Effectiveness of metronomic chemotherapy in a child with medulloblastoma: A case report

ELENA LYGINA[1], DARIA MORGACHEVA[1], AVINASH KHADELA[2], HUMZAH POSTWALA[3], YESHA SHAH[3] and YULIA DINIKINA[1]

[1]Department of Chemotherapy for Hematologic Diseases and Bone Marrow Transplantation for Children, Almazov National Medical Research Centre, St. Petersburg 197341, Russia; [2]Department of Pharmacology; [3]Pharm D Section, L.M. College of Pharmacy, Navrangpura, Ahmedabad, Gujarat 380009, India

Received November 22, 2022; Accepted February 28, 2023

DOI: 10.3892/ol.2023.13780

Abstract. Medulloblastoma (MB) is one of the most common pediatric malignant tumors arising from the central nervous system with an unknown etiology and variable prognosis. Relapsed or refractory MB in pediatric patients after intensive anticancer therapy (chemo-, radiotherapy) is associated with treatment resistance and poor survival prognosis. Metronomic chemotherapy in combination with mTOR inhibitors may have advantages due to an alternate mechanism of cytotoxicity and a favourable adverse effects profile. Furthermore, it is considered to be a prospective anticancer regimen regardless of the presence/absence of molecular targets. The present study reported a successful result of this treatment option with optimal tolerability in relapsed MB in a pediatric male patient and highlighted the advantages for a selected group of patients.

Introduction

Medulloblastoma (MB) is one of the most common forms of malignant tumor arising from the cerebellum and posterior fossa with unknown etiology. MB occurs at the age of 3-7 years, but may also be diagnosed in adolescents and young adults (1,2). Most cases of MB have a sporadic occasion but there has been a certain association with familial syndromes (3,4). Despite the standard therapeutic options for primary care, including chemo-/radiotherapy and even high-dose chemotherapy, the 10-year mortality rate of MB is 34,6% (5). Relapsed or refractory MBs in pediatric patients are reported to have poor outcomes and, in most cases, intensive chemotherapy and radiation are inappropriate treatment options due to the high risk of adverse events, intolerance and low effectiveness. Thus, there is a need to develop a less toxic and more precise strategy with a modality of targeted therapy in order to improve survival rates (6).

Metronomic chemotherapy (MCT), acting through various mechanisms by producing direct and indirect effects on the tumor cells and their microenvironment, was reported to be a feasible and potentially effective approach for relapsed and refractory central nervous system (CNS) tumors (7). A significant role in tumor progression is assigned to neoangiogenesis, while antiangiogenic drugs in combination are considered to be more promising (8). Thus, the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is known to have a significant role in the development, progression and relapse of various tumors, including MBs (9), and accordingly, the addition of PI3K/Akt/mTOR inhibitor to the MCT regimen may be rational and has been confirmed by various in-vitro and in-vivo studies (10-23).

The present study reported a successful case of long-term stabilization of relapsed MB in a pediatric patient on metronomic regimen chemotherapy along with mTOR inhibitor with optimal tolerability. The literature review demonstrates the mechanisms of MCT and mTOR inhibitors and underlines their advantages for a selected group of patients.

Case report

A 3-year-old Caucasian male patient was admitted to the Department of Pediatric Oncology of Almazov National Medical Research Centre (St. Petersburg, Russia) in August 2017 with complaints of acute headache and neck pain, as well as vomiting and fatigue. CT scan of the brain indicated a tumor in the cerebellar vermis and in the IV ventricle with a size of 42.6x43.7x47.5 mm. Surgical resection of the tumor was performed and in the postoperative MRI of the brain with contrast enhancement (Fig. 1A), a residual tumor in the posterior fossa was visualized. In addition, multiple metastatic lesions in the meninges of the brain and spinal cord and signs of spinal compression at the level of Th9-Th10 were observed (Fig. 1A and B). The patient did not have any co-morbidities at the time of the initial diagnosis.

Correspondence to: Dr Yulia Dinikina, Department of Chemotherapy for Hematologic Diseases and Bone Marrow Transplantation for Children, Almazov National Medical Research Centre, 2 Akkuratova Street, St. Petersburg 197341, Russia
E-mail: dinikina_yuv@almazovcentre.ru

Key words: medulloblastoma, children, metronomic chemotherapy, mTOR inhibitors, pediatric oncology

Histological examination (24) of the tumor sample revealed small round undifferentiated cells with hyperchromatic nuclei, rosettes and pseudorosettes, foci of necrosis and hemorrhages, as well as pathologic mitoses. Based on the histological and immunohistochemical (24) profile (File S1) and radiological data, the diagnosis of anaplastic MB of the posterior fossa, stage R+M3 was confirmed. There was no technological opportunity to provide full molecular genetic testing to determine the subtype of MB.

After the surgery, the patient had neurological symptoms, including cerebellar mutism syndrome, ataxia and cognitive deficit. Considering the patient's age, histological type of the tumor and stage of the disease, adjuvant treatment was initiated. According to the HIT MED 2014 (version 4.0, 2017) protocol, the patient was given 3 cycles of intensified induction, including cisplatin, etoposide, high-dose methotrexate and intraventricular methotrexate (25). The most common complications of the chemotherapy in the patient of the present study were myelosuppression, febrile neutropenia, toxic hepatitis, catheter-related bloodstream infection and toxic dermatitis.

The subsequent MRI examination in October 2017 revealed a 50% decrease in tumor size. Next, two cycles of high-dose chemotherapy (HDCT) with a conditioning regimen of carboplatin/etoposide and thiotepa/cyclophosphamide followed by autologous stem cell rescue (ASCR) were provided (25). Complications after HDCT with ASCR in the patient of the present study were pancytopenia, mucositis grade 3, enterocolitis associated with *Klebsiella pneumoniae* and toxic dermatitis. The median time to neutrophil and platelet recovery was 11 and 13 days, respectively.

After the HDCT with ASCR, the patient underwent brain and spinal cord MRI, which revealed the positive clinical effect of the therapy. There was a decrease in the size of the metastatic lesions in the spinal meninges at the level of Th10-Th11, L1-L2 and L5, but the number of lesions remained stable. In the brain meninges, a decrease in both the size and the degree of the contrast accumulation of the metastatic lesions was observed.

As a result, the patient did not achieve complete remission after surgery and chemotherapeutic treatment, and thus, radiation therapy was provided by craniospinal irradiation with a dose of 35.2 Gy with a boost on spinal metastases to 44.2 Gy and posterior fossa to 55 Gy. MRI was performed 6.5 weeks post-radiation therapy, indicating postoperative changes with no evidence of residual tumor in cerebellum and IV ventricle. The metastases in the region of the interpeduncular cistern were stable. Detectable spinal metastases remained with a slight decrease in the degree of contrast enhancement. According to the clinical and radiological data, the patient achieved stable disease and continued to be monitored (Fig. 2A and B). Considering the high risk of disease progression, maintenance therapy with temozolomide at a dose of 150 mg/m^2 was initiated. The patient tolerated the treatment well and there were no reported adverse reactions.

Interim neuroimaging investigation revealed stabilization of the disease and maintenance chemotherapy was continued. The patient was given 6 cycles of temozolomide in total. A month later, after the 6th cycle, the patient still had ataxia, dysarthria and strabismus. MRI of the brain with contrast enhancement indicated new leptomeningeal metastases in the brain, suggesting continuous disease progression (Fig. 3A and B). Considering the scientific data about the potential effectiveness of MCT with mTOR inhibitors (17,26,27), it was decided to prescribe this scheme. The treatment protocol was approved by the institutional scientific committee (protocol no. 45 from September 2019). The patient was treated with celecoxib at a dose of 100 mg twice a day, alternate cycles of etoposide 50 mg/m^2/day for the first 3 weeks, followed by cyclophosphamide 2.5 mg/kg/day from the 4th to the 6th week of each cycle, along with sirolimus with an initial dose of 2 mg/m^2/day. All medications were administered orally. Side effects were monitored regularly according to criteria (File S2) and the patient exhibited grade 1-2 (not severe) recurrent episodes of neutropenia and thrombocytopenia, but there were no indications for antimicrobial therapy and hospitalization. After the maximum cumulative dose of etoposide (2,100 mg/m^2) was reached, the drug was discontinued. During the metronomic therapy, the clinical condition and MRI data of the patient remained stable. The patient was given this therapy for 2 years and after finishing the treatment, monitoring was continued.

At 4 months after discontinuation of the metronomic therapy, MRI was performed. The investigation revealed a decrease in the size of leptomeningeal lesions at the level of Th5-Th6 to 4x1 mm (previously 6x2 mm), at the level of Th10 to 8x4 mm (previously 20x4 mm) and at the level of Th12-L1 to 14x2 mm (previously 16x2.5 mm), while the previously described metastatic lesion at the level of Th1 was not detected. MRI data of the brain were stable (Fig. 4A and B). At eight months after discontinuation of the metronomic therapy, MRI confirmed disease stabilization.

At the time of writing of this report, the patient had been under surveillance for 14 months. The last MRI examination was performed in June 2022, which indicated stabilization of the disease.

Discussion

Despite the currently used multimodal therapy, the prognosis for high-risk group patients remains dismal and almost 30% relapse during the 1st year of treatment completion (28,29). Also von Bueren *et al* (30) demonstrated poor survival rates for children with localized MB with unfavorable histology.

Treatment modalities for recurrent MBs are limited due to the tendency to develop resistance to conventional treatment and high rate of toxicity as limiting factors for intensified chemotherapy and repeated radiotherapy (28,29). Novel strategies, including targeted therapy, are necessary in order to improve overall and progression-free survival in these patient groups (6).

The present results and previous reports (17,26,27,31-38) confirm the effectiveness of MCT in pediatric patients with refractory or relapsing CNS tumors with a satisfactory toxicity profile. For the past 15 years, MCT regimens have been assessed for replacing conventional regimens in miscellaneous cancers (39). While complete responses are rare, MCT may lead to partial responses and long-term disease stabilization with a significant improvement in the quality of life of patients and their families (26,40,41). Apparent advantages of MCT are cost-effectiveness and outpatient treatment

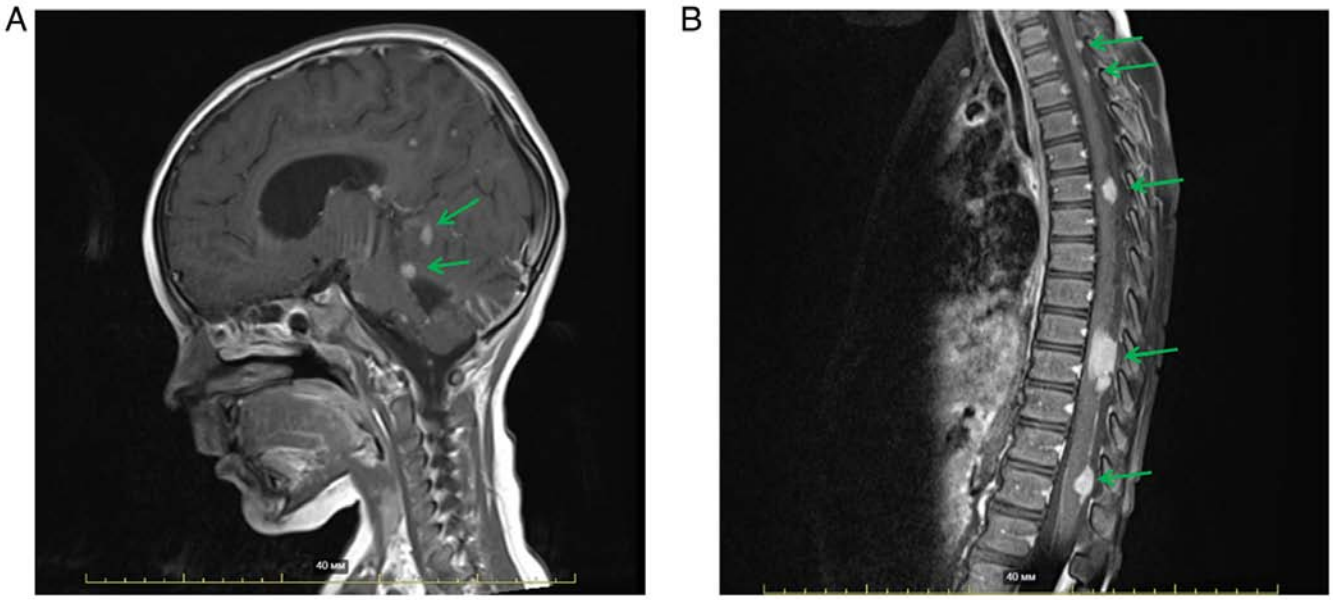

Figure 1. Central nervous system MRI of the patient performed at 4 weeks after the surgery. (A) Brain MRI (Sag T1 SE + C). Diffuse infiltration of the meninges of the cerebral hemispheres in the area of the interpeduncular cistern was observed with intensive contrast enhancement (green arrows; scale bar, 40 mm). (B) Spinal cord MRI (Sag T1 TSE + C). Multiple metastatic lesions of the meninges of the spinal cord (Th5, Th9-Th10, Th12-L1) and signs of spinal compression at the level of Th9-Th10 were observed with intense contrast enhancement (green arrows; scale bar, 40 mm). Sag, sagittal.

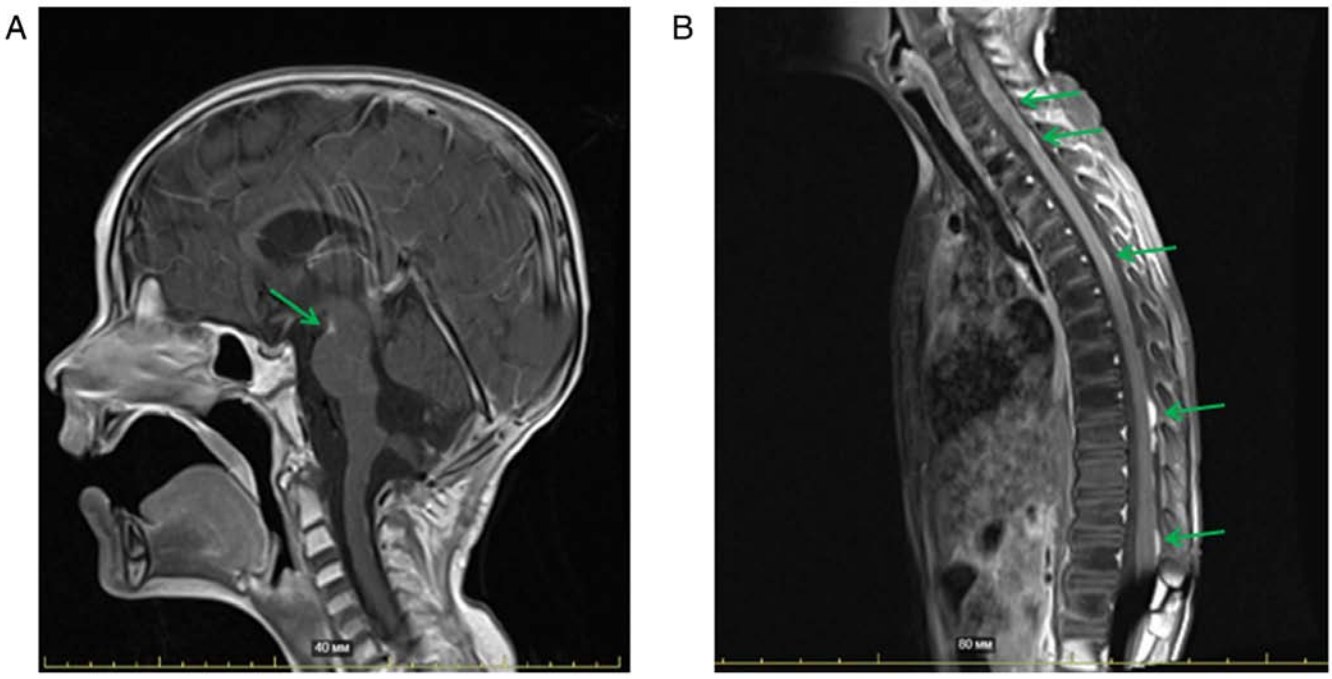

Figure 2. Central nervous system MRI of the patient at 3 months after discontinuation of the therapy. (A) Brain MRI (Sag T1 SE + C). Diffuse infiltration of the meninges of the cerebral hemispheres was observed in the area of the interpeduncular cistern with intensive contrast enhancement. Decrease in the size of the focus in the right occipital lobe (green arrow; scale bar, 40 mm). (B) Spinal cord MRI (Sag T1 TSE + C). Multiple metastatic lesions of the meninges of the spinal cord (C5, C7, Th5, Th9-Th10, L1) and signs of posterior subarachnoid space compression were observed at the level of Th9-Th10 with intensive contrast enhancement. A slight decrease in the size of the lesions at the level of C5 and Th5 was observed (green arrows; scale bar, 80 mm). Sag, sagittal.

administration (39). In cases of progressive disease and limited options for anticancer therapy, this treatment remains available for palliative care.

Today, MCT remains empirical, but ongoing preclinical and clinical studies define the best agents for use according to tumor type, number, type and doses of drugs, and timing of administration. It should be emphasized that childhood malignancies may feature recurrent genomic alterations, but their frequency is <10%. This is a limiting factor for designing and conducting clinical trials of targeted therapy according to revealed alterations and tumor histology (42).

Clear differences between MCT and conventional cytotoxic chemotherapy have been defined and explain differences in mechanisms of action. The MCT regimen usually consists

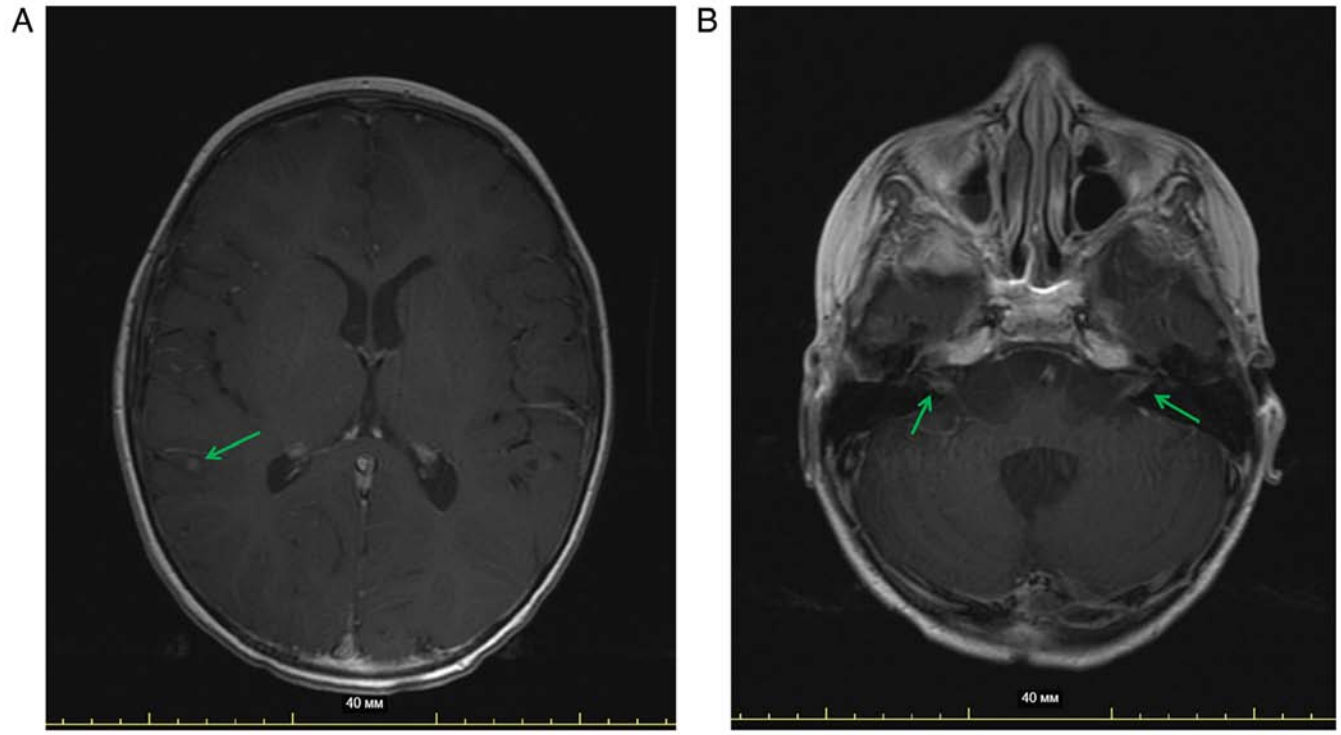

Figure 3. Central nervous system MRI of the patient after the 6th cycle of maintenance therapy with temozolomide indicated disease progression (new leptomeningeal metastases in the brain). Brain MRI (Ax T1 SE + C) indicated new lesions of contrast enhancement in (A) the region of the right temporal lobe and (B) membranes of the vestibulocochlear nerves (green arrows; scale bars, 40 mm).

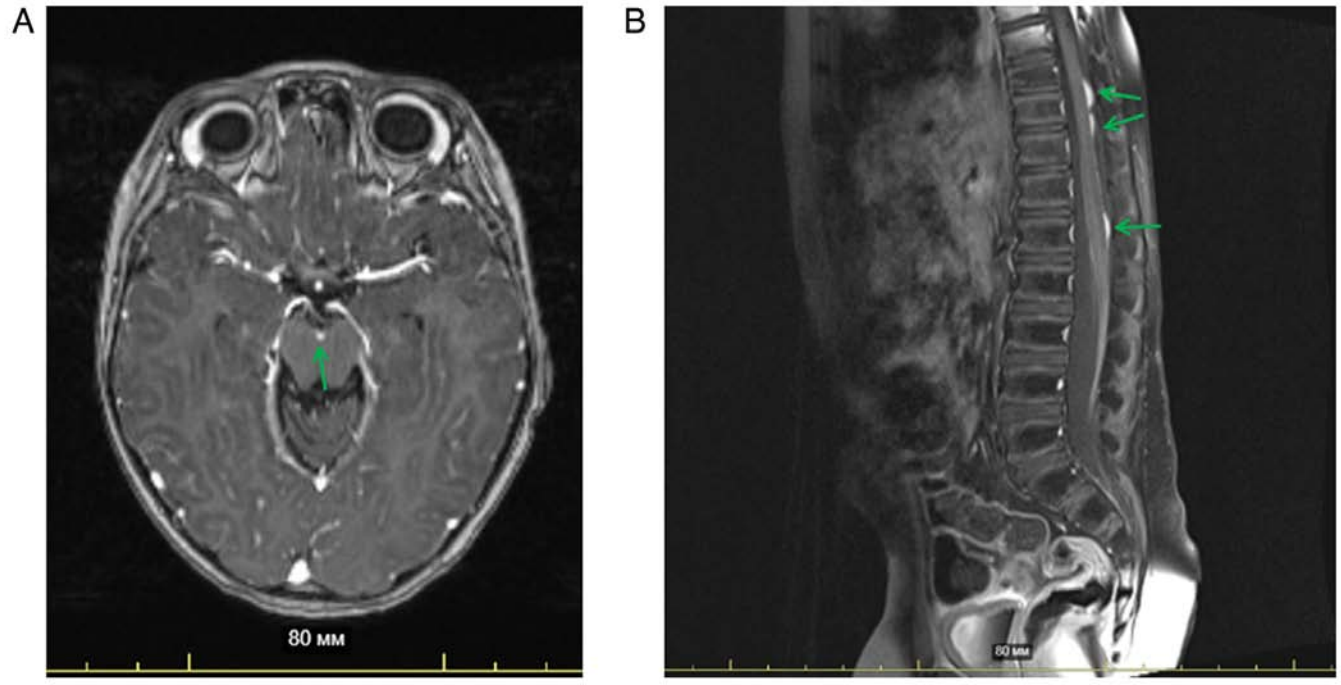

Figure 4. Central nervous system MRI of the patient at 14 months after discontinuation of the metronomic chemotherapy. (A) Brain MRI (Ax T1 MPR + C) indicating contrast enhancement in the region of the interpeduncular cistern (green arrow; scale bar, 80 mm). (B) Spinal cord MRI (Sag T1 TSE + C) revealing multiple metastatic lesions of the meninges of the spinal cord at the level of Th6, Th11-12, Th12-L1 with intensive contrast enhancement (green arrows; scale bar, 80 mm).

of a combination of various drugs with antiangiogenic, immunostimulatory and apoptotic mechanisms (31). MCT may be the most efficacious treatment for minimal residual disease or significantly cytoreduced disease. Frequently used drugs are cyclophosphamide, etoposide, methotrexate, vinblastine, temozolomide, irinotecan and topotecan (32-34). In preclinical studies, cyclo-oxygenase 2 (COX2) inhibitors have demonstrated antitumor activity when given at subtherapeutic doses

due to inhibition of angiogenesis and cell cycle arrest (35). A significant reduction in tumor invasion and proliferation was achieved via the COX-2 independent pathway. Also, when given at a metronomic dose, celecoxib is free from its well-established cardiovascular adverse events, which otherwise limit its use (31).

One of the important points of the natural course of malignancy is tumor dormancy, which occurs initially, during the very early phase of cancer, and later, after completion of anticancer treatment (remission phase), which is also regulated by the initiation of angiogenesis (27). Thus, it may be assumed that inhibition of the angiogenic switch by MCT may prevent the progression of tumors and their metastases (27).

Further agents were described to be used in the MCT regimen, including isotretinoin (inhibits cell proliferation and induces differentiation), thalidomide (immunomodulator with powerful antiangiogenic activity) (36), valproic acid (37), bevacizumab (37), rapamycin (17) and intraventricular liposomal cytarabine-etoposide (38). mTOR proteins have an essential role in the disease pathogenesis of MB and the PI3K/AKT pathway is considered one of the major mechanisms that are activated during MB development (26). Multiple drugs have been reported to target mTOR through different binding sites or mechanisms, but the importance of combination therapy in MB due to its highly resistant nature is highlighted (26).

In the case of the present study, alternating cyclophosphamide with etoposide and celecoxib, combined with the mTOR inhibitor sirolimus, was used. It should be emphasized that mTOR inhibitors were administered without the confirmation of the presence of PIK3CA mutations, but the opportunity of tumor DNA sequencing should be taken in order to predict the possible effectiveness of treatment. Apart from targeting certain mutations, PI3K/mTOR inhibitors exert their cytotoxic effects through other mechanisms, as mentioned above. Concomitant administration of molecular-targeted drug molecules on a daily basis may have immense potential (26).

Despite the minimal associated toxicity of MCT, there are several reports of secondary leukemia after prolonged chemotherapy with temozolomide and etoposide (31,43). Therefore, total doses of anticancer agents and treatment toxicity should be closely monitored.

The current experience of MCT in combination with mTOR inhibitors confirms the possibility of achieving long-term survival in patients with MB refractory to previous treatment options. In the present study, a good partial radiographic response compared to the baseline measurement with the absence of significant toxicity was obtained. Considering the duration of the progression-free follow-up period, a favorable outcome may be expected for the patient of the present study. Further investigations of this strategy are necessary to define the potential efficacy, toxicity and feasibility in similar treatment groups.

Of note, the treatment strategy of the present study cannot be considered a standard therapy at present, but may be discussed as an option for second and subsequent lines of therapy in heavily pretreated pediatric patients with relapsed or refractory CNS tumors. Future investigations are warranted.

In conclusion, there is no doubt that multidrug MCT in combination with mTOR inhibitors is a rational option for heavily pretreated pediatric patients with recurrent or progressive MBs with prolonged or persistent disease-free survival. The most significant advantages of this option are no age restrictions, oral low-dose form of cytotoxic drugs, absence of major toxicities and potential effectiveness in different cancer types. It is necessary to emphasize that in pediatric cancers, recurrent genomic alterations occur at a frequency of <10%, making it difficult to apply targeted therapy in most patients. Due to the mechanism of action of MCT in combination with mTOR inhibitors, it appeared to be a prospective anticancer regimen regardless of the presence/absence of molecular targets. In general, MCT is a palliative care option and is continued until the progression of the disease, but there are plenty of case reports with complete tumor response and long-term disease-free survival. Further cohort investigations on this strategy are necessary to achieve an impact on survival and long-term toxicity in definite cancer types.

Acknowledgements

Not applicable.

Funding

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (agreement no. 075-15-2022-301).

Authors' contributions

YD determined the treatment strategy for the patient. YD and AK were involved in the conceptualization of the study. EL, AK, HP, YS, DM and YD were involved in acquisition of data, wrote the text of the manuscript, analysed and interpreted literature data and edited the manuscript. All authors participated in group discussions and provided comments on drafts of the paper. All authors read and approved the final manuscript. EL, DM, AH, HP, YS and YD confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The treatment protocol of MCT with mTOR inhibitors in children with relapsed or refractory CNS tumors was approved by the Clinical and Research Board of Almazov National Medical Research Centre (St Petersburg, Russia; protocol no. 45 from 06.09.2019). Individual usage of this treatment protocol was permitted by the medical commission according to local institutional practice. Written informed consent to the treatment was obtained from the patient's guardian.

Patient consent for publication

Written informed consent was obtained from the legal guardian of the patient for publication of any potentially identifiable information/images or data included in this article in an online open-access publication.

Competing interests

The authors declare that they have no competing interests.

References

1. Johnston DL, Keene D, Strother D, Taneva M, Lafay-Cousin L, Fryer C, Scheinemann K, Carret AS, Fleming A, Afzal S, *et al*: Survival following tumor recurrence in children with medulloblastoma. J Pediatr Hematol Oncol 40: e159-e163, 2018.
2. Board PDQPTE: Childhood medulloblastoma and other central nervous system embryonal tumors treatment (PDQ®). PDQ Cancer Information Summaries. National Cancer Institute, Bethesda, MD, 2008.
3. Khattab A and Monga DK: Turcot syndrome. StatPearls. StatPearls Publishing, Treasure Island, FL, 2022.
4. Onodera S, Nakamura Y and Azuma T: Gorlin syndrome: Recent advances in genetic testing and molecular and cellular biological research. Int J Mol Sci 21: 7559, 2020.
5. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol 20 (Suppl 4): iv1-iv86, 2018.
6. Zapletalová D, André N, Deak L, Kyr M, Bajciova V, Mudry P, Dubska L, Demlova R, Pavelka Z, Zitterbart K, *et al*: Metronomic chemotherapy with the COMBAT regimen in advanced pediatric malignancies: A multicenter experience. Oncology 82: 249-260, 2012.
7. Panigrahy D, Kaipainen A, Butterfield CE, Chaponis DM, Laforme AM, Folkman J and Kieran MW: Inhibition of tumor angiogenesis by oral etoposide. Exp Ther Med 1: 739-746, 2010.
8. Pasquier E, Kavallaris M and André N: Metronomic chemotherapy: New rationale for new directions. Nat Rev Clin Oncol 7: 455-465, 2010.
9. Eckerdt F, Clymer J, Bell JB, Beauchamp EM, Blyth GT, Goldman S and Platanias LC: Pharmacological mTOR targeting enhances the antineoplastic effects of selective PI3Kα inhibition in medulloblastoma. Sci Rep 9: 12822, 2019.
10. Chaturvedi NK, Kling MJ, Coulter DW, McGuire TR, Ray S, Kesherwani V, Joshi SS and Sharp JG: Improved therapy for medulloblastoma: Targeting hedgehog and PI3K-mTOR signaling pathways in combination with chemotherapy. Oncotarget 9: 16619-16633, 2018.
11. Borders EB, Binova C and Medina PJ: Mammalian target of rapamycin: Biological function and target for novel anticancer agents. Am J Health Syst Pharm 67: 2095-2106, 2010.
12. Brown RE, Tan D, Taylor JS, Miller M, Prichard JW and Kott MM: Morphoproteomic confirmation of constitutively activated mTOR, ERK, and NF-kappaB pathways in high risk neuro-blastoma, with cell cycle and protein analyte correlates. Ann Clin Lab Sci 37: 141-147, 2007.
13. Zenali MJ, Zhang PL, Bendel AE and Brown RE: Morphoproteomic confirmation of constitutively activated mTOR, ERK, and NF-kappaB pathways in Ewing family of tumors. Ann Clin Lab Sci 39: 160-166, 2009.
14. Mateo-Lozano S, Gokhale PC, Soldatenkov VA, Dritschilo A, Tirado OM and Notario V: Combined transcriptional and translational targeting of EWS/FLI-1 in Ewing's sarcoma. Clin Cancer Res 12: 6781-6790, 2006.
15. Houghton PJ, Morton CL, Kolb EA, Gorlick R, Lock R, Carol H, Reynolds CP, Maris JM, Keir ST, Billups CA and Smith MA: Initial testing (stage 1) of the mTOR inhibitor rapamycin by the pediatric preclinical testing program. Pediatr Blood Cancer 50: 799-805, 2008.
16. Johnsen JI, Segerström L, Orrego A, Elfman L, Henriksson M, Kågedal B, Eksborg S, Sveinbjörnsson B and Kogner P: Inhibitors of mammalian target of rapamycin downregulate MYCN protein expression and inhibit neuroblastoma growth in vitro and in vivo. Oncogene 27: 2910-2922, 2008.
17. Vo KT, Karski EE, Nasholm NM, Allen S, Hollinger F, Gustafson WC, Long-Boyle JR, Shiboski S, Matthay KK and DuBois SG: Phase 1 study of sirolimus in combination with oral cyclophosphamide and topotecan in children and young adults with relapsed and refractory solid tumors. Oncotarget 8: 23851-23861, 2017.
18. Houghton PJ, Morton CL, Gorlick R, Lock RB, Carol H, Reynolds CP, Kang MH, Maris JM, Keir ST, Kolb EA, *et al*: Stage 2 combination testing of rapamycin with cytotoxic agents by the pediatric preclinical testing program. Mol Cancer Ther 9: 101-112, 2010.
19. Semela D, Piguet AC, Kolev M, Schmitter K, Hlushchuk R, Djonov V, Stoupis C and Dufour JF: Vascular remodeling and antitumoral effects of mTOR inhibition in a rat model of hepatocellular carcinoma. J Hepatol 46: 840-848, 2007.
20. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, *et al*: Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: Involvement of vascular endothelial growth factor. Nat Med 8: 128-135, 2002.
21. Qayed M, Cash T, Tighiouart M, MacDonald T, Goldsmith KC, KeanPatty Church LS and Katzenstein HM: A phase I study of sirolimus in combination with metronomic therapy in children with recurrent and refractory solid/CNS tumors. J Clin Oncol: May 20, 2015 (Epub ahead of print).
22. Morgenstern DA, Marzouki M, Bartels U, Irwin MS, Sholler GL, Gammon J, Yankanah R, Wu B, Samson Y and Baruchel S: Phase I study of vinblastine and sirolimus in pediatric patients with recurrent or refractory solid tumors. Pediatr Blood Cancer 61: 128-133, 2014.
23. Cash T: Sirolimus in combination with metronomic chemotherapy in children with recurrent and/or refractory solid and CNS tumors (AflacST1502). ClinicalTrials.gov Identifier: NCT02574728, 2022.
24. Putnam AR and Wallentine JC (eds): Diagnostic Pathology: Pediatric Neoplasms. Salt Lake City, UT, pp984, 2012.
25. Ole Juhnke B, Mynarek M, von Hoff K, Klagges S, Kortmann RD and Rutkowski S: HIT-MED guidance for patients with newly diagnosed medulloblastoma ependymoma CNS embryonal tumour and pineoblastoma. Version 4.0-02, 2017.
26. Alammar H, Nassani R, Alshehri MM, Aljohani AA and Alrfaei BM: Deficiency in the treatment description of mTOR inhibitor resistance in medulloblastoma, a systematic review. Int J Mol Sci 23: 464, 2021.
27. Bergers G and Benjamin LE: Tumorigenesis and the angiogenic switch. Nat Rev Cancer 3: 401-410, 2003.
28. Wen J and Hadden MK: Medulloblastoma drugs in development: Current leads, trials and drawbacks. Eur J Med Chem 215: 113268, 2021.
29. Kumar V, Kumar V, McGuire T, Coulter DW, Sharp JG and Mahato RI: Challenges and recent advances in medulloblastoma therapy. Trends Pharmacol Sci 38: 1061-1084, 2017.
30. von Bueren AO, von Hoff K, Pietsch T, Gerber NU, Warmuth-Metz M, Deinlein F, Zwiener I, Faldum A, Fleischhack G, Benesch M, *et al*: Treatment of young children with localized medulloblastoma by chemotherapy alone: Results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. Neuro Oncol 13: 669-679, 2011.
31. Bahl A and Bakhshi S: Metronomic chemotherapy in progressive pediatric malignancies: Old drugs in new package. Indian J Pediatr 79: 1617-1622, 2012.
32. Bowers DC, Aquino VM, Leavey PJ, Bash RO, Journeycake JM, Tomlinson G, Mulne AF, Haynes HJ and Winick NJ: Phase I study of oral cyclophosphamide and oral topotecan for children with recurrent or refractory solid tumors. Pediatr Blood Cancer 42: 93-98, 2004.
33. Sterba J, Pavelka Z, Andre N, Ventruba J, Skotakova J, Bajciova V, Bronisova D, Dubska L and Valik D: Second complete remission of relapsed medulloblastoma induced by metronomic chemotherapy. Pediatr Blood Cancer 54: 616-617, 2010.
34. Peyrl A, Chocholous M, Kieran MW, Azizi AA, Prucker C, Czech T, Dieckmann K, Schmook MT, Haberler C, Leiss U and Slavc I: Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors. Pediatr Blood Cancer 59: 511-517, 2012.
35. Yoshida S, Amano H, Hayashi I, Kitasato H, Kamata M, Inukai M, Yoshimura H and Majima M: COX-2/VEGF-dependent facilitation of tumor-associated angiogenesis and tumor growth in vivo. Lab Invest 83: 1385-1394, 2003.
36. D'Amato RJ, Loughnan MS, Flynn E and Folkman J: Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 91: 4082-4085, 1994.
37. Carcamo B and Francia G: Cyclic metronomic chemotherapy for pediatric tumors: Six case reports and a review of the literature. J Clin Med 11: 2849, 2022.
38. Slavc I, Peyrl A, Gojo J, Holm S, Blomgren K, Sehested AM, Leblond P and Czech T: MBCL-43. Reccurent medulloblastoma-long-term survival with a 'MEMMAT' based antiangiogenic approach. Neuro Oncol 22 (Suppl 3): iii397, 2020.
39. Simsek C, Esin E and Yalcin S: Metronomic chemotherapy: A systematic review of the literature and clinical experience. J Oncol 2019: 5483791, 2019.

40. Stempak D, Gammon J, Halton J, Moghrabi A, Koren G and Baruchel S: A pilot pharmacokinetic and antiangiogenic biomarker study of celecoxib and low-dose metronomic vinblastine or cyclophosphamide in pediatric recurrent solid tumors. J Pediatr Hematol Oncol 28: 720-728, 2006.
41. Sterba J, Valik D, Mudry P, Kepak T, Pavelka Z, Bajciova V, Zitterbart K, Kadlecova V and Mazanek P: Combined biodifferentiating and antiangiogenic oral metronomic therapy is feasible and effective in relapsed solid tumors in children: Single-center pilot study. Onkologie 29: 308-313, 2006.
42. Allen CE, Laetsch TW, Mody R, Irwin MS, Lim MS, Adamson PC, Seibel NL, Parsons DW, Cho YJ and Janeway K; Pediatric MATCH Target and Agent Prioritization Committee: Target and agent prioritization for the children's oncology group-national cancer institute pediatric MATCH trial. J Natl Cancer Inst 109: djw274, 2017.
43. De Vita S, De Matteis S, Laurenti L, Chiusolo P, Reddiconto G, Fiorini A, Leone G and Sica S: Secondary Ph+ acute lymphoblastic leukemia after temozolomide. Ann Hematol 84: 760-762, 2005.