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THE SINGULARITIES OF TEMOZOLOMIDE PHARMACOTHERAPEUTIC EFFECTS IN BRAIN TUMOR THERAPEUTIC APPLICATIONS

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ტემოზოლომიდის ფარმაკოთერაპიული ეფექტის თავისებურებები თავის ტვინის სიმსივნეების მკურნალობაში

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, თბილისი, საქართველო

რეზიუმე

ტემოზოლომიდი არის ყველაზე ფართოდ გამოყენებული ქიმიოთერაპიული საშუალება გლიობლასტომით დაავადებული პაციენტებისთვის, მიუხედავად იმისა, რომ ნამკურნალები პაციენტების დაახლოებით ნახევარი რეზისტენტულია ტემოზოლომიდის მიმართ, სხვა ნაწილი პაციენტებისა საბოლოოდ გამოჯანმრთელდნენ. არსებული თერაპიის შეზღუდული ეფექტურობის გამო, იმუნოთერაპია ფართოდ არის გამოყენებული გლიობლასტომის მქონე პაციენტებში. თუმცა, იმუნოთერაპიის თავდაპირველმა კვლევებმა გლიობლასტომის მქონე პაციენტებში, როგორც მონოთერაპიის სახით, გამოიღო იმედგაცრუებული შედეგები. ამიტომ შესწავლილია კომბინირებული მკურნალობის სტრატეგიები. ტემოზოლომიდს აქვს რამდენიმე ეფექტი იმუნურ სისტემაზე, რაც დამოკიდებულია წამლის მიწოდების მეთოდზე და დოზირების სტრატეგიაზე, რამაც შეიძლება გამოიწვიოს იმუნოთერაპიის არაპროგნოზირებადი შედეგები. ტემოზოლომიდს აქვს როგორც პირდაპირი სიმსივნის საწინააღმდეგო მოქმედება, ასევე იმუნომოდულატორული თვისებები. ტემოზოლომიდის გამოყენების დრო და დოზა მნიშვნელოვნად ცვლის იმუნურ უჯრედებზე და სიმსივნის მიკროგარემოზე გამოვლენილ ეფექტს. ტემოზოლომიდის ეფექტი ახალ თერაპიებზე, როგორიცაა იმუნური ინჰიბიტორები, ამჟამად კვლევის პროცესშია. ტემოზოლომიდის გამოყენების დოზირებისა და დროის ეფექტი და იმუნური დათრგუნვა მუდმივი ყურადღების ცენტრშია. ტემოზოლომიდის კომბინატორული გამოყენების პერსპექტივები იმუნოთერაპიასთან ერთად საჭიროებს ფრთხილად განხილვას ოპტიმალური შედეგების უზრუნველსაყოფად.

Introduction: Although brain tumors account for only 2% of all adult malignancies, they are among the most disabling malignancies. Temozolomide, an oral alkylating agent, is approved for the treatment of recurrent malignant glioma in daily doses over 5-day cycles. Continuous dosing regimens with higher dosing rates are being studied, but no improvement in efficacy has yet been demonstrated. The benefit of temozolomide monotherapy in recurrent disease is best seen within a few weeks. Therefore, this drug is currently being clinically tested as neoadjuvant chemotherapy or with concomitant radiation therapy in patients with newly diagnosed glioma. The combination of temozolomide with other brain tumor drugs is being investigated in several phase I studies [1-3].

Aim of the research was to study and analyse the singularities of temozolomide pharmacotherapeutic effects in brain tumor therapeutic applications.

Methodology: The main question of this article was to research and analyses the singularities of temozolomide pharmacotherapeutic effects in brain tumor therapeutic applications. We have searched and analyzed PubMed, Web of Sciences, Clinical key, Tomson Routers and Google Scholar mostly, using search terms bases, including the words to research and analyses specificities of invocation, outlook and character of the clinical pharmacists globally. We brought together all published data to comprehensively examine the effects in a systematic review and overview, to define the singularities of temozolomide pharmacotherapeutic effects in brain tumor therapeutic applications.

Results and Discussion: Temozolomide is lipophilic in nature and acts as a potent alkylating agent. Along with surgery and radiation therapy, temozolomide is currently the standard adjuvant therapy for patients with newly diagnosed glioblastoma. Temozolomide, whose chemical name is 3,4-dihydro-3-

methyl-4-oxoimidazole, undergoes spontaneous hydrolysis to form the active metabolite 5-(3-methyl-1-triazen-1-yl) imidazole-4-carboxamide. Temozolomide is stable under acidic conditions, while this reaction proceeds at physiological pH and alkaline conditions and involves the interaction of the H2O molecule with the C4 atom of temozolomide, where the heterocyclic ring opens to form MTIK and a carbon dioxide molecule. The inherent properties of MTIC prevent it from effectively interacting with tumor cell membranes, thereby reducing its ability to penetrate target cells. MTIC is unstable and converted to methyl diazonium, a reactive compound that transfers a methyl group to DNA and forms a degradation product, 4-amino-5-imidazolecarboxamide (AIC), which is excreted from the body. The action of temozolomide is highly pH dependent; Slightly higher basic intracellular pH values in tumor cells (compared to normal cells) have been shown to contribute to temozolomide-induced damage to tumor cells. In fact, the goal is to elucidate the role of pH in the antitumor effects of temozolomide. According to the report, the combination of temozolomide with pH adjusting agents may enhance the therapeutic effect of temozolomide [4-6].

Temozolomide is an FDA-approved oral alkylating agent used in newly diagnosed and recurrent high-grade gliomas. Although temozolomide in combination with radiation therapy did not significantly improve overall survival in high-grade glioma, previous studies have shown that brain levels of temozolomide represent only 20% of systemic drug levels. The maximum concentration of temozolomide in the brain is reached approximately 1-2 hours after ingestion. Following oral administration, temozolomide is cleaved from a prodrug to the highly reactive alkylating agent methyl triazenyl imidazole carboxamide (MTIC). Previous studies have used intracerebral micro dialysis (MDC) catheters to measure extracellular brain concentrations of temozolomide in primary or metastatic brain tumors. The use of continuous DCM for long-term monitoring of brain tissue is not new, and this method is mainly used in traumatic brain injury [7-9].

The most compelling role for temozolomide moving forward is as an immunomodulator for glioblastoma patients receiving immunotherapy. Temozolomide has the benefit of having direct antitumor effects in addition to significant effects on host immunity. Several studies have demonstrated the potential role of temozolomide for immunomodulation. Sampson et al demonstrated that combination of standard or dose-intensified temozolomide with EGFRvIII targeted peptide vaccine enhanced EGFRvIII-specific immune responses. Compensated homeostatic cytokines after lymphodepleted temozolomide cause enhanced immune responses by reduction of the T-cell activation threshold and proliferation induction. Although both standard and dose-intense temozolomide were capable of eliminating EGFRvIII-expressing tumor cells in glioblastoma patients, dose-intensified temozolomide produced higher humoral and delayed-type hypersensitivity responses in EGFRvIII targeted immunotherapy [10,11].

Temozolomide is an imidazotetrazine derivative and a second-generation alkylating agent with antitumor activity. When taken orally, temozolomide capsules are completely absorbed and well distributed in tissues; Thus, the drug crosses the blood-brain barrier, which leads to predictable side effects. The toxic profile and side effects of temozolomide are relatively mild and well tolerated by patients who have completed six or more courses. Temozolomide has been associated with anemia, lymphopenia, neutropenia, and severe thrombocytopenia. In clinical practice, temozolomide is widely used to treat glioma, non-small cell lung cancer, leukemia, melanoma, lymphoma, and some solid tumors. Among other chemotherapy drugs, temozolomide has the strongest antitumor effect in glioblastoma. Temozolomide has been on the market for almost 20 years. Due to the pronounced therapeutic effect in patients with glioma, temozolomide has become the drug of choice for the treatment of malignant brain tumors [12,13].

Hematologic, gastrointestinal, and hepatic toxicities are common in patients receiving temozolomide therapy. Physicians should pay particular attention to important factors associated with the occurrence of toxicity, such as: B. Chemotherapy regimen, chemotherapy cycle, and patient's clinical stage.

First-line therapy, including duration of temozolomide maintenance therapy and survival in a population-based study in a large patient with glioblastoma. Prolongation of adjuvant temozolomide therapy for more than 6 cycles in patients with non-progressive disease has been shown to have a positive

effect on survival. Further analysis, including treatment side effects, quality of life, and biology, requires a dedicated randomized clinical trial or a large population-based prospective international study.

Side effects of temozolomide: digestive disorders: nausea and vomiting. These phenomena are moderate or mild (no more than 5 attacks of vomiting per day), disappear on their own or are easily stopped by conventional methods of treating nausea. In many cases, severe vomiting and nausea occur. Fatigue, constipation, headache, anorexia, diarrhea, rash, fever, and drowsiness have also been observed. In frequent cases - asthenia, pain, abdominal pain, dizziness, weight loss or weight loss, shortness of breath, dyspepsia, alopecia, chills, itching, loss of taste or paresthesia [14,15].

Temozolomide is rapidly absorbed from the gastrointestinal tract when taken orally and is also rapidly excreted from the body in the urine. It quickly crosses the blood-brain barrier and enters the cerebrospinal fluid. The maximum plasma concentration is reached on average 0.5-1.5 hours (no earlier than 20 minutes) after taking the drug. The half-life of the drug in plasma is about 1.8 hours. Clearance, volume of distribution in plasma and half-life are independent of drug dose.

Temozolomide binds poorly to blood proteins (10–20%), so it does not interact with substances that are characterized by strong protein binding. Temozolomide is eliminated from the body primarily through the kidneys. About 5-10% of the dose is excreted unchanged in the urine 24 hours after oral administration of temozolomide; The remainder is excreted as 4-amino-5-imidazolecarboxamide hydrochloride or unidentified polar metabolites. Pharmacokinetic analysis of temozolomide in different populations showed that the plasma clearance of the drug is independent of age, renal function and smoking status.

Conclusion. Temozolomide has both direct antitumor activity and immunomodulatory properties. The time and dose of temozolomide significantly alters its effect on immune cells and the tumor microenvironment. The effect of temozolomide on response to new therapies such as immune checkpoint inhibitors is currently unknown. Previous research includes other treatment options such as responding to radiation exposure or suppressing immune checkpoints. The effects of dosing and timing of temozolomide, as well as inhibition of immune checkpoints, are the subject of ongoing attention. Combination strategies involving temozolomide and immunotherapy must be carefully considered to ensure optimal results.

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SUMMARY

Temozolomide is the most commonly used chemotherapy drug in patients with glioblastoma, although about half of those treated are resistant to temozolomide, and some patients eventually fail. Due to the limited effectiveness of existing therapies, immunotherapy in patients with glioblastoma is under intense investigation. However, early attempts at immunotherapy in glioblastoma patients as monotherapy have had disappointing results. Therefore, combinatorial treatment strategies are being explored. Temozolomide has multiple effects on the immune system that depend on the route of administration and dosing strategy and may have unpredictable consequences for immunotherapy. Temozolomide has both direct antitumor activity and immunomodulatory properties. The timing and dose of temozolomide significantly alters its effects on immune cells and the tumor microenvironment. The effect of temozolomide on response to new treatments such as immune checkpoint inhibitors is currently unknown. The effects of temozolomide dosing and timing, as well as the inhibition of immune checkpoints, are the subject of constant attention. Combination strategies involving temozolomide and immunotherapy should be carefully considered to ensure optimal results.

Keywords: Temozolomide, pharmacotherapeutic effects, brain tumor, therapeutic applications