Case Report
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Successful Management of Neuroblastoma with Leptomeningeal Metastasis: An Interesting Case

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Abstract

Neuroblastoma is an extracranial solid tumor that is most commonly observed in children, yet it is rare to have brain metastasis in neuroblastoma during primary involvement or relapse. In this article, we report a successful treatment of high risk neuroblastoma with primary leptomeningeal metastasis based on developing countries facilities and explain combination chemotherapy (a classic regimen with salvage regimen based on temozolamid and methotroxate intratechal chemotherapy and localized radiation therapy) as a multimodal therapy.

Keywords: Neuroblastoma, Brain metastasis, Leptomeningeal metastasis

Introduction

Neuroblastoma is a type of extracranial solid tumor that is most commonly observed in children. The broad spectrum of clinical behavior ranges from spontaneous regression or differentiation into benign ganglioneuroblastoma, or aggressive invasion or metastasis into the liver, bone, bone marrow, and rarely to central nervous system (CNS).[1]

The overall incidence of secondary brain metastasis in neuroblastoma following primary treatment ranges from 1.7% to 11.7%.[1] Primary metastasis to the brain is rarer than secondary metastasis.[1] We found no report of metastasis to the CNS as the main site of progression or recurrence in neuroblastoma patients in Iran.

Case presentation

A 14-months-old girl with bone pain as unable to walk and bilateral preorbital ecchymosis was admitted

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to Imam Hosein hospital (educational hospital of Shahid Beheshti University in Tehran).Vital signs were normal and hypertension was not detected. Urinary Homovanillic and vanillylmandelic acid were not measured because of the complete labial adhesion. The brain and spinal magnetic resonance imaging (MRI) and computerized tomography revealed involvement of cranial bones, leptomeningeal membrane (Figure 1), cranial base, bilateral orbits and left pleura, thoracic paravertebral soft tissue involvement by metastasis (Figure 2). Left adrenal tumor with calcification and para-aortic lymph nodes, soft tissue in the sacral canal and bilateral kidneys (Figure 3), and multiple metastatic lesions in bone -scintigraphy were shown in imaging and bone Tc 99m – scintigraphy. MIBG scan was not performed in beginning of patient work-up. The blood and urine tests indicated no impairment of renal function. Bilateral bone marrow aspiration and tumor biopsy were performed and a diagnosis of poorly differentiated neuroblastoma with high mitosis-karyorrhexis index was confirmed. Our patient had the following immunopositivity: Vimentin 0/6, chromogranin 5/6, synaptophysin 4/6, and S100 protein 0/6 (tumor cells), neurofilament 5/6, J1 6/6, microtubule-associated protein-2 6/6, glial fibrillary acidic protein 1/6, and peanut agglutinin 6/6 and NSE (Neuron Specific Enolase). Overall, histology was unfavorable based on bone marrow examination and showed tumor cells with a highly amplified MYCN oncogene. The patient was diagnosed as high-risk according to the International Neuroblastoma Risk Group Classification System.

After treatment protocol, there was no evidence of relapse during follow-up. The last MIBG scan revealed no distinct area with abnormal increased accumulation of radiotracer and was negative for avid metastasis. The CSF cytology revealed no malignant cells before treatment, but because of drop metastasis prophylaxis, intratechal chemotherapy was continued. The bone marrow aspiration and biopsy after treatment demonstrated normocellular marrow. No granuloma or metastasis identified.

Treatment Details

Chemotherapy

The patient received 2 cycles of induction chemotherapy with topotecan and cyclophosphamide. Aggressive chemotherapy regimen was assigned combination topotecan 0.75 mg/m^2 and cyclophosphamide 250 mg/m^2 for 5 days.

The patient received a course of vincristine 1.5 mg/m^2 for one day, two courses of carboplatin 750 mg/m^2, etoposide175 mg/m^2 for two days, and two courses of vincristine 1.5 mg/m^2 and a course of cisplatin 80 mg/m^2 for one day. Further scheduled for the patients was three courses of Vincristine (1.5 mg/m^2 day 1), Irinotecan (50 mg/m^2 days 1-5) and temozolomide (125 mg/m^2 days 1-5 orally) (VIT) with MTX 10 mg and dexamethasone 4 mg intrathecally twice per week.

The patient was then allowed to receive concomitant therapy upon neurologic improvement and radiotherapy tolerance. Supporting therapy was provided with low Karnofski Performance Score (KPS score). Concomitant therapy included consolidation intrathecal chemotherapy and fractional RT (MTX 12.5-15 mg, plus dexamethasone 5 mg, once per week for a total of four weeks) and IF-RT.

Radiation therapy

The radiotherapy consisted of fractionated, conformal radiation given at a daily dose of 2 Gy. The planning volume comprised the sites of

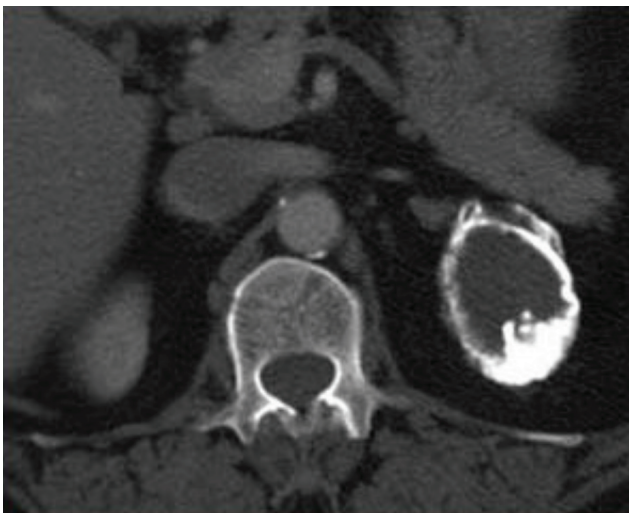

Figure 1. Left adrenal mass in abdominopelvic CT scan shows calcifiction.

symptomatic disease, the bulky disease observed on MRI. The whole brain and basis crania received 40 Gy in 20 fractions and/or segment of spinal canal received 40-50 Gy (the above segments of the first lumbar vertebra received 40 Gy in 20 fractions; the first lumbar vertebra and the inferior segments received 40-50 Gy in 20 fractions).

In intensity-modulated radiation therapy (IMRT) with tomotherapy, the field width, pitch and modulation factors, commonly employed for treatment planning and, optimization were 2.5, 0.287 and 2.5 cm, respectively. The dosimetry was performed with regards to certain organs at risk constraints. The volume of each kidney receiving 12 Gy (V12 Gy) was limited to 20% in cases where both kidneys were preserved and <15% if only one kidney was preserved. Due to the risk of a lack of homogeneous vertebrae growth if a uniform dose was not delivered to this bone, a uniform dose was required for all the vertebrae proximal to the targeted volume, meaning at least 80% of each irradiated vertebrae had to receive 80% of the prescribed dose.

At the end of the chemotherapy regimens, MIBG (Meta-Iodo-Benzylguanidine) scan was performed for the subject. Two focuses, hot spot and active lesions, were observed in calvarium and right adrenal gland. She received two courses of ICE-5 protocol as salvage regimen including ifosfamide (2000 mg/m^2 daily for five days), carboplatin (500 mg/m^2 daily for two days), and etoposide (100 mg/m^2 daily for five days).

Following salvage chemotherapy, adrenal lesion resected with oncosurgery approach, yet skull lesion was treated by IMRT.

Peripheral blood stem cell transplantation (auto-PBSCT)

The first high dose chemotherapy (HDC) course comprised of thiotepa 300 mg/m^2 per dose on three consecutive days in a 2-hour infusion up to a total dose of 900 mg/m^2. Oral busulfan was used until 2006 (150 mg/m^2 on four consecutive days in four equal doses), after which the IV route with busilvex (0.8–1.2 mg/kg per dose according to patient weight up to a total of 16 doses) was introduced. Following a 24-hour interval, a single dose of melphalan (140 mg/m^2) was administered. HDC was followed by ASCT (autologous stem cell transplantation) performed 24 h after the last chemotherapy. Clinical requirements were no organ dysfunction and the

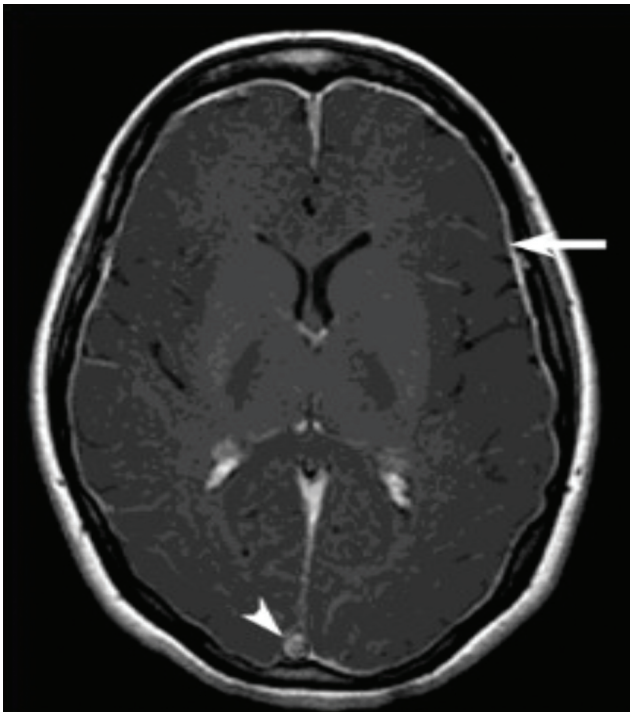

Figure 2. Left-sided diffuse leptomeningeal enhancement shows metastatic lesions.

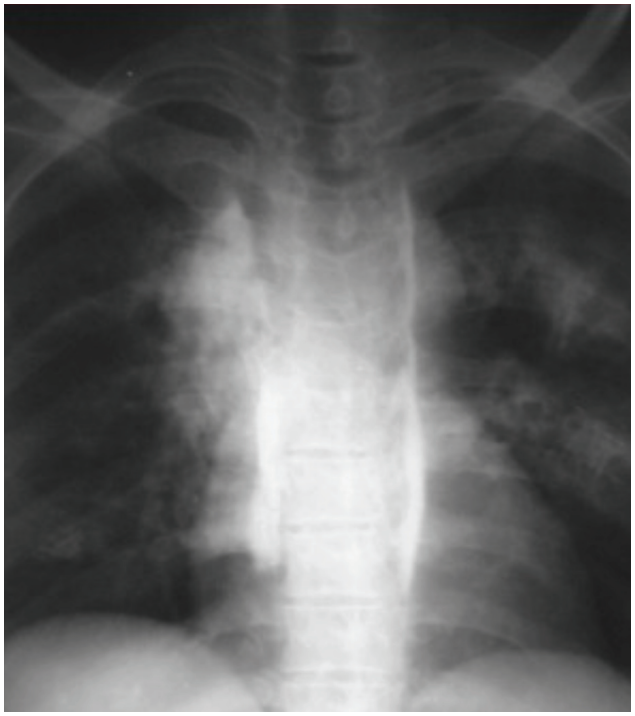

Figure 3. Thoracic paravertebral metastasis shown in chest X-ray.

platelet count had to be >50×10^9/L without transfusion.

Hematopoietic support

PBSC were collected by leukapheresis after mobilization with conventional chemotherapy and granulocyte-colony stimulating factor (G-CSF) at 5µg/kg. A total of 6×10^6 CD34+ cells/kg had to be collected and cryopreserved for the administration of the HDC course.

Supportive care

Clonazepam was administered as prophylaxis against seizures during busulfan administration. G-CSF, at a dose of 5µg/kg per day, was administered following each course from day 5 post-ASCT until stable neutrophil recovery (>500/mm^3). RBCs were transfused when the haemoglobin level was below 8 g/dL. Platelets were transfused to maintain a platelet count above 20×10^9/L or to control bleeding. All blood products were irradiated (25Gy). Acyclovir prophylaxis was not administered (Guerrini-Rousseau L, SIOP meeting 2014; P-0158). All patients received trimethoprim-sulfamethoxazole as prophylaxis against pneumocystis jiroveci.

Evaluation of toxicity

Toxicity was evaluated according to Bearman's grading system.

Other treatments

Due to surgical risk, resection of the primary tumor was postponed until after HDC. Radiotherapy was performed as a complementary local treatment at a dose of 21Gy. Maintenance treatment comprised six courses of retinoic acid (160 mg/m^2 per day×14 days) with a 14-day rest interval between the two courses.

Assessment of disease extent and tumor response

Tumor response was evaluated after each course of HDC and at the end of treatment. The primary tumor was assessed by computed tomography or magnetic resonance imaging. Disease extent was assessed by MIBG scan using

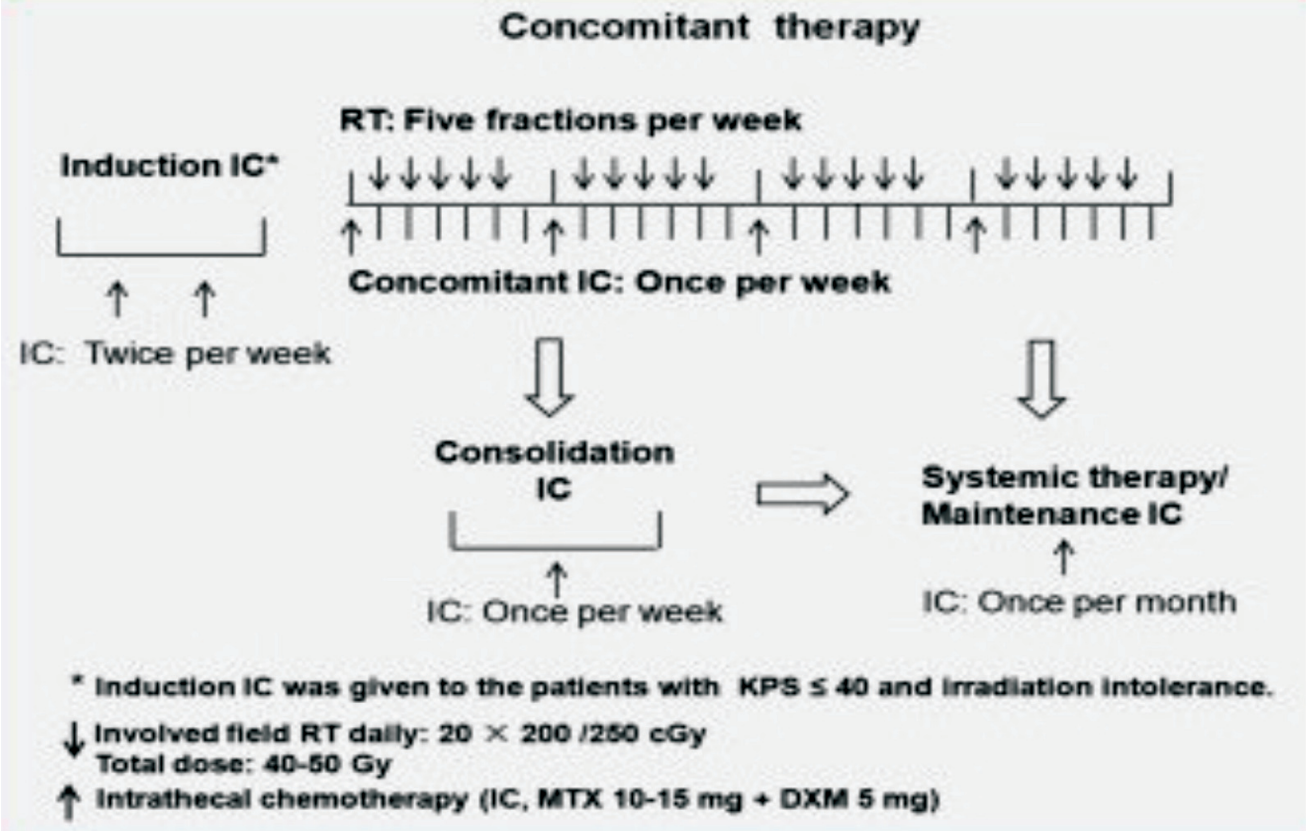

Figure 4. Protocol schema.
IC: intrathecal chemotherapy; RT: radiation therapy; KPS: Karnofsky performance status; MTX: methotrexate; DXM: dexamethasone

the SIOPEN scoring system. Two biopsies and four aspirates were obtained in the morphological evaluation of bone marrow. 17 months after the end of the treatment, the patient was negative for disease in urinary vanylilmandelic acid, abdominopelvic sonography and chest x-ray. Neither did the patient have any clinical neurologic signs/symptoms or organ dysfunctions.

Intracerebrospinal chemotherapy (IC)

Our intracerebrospinal fluid chemotherapy was done based on schema protocol (Figure 1). The regimen of concomitant therapy consisted of IC via lumbar punctures (MTX 12.5-15 mg, plus dexamethasone 5 mg, once per week, 4 weeks in total) and IF-RT (drugs dose adjusted based on the case's age). Based on the protocol, patients with KPS of ≤40 and irradiation intolerance are required to receive induction IC (MTX 12.5–15 mg, plus dexamethasone 5 mg, twice per week). We prescribed 4 mg dexamethasone and 10 mg methotrexate and the patient was allowed to receive concomitant therapy upon neurologic improvement and radiotherapy tolerance. Supporting therapy was provided with low KPS score. Subsequent treatment was recommended after concomitant therapy. Consolidation IC (MTX 12.5–15 mg, plus dexamethasone 5 mg) was recommended once per week. The total cycles of IC, including induction therapy, concomitant therapy and consolidation therapy should be <8 times within 2 months. Maintenance IC (MTX 12.5–15 mg, plus dexamethasone 5 mg) was recommended once per month after the concomitant therapy. Consolidation therapy is recommended to patients with stable systemic disease or longer expected survival. The patient with active systemic disease is proposed to systemic therapy (chemotherapy or molecular target therapy) according to the NCCN guidelines of related tumors (Figure 4).

Discussion

CNS metastases of neuroblastoma are rare and more fatal than high-risk neuroblastoma without CNS involvement. The overall incidence of secondary brain metastasis (after treatment) in neuroblastoma ranges from 1.7% to 11.7%.[1] Certain studies have shown that metastases to the CNS are more common in the first 18 months following diagnosis, with an estimated risk of 8% during three years.[2] The median survival after the development of metastasis to the CNS was four months.[1]

Primary CNS neuroblastoma incidence is yet to be elucidated, but seemingly, it has lesser incidence compared with secondary metastases. Our patient had primary CNS involvement, hence unique in this regard.

In China, Zhu et al. performed a study on 106 patients with stage 4 neuroblastoma, reviewing the incidence, risk factors, and survival status. They showed that high-risk factors for brain metastasis in neuroblastoma were bone marrow involvement and young age at initial diagnosis. Moreover, multiple treatment modalities can enhance disease-free survival.[1]

Half of the patients who develop recurrent CNS disease have isolated parenchymal metastasis. Predictive features at CNS recurrence diagnosis time are 2-3 years of age and tumor MYCN amplification.

Literatures have not fully clarified the optimal treatment for a patient presenting with brain metastasis in neuroblastoma. A small proportion of children can be cured with aggressive multimodality treatment. The combination of vincristine, temozolomide, and irinotecan (VIT), crossing the blood-brain barrier, was effective against refractory neuroblastoma. If temozolomide is administered 1 h prior to irinotecan, the two agents will have a synergistic antineoplastic activity for brain and bone marrow metastases. Disease-free survival by this regimen was 47 months[1] and our patient received three courses of this regimen, two courses topotecan 4 mg/m^2 and cyclophosphamide 250 mg/m^2, followed by a classic protocol including: vincristine,VP16, carboplatin, cisplatin, adriamycin and, as chemotherapy treatment, two courses of ifosfamide, carboplatin, and etoposide (ICE) every 28 days. Alternative regimen including temozolamid-based protocol was also prescribed for the present case. This regimen has confirmed

a major response rate of 85% with 41% complete metastatic response in high-risk neuroblastoma.[3]

MIBG scan is not a reliable indicator of CNS disease and other modalities should be utilized to rule out CNS metastasis.[4] Moreover, PET/CT may not be suitable for response evaluation in the bone due to reactive changes. Certain neuroblastomas which present somatostatin receptors are low-risk diseases and have better prognosis. Therefore, octerotide scan may be considered in primary MIBG-negative tumor.[5]

The levels of urinary homovanillic acid and vanillyl mandelic acid were not measured because of labial adhesion. However, the levels of urinary and plasma catecholamine are usually normal in CNS neuroblastoma.

In Paulino and colleagues study on 611 patients with solid tumors such as neuroblastoma, 30 patients had CNS involvement. Four patients out of the 30 patients with CNS metastasis died. Treatment in other 26 patients included: surgery(S)+ post-surgery radiotherapy (RT)+ chemotherapy (CT) in two patients, S+post-surgery RT in one, RT+CT in 16, S alone in two, CT alone in two and RT alone in one patient. Two patients did not receive any treatment. This study proved that radiotherapy improves the survival of the patients.[2] The patient in the present study received IMRT.

IMRT with HT (helical tomotherapy) allows for a better conformity treatment, a more frequently acceptable (95%) PTV (planning target volume) compared with 3D-RT and, concomitantly, a better shielding of the kidneys.[5]

In children with neuroblastoma and brain metastasis, radiation therapy can result in a better neurologic prognosis.[2]

Diagnostic work-up for brain metastasis should include CSF cytology and whole spine MRI because a substantial number of children will have neuraxis dissemination. An aggressive treatment approach employing a combination of chemotherapy, surgery, ABMT, and RT seems to be indicated.[2]

Over the recent years, some treatment modalities have been administered in developed countries such as coadministration of exclusive targeted therapy and immunotherapy such as MIBG and anti-GD2 or "intrathecal 8H9 antibody" as part of a multimodal protocol to treat neuroblastoma relapses in the brain and CNS. These modalities; however, were not available to our patient.[6]

The overall response rate for IC was 86.4%, the overall survival ranged from 0.4 to 36.7 months (median 6.5 months), and one year survival rate was 21.3%. Treatment complication included meningitis, encephalopathy, radiculitis, myelosuppression, and mucositis.[7]

Leptomeningeal metastasis, in which cancer cells spread to membranes enveloping the brain and spinal cord, is a devastating complication of solid cancers. For the present case, the authors used combined intrathecal methotrexate with involved field radiotherapy in a concomitant regimen, showing that this approach can potentially improve the quality of life and increase overall survival rate. The findings suggest that the concomitant regimen could be an optimal treatment alternative for leptomeningeal metastasis.[7]

55 patients with leptomeningeal carcinomatosis of a solid tumor were treated by intratechal chemotherapy. In a group, only methotrexate 15 mg and in another group, MHA (methotrexate 15 mg, hydrocortisone 15 mg/m^2 and Ara-C 30 mg/m^2) were intrathecally administered twice a week until a clear cerebrospinal fluid was observed. Triple-therapy was more effective than single therapy.[8]

Combination IT chemotherapy in solid tumor, which includes liposomal cytarabine plus IT methotrexate with dexamethasone, resulted in cytologic clearance.[9]

Concurrent therapy consisting of concomitant IC (methotrexate 12.5-15 mg and dexamethasone 5 mg, weekly) and IF-RT (whole brain and/or spinal canal RT, 40 Gy/20f) had an overall response rate of 86.4%.[10]

At present, intra-CSF drug therapy include three chemotherapeutic agents, namely methotrexate, cytosine arabinoside and, thio-TEPA, successfully administered as intra-lumbar or intraventricular drug delivery.[11]

In summary, our recommendation for a pediatric oncologist in developing countries is the following protocol:

1. Induction phase: two courses of cyclophosphamide and topotecan

2. Consolidation phase: three courses of temozolamid+irinotecan+vincristin, alternate with classic protocol of neuroblastoma treatment including cisplatin, etoposide, carboplatin, vincristine and intratechal chemotherapy with dexamethason and methoterexate, and RT with AHSCT in a terminal phase.

3. Maintenance phase which includes accutane.

Conclusion

Multimodality treatment, comprising intrathecal chemotherapy combined with concomitant field radiation therapy and combination chemotherapy along with conventional classic protocol and salvage regimens, has significant effectiveness and acceptable toxicity and may be an optimal therapeutic alternative for the treatment of solid tumors such as high-risk neuroblastoma with leptomeningeal metastasis.

Informed Consent

Written informed consent was signed by the patient's father.

Conflict of Interest

None declared.

References

1. Zhu J, Wang J, Zhen ZJ, Lu SY, Zhang F, Sun FF, et al. Brain metastasis in children with stage 4 neuroblastoma after multidisciplinary treatment. *Chin J Cancer.* 2015;34(11):531-7.
2. Paulino AC, Nguyen TX, Barker JL Jr. Brain metastasis in children with sarcoma, neuroblastoma, and Wilms' tumor. *Int J Radiat Oncol Biol Phys.* 2003;57(1):177-83.
3. De Ioris MA, Castellano A, Ilari I, Garganese MC, Natali G, Inserra A, et al. Short topotecan-based induction regimen in newly diagnosed high-risk neuroblastoma. *Eur J Cancer.* 2011;47(4):572-8.
4. Matthay KK, Brisse H, Couanet D, Couturier J, Benard J, Mosseri V, et al. Central nervous system metastases in neuroblastoma: radiologic, clinical, and biologic features in 23 patients. *Cancer.* 2003;98(1):155-65.
5. Beneyton V, Niederst C, Vigneron C, Meyer P, Becmeur F, Marcellin L, et al. Comparison of the dosimetries of 3-dimensions radiotherapy (3D-RT) with linear accelerator and intensity modulated radiotherapy (IMRT) with helical tomotherapy in children irradiated for neuroblastoma. *BMC Med Phys.* 2012;12:2.
6. Kramer K, Kushner BH, Modak S, Pandit-Taskar N, Smith-Jones P, Zanzonico P, et al. Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. *J Neurooncol.* 2010;97(3):409-18. doi: 10.1007/s11060-009-0038-7.
7. Pan Z, Yang G, He H, Zhao G, Yuan T, Li Y, et al. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: A prospective and single-arm study. *Int J Cancer.* 2016;139(8):1864-72.
8. Kim DY, Lee KW, Yun T, Park SR, Jung JY, Kim DW, et al. Comparison of intrathecal chemotherapy for leptomeningeal carcinomatosis of a solid tumor: methotrexate alone versus methotrexate in combination with cytosine arabinoside and hydrocortisone. *Jpn J Clin Oncol.* 2003;33(12):608-12.
9. Scott BJ, van Vugt VA, Rush T, Brown T, Chen CC, Carter BS, et al. Concurrent intrathecal methotrexate and liposomal cytarabine for leptomeningeal metastasis from solid tumors: a retrospective cohort study. *J Neurooncol.* 2014;119(2):361-8. doi: 10.1007/s11060-014-1486-2. Epub 2014 Jun 19.
10. Pan Z, Yang G, He H, Zhao G, Yuan T, Li Y, et al. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: A prospective and single-arm study. *Int J Cancer.* 2016;139(8):1864-72. doi: 10.1002/ijc.30214.
11. Chamberlain MC. Leptomeningeal metastases: a review of evaluation and treatment. *J Neurooncol.* 1998;37(3):271-84.