HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

PRINCIPLES OF CHEMOTHERAPY IN CANCER TREATMENT

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Doi: https://doi.org/10.5281/zenodo.23739570

Abstract. Chemotherapy is one of the principal methods of treating oncological diseases: the drugs spread through the bloodstream throughout the body and act on both the primary tumor and metastases. This article analyzes the mechanisms of action of the main groups of cytostatic agents, namely alkylating agents, antimetabolites, topoisomerase inhibitors, and antitubulin agents, in relation to the phases of the cell cycle. The principles of combination regimens and the aims and effectiveness of neoadjuvant and adjuvant chemotherapy are described. Particular attention is paid to the mechanisms of drug resistance in tumor cells, including the Goldie–Coldman hypothesis. The main toxic complications, such as bone marrow suppression, nausea, cardiotoxicity, and neurotoxicity, and ways of preventing them are also considered. The combination of chemotherapy with targeted therapy and immunotherapy is discussed. The findings may be useful for individualizing treatment.

Keywords. chemotherapy, oncological diseases, cytostatic agents, combination therapy, neoadjuvant and adjuvant therapy, drug resistance, toxicity, targeted therapy, immunotherapy.

Аннотация.Химиотерапия является одним из основных методов лечения онкологических заболеваний: лекарственные препараты распространяются с кровотоком по всему организму и воздействуют как на первичный опухолевый очаг, так и на метастазы. В статье анализируются механизмы действия основных групп цитостатических препаратов, а именно алкилирующих средств, антиметаболитов, ингибиторов топоизомеразы и антитубулиновых препаратов, в связи с фазами клеточного цикла. Рассматриваются принципы применения комбинированных режимов, цели и эффективность неоадъювантной и адъювантной химиотерапии. Особое внимание уделяется механизмам лекарственной устойчивости опухолевых клеток, в том числе гипотезе Гольди–Колдмана. Также освещаются основные токсические осложнения, такие как угнетение костномозгового кроветворения, тошнота, кардиотоксичность и нейротоксичность, и пути их профилактики. Обсуждается сочетание химиотерапии с таргетной терапией и иммунотерапией. Результаты могут быть полезны для индивидуализации лечения.

Ключевые слова.химиотерапия, онкологические заболевания, цитостатики, комбинированная терапия, неоадъювантная и адъювантная терапия, лекарственная устойчивость, токсичность, таргетная терапия, иммунотерапия.

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Introduction. Oncological diseases are currently among the leading causes of mortality worldwide, and their prevalence continues to grow in connection with increasing life expectancy, environmental factors, and changes in lifestyle [2]. Therefore, improving methods for the effective treatment of tumors is one of the most pressing tasks of modern medicine. In the treatment of oncology patients, surgery, radiation therapy, and drug therapy are used, and they are often applied in a complementary manner within a comprehensive approach [1, 2]. Chemotherapy, that is, acting on tumor cells with the help of cytostatic drugs, occupies a special place in this field. In recent years, the emergence of targeted therapy and immunotherapy has changed treatment strategy in oncology. However, these methods have not completely displaced traditional chemotherapy: in many types of tumors, chemotherapy is used in combination with new drugs, thereby increasing treatment effectiveness [12, 13]. For this reason, a deep knowledge of the basic principles, mechanisms of action, and limitations of chemotherapy is essential for the modern physician.

Research aim. The aim of the study is to analyze the scientific basis of chemotherapy in the treatment of oncological diseases, the principles of its application, the mechanisms of drug resistance, and its toxic complications, as well as to assess its place in modern comprehensive treatment.

Materials and methods. The study was conducted on the basis of an analysis of the scientific literature on chemotherapy in oncology. In the scientific sources, the mechanisms of action of cytostatic drugs, their activity in different phases of the cell cycle, and their effects on tumor cells have been studied at the molecular level. In many studies, the efficacy of the drugs was evaluated in cell cultures (in vitro), experimental animal models, and clinical trials, and it was measured by tumor shrinkage, complete and partial response, and relapse-free and overall survival rates. In the analysis of drug resistance and toxicity, molecular markers (P-glycoprotein, DNA repair enzymes), laboratory parameters (complete blood count, liver and kidney function tests), and cardiological monitoring methods (echocardiography, biomarkers) were used. The analysis procedure included the stages of selecting sources, systematizing data by drug groups, comparing efficacy and complications, and summarizing the results through tables and diagrams [1][2][3].

Results. As a result of laboratory analysis, the following data on the efficacy, resistance, and safety of chemotherapy were systematized. In experimental models, it was found that each drug dose eliminates a constant fraction of tumor cells (log-kill), and for this reason treatment is repeated over several cycles [4]. In metastatic germ cell tumors, cisplatin-based combination chemotherapy leads to a cure in more than 80% of patients; by risk group, five-year survival was 91% in the good prognosis group, 79% in the intermediate prognosis group, and 48% in the poor prognosis group [16]. In childhood acute lymphoblastic leukemia, the five-year survival rate has reached approximately 90% [17]. In HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy (469 patients) extended the time to tumor progression from 4.6 months to 7.4 months, and median overall survival from 20.3 months to 25.1 months [12]. In metastatic nonsquamous non-small cell lung cancer (without EGFR/ALK mutations), the combination of pembrolizumab with pemetrexed and platinum (616 patients) increased 12-month overall survival from 49.4% to 69.2%, and extended median progression-free survival from 4.9 months to 8.8 months [13]. With doxorubicin use, the cumulative risk of heart failure is dose-dependent, amounting to 5% at 400 mg/m², 26% at 550 mg/m², and 48% at

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700 mg/m² [15]. In regimens with a febrile neutropenia risk of approximately 20% or higher, primary prophylaxis with G-CSF is recommended [11, 18], while with highly emetogenic drugs such as cisplatin, a four-drug antiemetic regimen (NK1 antagonist, 5-HT3 antagonist, dexamethasone, olanzapine) is recommended [9]. According to the Goldie–Coldman hypothesis, the probability of resistant clones increases with tumor size, and for this reason it is advisable to use drugs early and in combination [5].

Discussion. The analysis of the literature shows that chemotherapy has retained its importance in modern oncology, but that its role is changing as it is integrated with new treatment methods. High results have been recorded when chemotherapy matches tumor biology: in metastatic germ cell tumors, cisplatin-based regimens led to a cure in more than 80% of patients [16], and in childhood acute lymphoblastic leukemia, the five-year survival rate has reached approximately 90% [17]. However, such results were obtained mainly in well-resourced systems, and therefore they cannot be directly transferred to other settings.

When chemotherapy was used together with targeted and immune drugs, efficacy increased further. In HER2-positive breast cancer, trastuzumab extended median overall survival from 20.3 months to 25.1 months [12], and in nonsquamous lung cancer, pembrolizumab increased 12-month survival from 49.4% to 69.2% [13]. In these cases, the new drug did not displace chemotherapy but was added on top of it. At the same time, the results relate to a specific tumor type and patient selection, and they cannot be generalized to other tumors.

The second side of efficacy is toxicity. With doxorubicin, the cumulative risk of heart failure increased in a dose-dependent manner from 5% at 400 mg/m² to 48% at 700 mg/m² [15], which shows the necessity of cardiological monitoring. Supportive therapy (G-CSF prophylaxis [18], modern antiemetic regimens [9]) makes it possible to deliver chemotherapy at full dose.

Drug resistance remains the main limitation. The Goldie–Coldman hypothesis theoretically substantiates the early and combined use of drugs [5], and the molecular mechanisms of resistance have been widely studied [6, 7, 8]. However, this hypothesis is a mathematical model, and its clinical significance differs depending on the tumor type.

Conclusion. Chemotherapy remains an important treatment method in oncology: high cure rates have been achieved in certain tumors, including metastatic germ cell tumors and childhood leukemia. Its combination with targeted therapy and immunotherapy has increased efficacy, but toxicity, including doxorubicin cardiotoxicity, and drug resistance remain the main limitations. For this reason, it is necessary to select the regimen individually according to the tumor type, molecular profile, and the patient's condition, to apply supportive therapy, and to carry out continuous monitoring. Future research should be directed toward improving biomarker-based individualized treatment, reducing complications, and finding ways to overcome resistance.

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