 14: 244-248.
19. Aversa C, Rossi V, Geuna E, Martinello R, Milani A, et al., (2014) Metastatic breast cancer subtypes and central nervous system metastases. Breast 23: 623-628.
20. Mego M, Sycova-Mila Z, Obertova J, Rajec J, Liskova S, et al., (2011) Intrathecal administration of trastuzumab with cytarabine and methotrexate in breast cancer patients with leptomeningeal carcinomatosis. Breast. 20: 478-80.
21. Mir O, Ropert S, Alexandre J, Goldwasser F (2009) Hypertension as a surrogate marker for the activity of anti-VEGF agents. Ann Oncol 20: 967-970.
22. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J (2011) Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. Breast Cancer Res Treat 127: 841-844.
23. Stemmler HJ, Mengele K, Schmitt M, Harbeck N, Laessig D, et al., (2008) Intrathecal trastuzumab (Herceptin) and methotrexate for meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer: A case report. Anticancer Drugs 19: 832-836.
24. Tom Wei Wu Chen, I Shiow Jan, Dwang Ying Chang, Ching-Hung Lin, I Chun Chen, et al., (2020) Systemic treatment of breast cancer with leptomeningeal metastases using bevacizumab, etoposide and cisplatin (BEEP regimen) significantly improves overall survival. J Neurooncol 148: 165-172.
25. Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, Van der Sande JJ, et al., (2004) The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. Eur J Cancer 40: 2726-2733.
26. Rudnicka H, Niwinska A, Murawska M (2007) Breast cancer leptomeningeal metastasis-The role of multimodality treatment. J Neuro-oncol 84: 57-62.
27. Segura PP, Gil M, Balañá C, Chacón I, Langa JM, et al., (2012) Phase II trial of temozolomide for leptomeningeal metastases in patients with solid tumors. J Neuro-oncol 109: 137-142.
28. Lu YS, Chen TW, Lin CH, Yeh DC, Tseng LM, et al., (2015) Taiwan Breast Cancer C. Bevacizumab preconditioning followed by Etoposide and Cisplatin is highly effective in treating brain metastases of breast cancer progressing from whole-brain radiotherapy. Clin Cancer Res 21: 1851-1858.
29. Chamberlain MC, Kormanik PA (1997) Prognostic significance of coexistent bulky metastatic central nervous system disease in patients with leptomeningeal metastases. Arch Neurol 54: 1364-1368.
30. Halina Rudnicka, Anna Niwińska, Magdalena Murawska (2007) Breast cancer leptomeningeal metastasis-The role of multimodality treatment. J Neurooncol 84: 57-62.
31. Marinova L, Petrova K (2020) Re-Craniospinal Radiation Therapy of Subependimal Periventricular and Leptomeningeal Metastases in Adult Medulloblastoma-Clinical Case with Literature Overview. SAJ Case Report 6: 408.
32. Nayar G, Ejikeme T, Chongsathidkiet P, Elsamadicy AA, Blackwell KL, et al., (2017) Leptomeningeal disease: Current diagnostic and therapeutic strategies. Oncotarget 8: 73312-73328.