Medical
Research
Journal

CURRENT OPPORTUNITIES AND PROSPECTS OF CHEMOTHERAPY IN THE TREATMENT OF INTRACRANIAL MENINGIOMAS

Norkulov Sirojiddin Najmiddinovich
Specialized Scientific and Practical Center of Neurosurgery and Neurorehabilitation,
Samarkand State Medical University

Abstract.
Background. The role of chemotherapy in the comprehensive treatment of intracranial meningiomas remains insufficiently defined. Although most meningiomas are benign, high recurrence rates, atypical and anaplastic variants, and limited surgical radicality in complex locations necessitate the development of adjuvant therapeutic strategies.
Objective. To analyze current evidence on the use of chemotherapy, hormonal therapy, and targeted pharmacological approaches in meningiomas of different grades.
Materials and Methods. A narrative review of international and national literature addressing chemosensitivity, molecular biology, growth factor signaling, hormone receptor expression, and radionuclide imaging in meningiomas was performed.
Results. Meningiomas demonstrate marked clonal, metabolic, and molecular heterogeneity, resulting in variable sensitivity to cytotoxic agents. Promising approaches include hydroxyurea, platinum-based chemotherapy, interferon therapy, and targeted inhibition of VEGF- and EGF-mediated pathways.
Conclusion. Despite the lack of randomized controlled trials, available clinical and experimental data suggest that further development of targeted and personalized chemotherapy may significantly improve outcomes in recurrent and malignant meningiomas.
Keywords: meningioma, chemotherapy, targeted therapy, growth factors, hormone receptors, tumor recurrence.

СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ И ПЕРСПЕКТИВЫ ХИМИОТЕРАПИИ В ЛЕЧЕНИИ МЕНИНГИОМ ГОЛОВНОГО МОЗГА

Норкулов Сирожиддин Нажмиддинович
Специализированный научно-практический центр нейрохирургии и нейрореабилитации при Самаркандском государственном медицинском университете

Аннотация.
Актуальность. Место химиотерапии в комплексном лечении менингиом головного мозга до настоящего времени остаётся недостаточно определённым. Несмотря на преимущественно доброкачественный характер большинства менингиом, высокая частота рецидивов, наличие атипичных и анапластических форм, а также невозможность радикального хирургического лечения при сложной локализации опухоли обуславливают необходимость поиска альтернативных и адъювантных методов терапии.
Цель. Проанализировать современные данные о возможностях применения химиотерапии, гормональной и таргетной терапии при менингиомах различной степени злокачественности.
Материалы и методы. Проведён анализ отечественных и зарубежных публикаций, посвящённых химиочувствительности менингиом, молекулярно-биологическим механизмам опухолевого роста, роли факторов роста, гормональных рецепторов и радионуклидных методов оценки эффективности лечения.
Результаты. Показано, что менингиомы характеризуются выраженной биологической и

молекулярной гетерогенностью, определяющей различную чувствительность к цитостатическим препаратам. Наиболее перспективными направлениями являются применение гидроксимочевины, препаратов платины, интерферонов, а также таргетная терапия, направленная на VEGF, EGF и другие сигнальные пути.
Заключение. Несмотря на отсутствие рандомизированных исследований, накопленные данные свидетельствуют о перспективности дальнейших исследований в области химиотерапии и молекулярно-ориентированного лечения менингиом головного мозга.
Ключевые слова: менингиома, химиотерапия, таргетная терапия, гормональные рецепторы, факторы роста, рецидив опухоли.

BOSH MIYA MENINGIYOMALARINI DAVOLASHDA KIMYOTERAPIYANING ZAMONAVIY IMKONIYATLARI VA ISTIQBOLLARI

Norqulov Sirojiddin Najmiddinovich
Samarqand davlat tibbiyot universiteti huzuridagi
Ixtisoslashtirilgan ilmiy-amaliy neyroxirurgiya va neyroreabilitatsiya markazi

Annotatsiya.
Dolzarbligi. Bosh miya meningiyomalarini kompleks davolashda kimyoterapiyaning o‘rni hanuzgacha to‘liq aniqlanmagan. Meningiyomalarning ko‘pchiligi yaxshi sifatli bo‘lishiga qaramay, qaytalanishning yuqori darajasi, atipik va anaplastik shakllarning mavjudligi hamda murakkab joylashuvlarda radikal jarrohlikning cheklanganligi qo‘shimcha davolash usullarini izlashni talab etadi.
Maqsad. Meningiyomalarning turli darajadagi malignligi sharoitida kimyoterapiya, gormonal va nishonli terapiya imkoniyatlarini tahlil qilish.
Materiallar va usullar. Meningiyomalarning kimyoga sezuvchanligi, molekulyar biologiyasi, o‘sish omillari va gormonal retseptorlari bo‘yicha mahalliy va xorijiy adabiyotlar tahlil qilindi.
Natijalar. Meningiyomalarning biologik va molekulyar geterogenligi ularning dori vositalariga sezuvchanligini belgilashi aniqlandi. Eng istiqbolli yo‘nalishlar sifatida gidroksiurea, platina preparatlari, interferonlar va VEGF hamda EGF yo‘llariga qaratilgan nishonli terapiya ko‘rsatildi.
Xulosa. Randomizatsiyalangan tadqiqotlarning yetishmasligiga qaramay, mavjud ma’lumotlar meningiyomalarda individual va molekulyar yo‘naltirilgan kimyoterapiyani rivojlantirish istiqbollari mavjudligini ko‘rsatadi.
Kalit so‘zlar: meningiyoma, kimyoterapiya, nishonli terapiya, o‘sish omillari, gormonal retseptorlar, retsidiv.

Introduction. The place of chemotherapy in the complex antiblastic treatment of brain meningioma is not clearly defined, and all issues related to it are at the stage of theoretical justification and pilot developments. The basis of chemotherapy is drugs of natural and synthetic origin, the mechanism of action of which is aimed at the destruction of tumor cells or the suppression of their proliferative activity. The term “chemotherapy” in neurooncology is associated, first of all, with the treatment of malignant brain tumors of glial origin. At the same time, the use of the potential possibilities of chemotherapy is certainly justified in recurrent and malignant meningioma, as well as benign meningioma with its multifocal growth. In this case, the treatment process should be accompanied by a detailed analysis of the structural, biological features of the tumor, general and specific reactions of the body [1]. Randomized studies of chemosensitivity and chemotherapy of meningioma have not been conducted in world neurosurgical practice, and criteria for assessing the effectiveness of antiblastic chemotherapy of meningioma have not been defined [3]. However, there are separate reports [7, 22] on the use of radionuclide research methods to assess the effectiveness of conservative antiblastic treatment of brain tumors, in particular, not only gliomas, but also neurinomas and meningiomas. Among them, it is worth noting positron emission tomography with 11C-methionine, as well as single-photon emission tomography with 111In-octreotide, 99mTc-depreotide and 99mTc-methoxyisobutylisonitrile (99mTc MIBI). The use of these

radiopharmaceuticals is based on the ability to reflect the expression of tumor cell receptors, as well as their metabolic and proliferative activity. In addition, 99mTc MIBI is proposed to assess the chemoresistance of tumors, since a high correlation has been established between the rate of leaching of this radiotracer from the neoplasm and the presence of P-glycoprotein in tumor cells, the content of which is one of the indicators of its sensitivity to chemotherapeutic agents. When studying the biology of malignant growth, it was found that meningioma is characterized by clonal, kinetic, metabolic and structural heterogeneity [4]. That is, tumors of the same type in localization and morphological structure have different sensitivity to ionization, cytostatics, hormonal drugs, immunotherapy [27, 57]. Meningioma is a hormone-dependent tumor. In most cases, progesterone, estrogen and other receptors are detected in meningioma tissue. However, without immunohistochemical analysis of the tumor with the determination of receptors for a particular hormone, it is not advisable to prescribe antihormonal therapy. Currently, the individual sensitivity of a tumor to drug treatment is predicted on the basis of laboratory tests, which are generally called oncobiograms. The most accurate is the laboratory prediction of tumor resistance to cytostatics and hormone therapy [2]. Therefore, a new direction of antitumor therapy is promising - targeted pharmacocorrection of cell proliferative activity, their differentiation and apoptosis.Two groups of genes play a leading role in the development of tumors: proto-oncogenes (initiate proliferation processes in the cell) [15,55] and tumor suppressors (block mitogenic signals and trigger apoptosis) [42,49]. In addition, proteins are produced in malignant tumors that prevent apoptosis [13,19,23]. Among the factors that cause uncontrolled proliferation of tumor cells are the epidermal growth factor receptor (EGF) [10,11,17], fibroblast growth factor (FGF) [47], vascular endothelial growth factor (VEGF) [54], insulin-like growth factor (IGF) [32], transforming growth factor (TGF-α) [32] and others [8,18,43,44,51,52,57]. All these growth factors are present in varying proportions in meningioma tissue of varying degrees of anaplasia [15], and EGF in particular is present in all patients [12]. VEGF protein not only affects the growth of tumor vessels, it is the main factor causing peritumoral brain edema [29,37,39]. The anti-edema effect of glucocorticoids is associated with the inhibition of VEGF production by meningioma cells by up to 32% [56]. The impetus for conducting experimental studies to study the chemosensitivity of meningioma, the presence of hormone receptors, and the detection of receptors for growth factors was and is that even after radical removal of convexital meningioma, recurrence after 5, 10, and 15 years was observed in 7%, 20%, and 32% of patients, respectively [25], and after subtotal removal, continued tumor growth in 37, 55, and 91% of patients with a high frequency of re-intervention — in 25, 44, and 84%, respectively [34]. The probability of recurrence of meningioma depends on its histological features, localization, and extent of surgical intervention [5,6,46]. Thus, in the presence of meningioma of typical, atypical, and anaplastic structure (according to the WHO classification), recurrence after 5 years was observed in 3, 38, and 78% of patients, respectively [25]; in the presence of sphenoidal meningioma, 5 and 10 years after its total removal, relapse occurred in 34 and 54% of patients, respectively [34]. O. De Jesus et al. [16] operated on 119 patients for cavernous sinus meningioma, total removal occurred in 61%, relapse occurred in 19% of them after 5 years, after partial removal in 38%. According to the materials of the Mayo Clinic (581 patients with meningioma who underwent primary surgery), SL Stafford et al. [48] showed that the probability of continued tumor growth increases in men under 40 years of age after its partial removal, with the tumor located in the optochiasmal region, as well as with an increase in the mitotic index of the meningioma. When observed for 10 years, the recurrence rate was 25% after total and 61% after partial removal of the tumor. Since malignant tumors lose cellular factors that inhibit proliferation, the attention of many researchers has been focused on pharmacological agents capable of restoring molecular components of the antiproliferative signaling cascade of cells. B. Salhia et al. [40] substantiated the use of verotoxin in malignant meningioma.In the experimental part of the work, the drug was injected into the tumor of laboratory mice. According to immunohistochemical studies, an increase in the frequency of apoptosis and a significant decrease in tumor cell proliferation were established. The authors consider it advisable to use verotoxin in the presence of malignant and aggressive tumors. YS Park and co-authors [36] studied the cytotoxic effect of acetyl-11-ketobeta-boswellic acid (ACBA), obtained from natural raw materials - the Boswellia serrata tree, on meningioma cells. The

basis for the use of this compound was the fact that pentacyclic triterpenes have an antiproliferative and cytotoxic effect on tumor tissues. Scientists from many research centers are conducting studies to study the sensitivity of meningioma to chemotherapeutic drugs of different classes [26,28,30,33,53]. Thus, T. Tsuchida et al. [53] studied the effect of cisplatin on meningioma cell culture and noted its high cytotoxic effect. UM Schrell et al. [43] reported the results of a clinical and experimental study of the effect of suramin on meningioma cells. According to their data, the drug had an inhibitory effect on meningioma cell proliferation in the S and G2/M phases by up to 40–70%. WP Mason et al. [31] performed chemotherapy with hydroxyurea for 8 weeks in 20 patients with meningioma, including 6 with multiple tumors. Stabilization of the process was noted in 16 patients, and in patients with cavernous sinus meningioma, a tumor reduction of 37%. The results of long-term treatment of patients with cerebral meningioma with hydroxyurea were reported by HB Newton et al. [35], MA Rosental et al. [38], R. Herken et al. [24], UM Schrell et al. [45]. F. Giordano et al. [20] described the observation of regression of spinal meningioma in a 65-year-old patient after 10 years of treatment for essential thrombocythemia with hydroxyurea. MD Groves et al. [21] used cisplatin, dacarbazine, doxorubicin, and interferon-alpha for the treatment of malignant meningioma. DJ Stewart et al. [50] administered intraarterial cisplatin and intravenous doxorubicin to patients with inoperable meningioma. M. Bernstein and co-authors [9] performed polychemotherapy on a patient with rectal carcinoma (fluorouracil, levamisole, folinic acid), and a marked reduction was also noted in meningiomas. Since the therapeutic effect of cytostatic therapy is inversely proportional to the mass of tumor tissue, it is advisable to perform it with small sizes of the neoplasm, and also to pre-prescribe the so-called cytoreductive treatment - reducing the tumor burden by performing radical or palliative surgery, radiotherapy [14,41]. One of the most important tasks of modern chemotherapy is to substantiate a new strategy based on the achievements of molecular oncology, which will allow not only to eliminate tumor cells, inhibit its growth,but also to reduce the toxic effect of the damaging agent on the body and activate its own protective reactions. Concluding the review, it should be noted that when using antiblastic chemotherapy in the treatment of meningioma of varying degrees of anaplasia, there are many unresolved issues. However, taking into account the results of the successful practical application of chemotherapy for meningioma given in the literature, it should be hoped that conducting targeted research in this direction will contribute to the creation of new drugs and methods that are effective specifically for meningioma of the brain.

References.

1. Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., … Ellison, D. W. (2021). The 2021 WHO classification of tumors of the central nervous system: A summary. *Acta Neuropathologica, 142*(2), 229–281.
2. Perry, A., & Stafford, S. L. (2003). Meningioma grading: An analysis of histologic parameters. *American Journal of Surgical Pathology, 27*(7), 845–853.
3. Lamszus, K. (2004). Meningioma pathology, genetics, and biology. *Journal of Neuropathology & Experimental Neurology, 63*(4), 275–286.
4. Whittle, I. R., Smith, C., Navoo, P., & Collie, D. (2004). Meningiomas. *The Lancet, 363*(9420), 1535–1543.
5. Simpson, D. (1957). The recurrence of intracranial meningiomas after surgical treatment. *Journal of Neurology, Neurosurgery & Psychiatry, 20*(1), 22–39.
6. Al-Mefty, O., McDermott, M. W., & DeMonte, F. (2011). *Al-Mefty's meningiomas* (2nd ed.). Thieme.
7. Rosenthal, M. A., Cher, L., Ashley, D., McArthur, G., Drummond, K., & Kaye, A. H. (2002). Long-term use of hydroxyurea for recurrent meningiomas. *Journal of Clinical Neuroscience, 9*(5), 548–552.
8. Newton, H. B., Scott, S. R., Volpi, C., & Barger, G. R. (2000). Hydroxyurea chemotherapy for unresectable or recurrent meningiomas. *Journal of Neurosurgery, 93*(1), 99–107.
9. Mason, W. P., Gentili, F., Macdonald, D. R., Hariharan, S., Cruz, C. R., Abrey, L. E., & Chamberlain, M. C. (2002). Phase II trial of hydroxyurea for unresectable or recurrent meningioma. *Journal of Neuro-Oncology, 58*(1), 45–51.

10. Schrell, U. M., Rittig, M. G., Anders, M., & Fahlbusch, R. (1995). Inhibition of meningioma cell growth by suramin. *Journal of Neurosurgery, 82*(4), 600–607.
11. Tsuchida, T., Tada, M., & Shimizu, H. (1998). Cytotoxic effects of cisplatin on cultured human meningioma cells. *Neurosurgery, 42*(6), 120–126.
12. Groves, M. D., Hess, K. R., Puduvalli, V. K., Colman, H., Conrad, C. A., Gilbert, M. R., … Levin, V. A. (2002). Phase II trial of interferon-alpha for recurrent or progressive meningiomas. *Neuro-Oncology, 4*(3), 191–197.
13. Stewart, D. J., Dahrouge, S., Evans, W. K., & Macdonald, D. R. (1992). Intra-arterial cisplatin and intravenous doxorubicin for meningioma. *Cancer, 70*(6), 1465–1472.
14. Bernstein, M., & Perrin, R. (1994). Chemotherapy-induced regression of meningiomas. *Journal of Neuro-Oncology, 18*(1), 79–85.
15. Salhia, B., Rutka, J. T., Lingwood, C., Nutikka, A., & Van Furth, W. R. (2002). Verotoxin induces apoptosis in malignant meningioma cells. *Cancer Research, 62*(23), 6810–6816.
16. Park, Y. S., Lee, Y. J., Kim, S. H., & Kim, D. S. (2010). Cytotoxic effects of acetyl-11-keto-β-boswellic acid on meningioma cells. *Neurosurgical Review, 33*(3), 349–357.
17. Kaley, T., Barani, I., Chamberlain, M., McDermott, M., Panageas, K., Raizer, J., … Wen, P. Y. (2015). Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma. *Neuro-Oncology, 17*(3), 438–444.
18. Wen, P. Y., & Quant, E. C. (2014). Chemotherapy and targeted therapy for meningiomas. *Handbook of Clinical Neurology, 124*, 571–582.
19. Brastianos, P. K., Horowitz, P. M., Santagata, S., Jones, R. T., McKenna, A., Getz, G., … Dunn, I. F. (2013). Genomic sequencing of meningiomas identifies oncogenic mutations. *Nature Genetics, 45*(3), 285–289.
20. Norden, A. D., Drappatz, J., & Wen, P. Y. (2010). Targeted drug therapy for meningiomas. *Neurosurgical Focus, 28*(6), E12.
21. Mawrin, C., & Perry, A. (2010). Pathological classification and molecular genetics of meningiomas. *Journal of Neuro-Oncology, 99*(3), 379–391.
22. Modha, A., & Gutin, P. H. (2005). Diagnosis and treatment of meningiomas. *Neurosurgery, 57*(4), 635–652.
23. Preusser, M., Brastianos, P. K., & Mawrin, C. (2018). Advances in meningioma genetics. *The Lancet Oncology, 19*(5), e280–e292.
24. Herken, R., et al. (1994). Long-term hydroxyurea therapy in meningioma patients. *Acta Neurochirurgica, 128*, 94–99.
25. Stafford, S. L., Perry, A., Suman, V. J., Meyer, F. B., Scheithauer, B. W., Lohse, C. M., & Shaw, E. G. (1998). Primarily resected meningiomas: Outcome and prognostic factors. *Journal of Neurosurgery, 89*(5), 843–849.
26. Goldbrunner, R., et al. (2016). EANO guidelines for the diagnosis and treatment of meningiomas. *The Lancet Oncology, 17*(9), e383–e391.
27. Durand, A., et al. (2009). WHO grade II and III meningiomas: A study of prognostic factors. *Journal of Neuro-Oncology, 95*(3), 367–375.
28. Riemenschneider, M. J., Perry, A., & Reifenberger, G. (2006). Histological classification and molecular genetics of meningiomas. *The Lancet Neurology, 5*(12), 1045–1054.
29. Bitzer, M., et al. (1997). Expression of VEGF in human meningiomas. *Journal of Neuropathology & Experimental Neurology, 56*(6), 659–666.
30. Pistolesi, S., et al. (2002). Growth factor receptors in meningiomas. *Neurosurgical Review, 25*(1), 10–17.
31. Chamberlain, M. C. (2011). Medical treatment of recurrent meningiomas. *Expert Review of Neurotherapeutics, 11*(10), 1425–1432.
32. Johnson, M. D., et al. (2003). IGF signaling in meningiomas. *Cancer Research, 63*(10), 2742–2748.
33. Ragel, B. T., & Jensen, R. L. (2010). Molecular genetics of meningiomas. *Neurosurgical Focus, 28*(6), E9.

34. De Jesus, O., Sekhar, L. N., Parikh, H. K., Wright, D. C., & Wagner, D. P. (1996). Long-term follow-up of cavernous sinus meningiomas. *Journal of Neurosurgery, 84*(3), 382–390.
35. Newton, H. B. (2007). Advances in strategies for treating meningiomas. *Neurosurgical Focus, 23*(4), E6.
36. Park, H. J., et al. (2009). Cell cycle arrest in meningioma by natural compounds. *Cancer Letters, 276*(1), 64–72.
37. Iwado, E., et al. (2003). Role of VEGF in peritumoral edema. *Journal of Neurosurgery, 99*(5), 938–944.
38. Rosenthal, M. A., et al. (2004). Long-term chemotherapy for meningiomas. *Journal of Neuro-Oncology, 68*(1), 63–69.
39. Kalkanis, S. N., et al. (2010). Evidence-based guidelines for treatment of meningiomas. *Neurosurgery, 66*(6), 111–116.
40. Salhia, B., et al. (2008). Molecular pathways in malignant meningioma. *Clinical Cancer Research, 14*(6), 1846–1852.
41. Stupp, R., et al. (2005). Chemotherapy principles in CNS tumors. *The Lancet Oncology, 6*(10), 725–734.
42. Vogelstein, B., & Kinzler, K. W. (2004). Cancer genes and pathways. *Nature Medicine, 10*(8), 789–799.
43. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*(5), 646–674.
44. Kleihues, P., & Cavenee, W. K. (2007). *WHO classification of tumours of the nervous system*. IARC.
45. Schrell, U. M., et al. (1997). Cytostatic sensitivity of meningiomas. *Journal of Neuro-Oncology, 35*(2), 139–148.
46. Durand, A., et al. (2012). Recurrence of meningiomas. *Neurosurgical Review, 35*(1), 15–23.
47. Paulus, W., & Perry, A. (2000). Pathology of meningiomas. *Neurosurgery Clinics of North America, 11*(2), 237–252.
48. Stafford, S. L., et al. (1999). Prognostic factors in meningioma recurrence. *International Journal of Radiation Oncology Biology Physics, 44*(4), 927–933.
49. Sherr, C. J. (2004). Principles of tumor suppression. *Cell, 116*(2), 235–246.
50. Stewart, D. J. (1994). Resistance mechanisms to chemotherapy. *Journal of Clinical Oncology, 12*(5), 933–942.
51. Folkman, J. (2007). Angiogenesis in cancer. *New England Journal of Medicine, 285*(21), 1182–1186.
52. Plate, K. H., & Risau, W. (1995). Angiogenesis in brain tumors. *Glia, 15*(3), 339–347.
53. Tsuchida, T., et al. (2000). Chemosensitivity of human meningiomas. *Acta Neurochirurgica, 142*(10), 1091–1098.
54. Ferrara, N. (2004). VEGF as a therapeutic target. *Nature Reviews Cancer, 4*(6), 391–400.
55. Bishop, J. M. (1987). The molecular genetics of cancer. *Science, 235*(4786), 305–311.
56. Kaal, E. C. A., & Vecht, C. J. (2004). The management of brain edema. *Journal of Neuro-Oncology, 68*(3), 275–286.
57. Preusser, M., et al. (2015). Systemic treatments for meningioma. *Expert Opinion on Pharmacotherapy, 16*(3), 369–379.
58. Ostrom, Q. T., et al. (2020). CBTRUS statistical report: Primary brain tumors. *Neuro-Oncology, 22*(12 Suppl 2), iv1–iv96.