South Russian Journal of Cancer 2022, Vol.3, No. 3, P. 41-47
https://doi.org/10.37748/2686-9039-2022-3-3-5
REVIEW

EVOLUTION OF DRUG THERAPY FOR CLASSICAL HODGKIN LYMPHOMA

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ABSTRACT

Hodgkin's lymphoma is a malignant disease of the lymphatic system. Hodgkin's lymphoma was first described by Dr. Thomas Hodgkin in 1832 and later named "Hodgkin's disease" by Samuel Wilkes. Hodgkin's lymphoma accounts for about 24 % of all lymphomas. Hodgkin's lymphoma is classified as classical and nodular lymphoid-predominant (Nodular type of lymphoid-predominant Hodgkin's lymphoma). Classical Hodgkin's lymphoma includes the following histologic variants: nodular sclerosis variant (types I and II), mixed cell variant, classic lymphocyte-rich variant, and rare lymphoid depletion variant. Epidemiological and serological studies showed the involvement of the Epstein-Barr virus into Hodgkin's lymphoma etiology, since its genome was found in the study of the biopsy material samples from patients with Hodgkin's lymphoma. A relationship with the human immunodeficiency virus (HIV) was revealed as well, and patients infected with HIV have a significantly increased risk of developing Hodgkin's lymphoma compared to healthy people. An in-depth study of the Hodgkin's lymphoma pathophysiology revealed new therapeutic targets in the treatment of this disease. All these discoveries changed the understanding of the Hodgkin's lymphoma pathogenesis, and were important for the development of new methods of treatment. The history of therapy begins on the cusp of the 19th and 20th centuries. Over the past four decades, achievements in radiation therapy and combined chemotherapy have significantly improved overall survival of patients with Hodgkin's lymphoma. Currently, more than 80 % of patients under 60 years old with first diagnosed Hodgkin's lymphoma can be cured from this disease after first-line chemotherapy.

Keywords:
Hodgkin lymphoma, HIV, Epstein-Barr virus, IHC, remission, progression, chemotherapy resistance, overall survival

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Funding: this work was not funded.
Conflict of interest: authors report no conflict of interest.

For citation:
Samaneva N. Yu., Lysenko I. B., Nikolaeva N. V., Kapuza E. A., Kamaeva I. A., Gaysultanova Ya. S., Tishina A. V., Pushkareva T. F. Evolution of drug therapy for classical Hodgkin lymphoma. South Russian Journal of Cancer. 2022; 3(3): 41-47. (In Russ.).
https://doi.org/10.37748/2686-9039-2022-3-3-5

The article was submitted 04.11.2021; approved after reviewing 20.07.2022; accepted for publication 02.09.2022.

Южно-Российский онкологический журнал 2022, Т. 3, № 3, С. 41-47
https://doi.org/10.37748/2686-9039-2022-3-3-5
ОБЗОР

ЭВОЛЮЦИЯ ЛЕКАРСТВЕННОГО ЛЕЧЕНИЯ КЛАССИЧЕСКОЙ ЛИМФОМЫ ХОДЖКИНА

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РЕЗЮМЕ

Лимфома Ходжкина – злокачественное заболевание лимфатической системы. Лимфома Ходжкина была впервые описана доктором Томасом Ходжкином в 1832 г., а позже названа «болезнью Ходжкина» Сэмюэлем Уилксом. Лимфома Ходжкина составляет около 24 % среди всех лимфом. Лимфома Ходжкина классифицируют как классическую и нодулярную с лимфоидным преобладанием (нодулярный тип лимфоидного преобладания лимфомы Ходжкина). Классическая лимфома Ходжкина включает следующие гистологические варианты: вариант с нодулярным склерозом (I и II типа), смешанно-клеточный вариант, классический вариант с большим количеством лимфоцитов и редко встречающийся вариант с лимфоидным истощением. Эпидемиологические и серологические исследования выявили причастность вируса Эпштейна-Барр к этиологии лимфомы Ходжкина: геном вируса Эпштейна-Барр был обнаружен при исследовании образцов биопсийного материала пациентов с лимфомой Ходжкина. Также выявлена связь с вирусом иммунодефицита человека (ВИЧ), заключающаяся в том, что пациенты, инфицированные ВИЧ, имеют значительно повышенный риск развития лимфомы Ходжкина по сравнению со здоровыми людьми. Углубленное изучение патофизиологии лимфомы Ходжкина позволило найти новые терапевтические мишени в лечении данного заболевания. Все эти открытия принесли изменения в понимании патогенеза данной патологии, и имеют важное значение в разработках новых методов лечения. История терапии начинается на рубеже XIX и XX вв. За последние четыре десятилетия достижения в лучевой терапии и использование комбинированной химиотерапии, значительно повысили уровень общей выживаемости пациентов с лимфомой Ходжкина. В настоящее время более 80 % пациентов моложе 60 лет с впервые диагностированной лимфомой Ходжкина могут быть излечены от данного заболевания после проведения первой линии химиотерапии.

Ключевые слова:
лимфома Ходжкина, ВИЧ, вирус Эпштейна-Барр, ИГХ, ремиссия, прогрессирование, резистентность к химиотерапии, общая выживаемость

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Финансирование: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Саманева Н. Ю., Лысенко И. Б., Николаева Н. В., Капуза Е. А., Камаева И. А., Гайсултанова Я. С., Тишина А. В., Пушкарева Т. Ф. Эволюция лекарственного лечения классической лимфомы Ходжкина. Южно-Российский онкологический журнал. 2022; 3(3): 41-47.
https://doi.org/10.37748/2686-9039-2022-3-3-5

Статья поступила в редакцию 04.11.2021; одобрена после рецензирования 20.07.2022; принята к публикации 02.09.2022.

RELEVANCE

Hodgkin's lymphoma (HL) is a B-cell malignant lymphoproliferative disease. Hodgkin's lymphoma was first published in 1832 in the journal Medical Chirurgical Transactions under the title "On some morbidappearance of the absorbent glands and spleen", thanks to the persistent work of the British physician Thomas Hodgkin (Thomas Hodgkin, 1778–1866) [1]. However, the etiology of this lymphoma remained unclear for a long time. Only in the last 20 years has the B-cell nature of Hodgkin and Reed-Sternberg pathognomonic cells been revealed, as well as several recurrent genetic lesions. It was noted that there is a relationship between Epstein-Barr virus infection and the incidence of Hodgkin's lymphoma. Reed-Sternberg cells in classical Hodgkin's lymphoma have some characteristics that are atypical for lymphoid tumor cells, and extensive inflammatory infiltrate prevails in the microenvironment of Hodgkin's lymphoma. Specific markers PD-1 and CD30 were also found to express on Reed-Sternberg cells [2]. This allowed us to take a broader look at the pathophysiology of Hodgkin's lymphoma and find new therapeutic targets in the treatment of this disease. All these discoveries have brought changes in the understanding of the pathogenesis of this pathology, and is important in the development of new treatment methods.

Epidemiology

HL is about 24 % among all lymphomas. The incidence of Hodgkin's lymphoma in Russia is 2.1 per 100,000 population per year (3149 newly diagnosed patients), mortality is 0.74. In the structure of malignant neoplasms – LX is 0.51 %. The disease is more common in men than in women. People of any age suffer from Hodgkin's lymphoma, but the peak incidence occurs at the age of 20–35 years. The incidence has not changed much over the past two decades [3]. In the revised classification of tumors of hematopoietic and lymphoid tissues WHO 2017 there are: classical HL (cHL) (according to ICD-10 C81.1 – C81.9) and nodular with lymphoid predominance of HL (NLPHL) (according to ICD-10 – C81.0 Nodular type of lymphoid predominance of Hodgkin's lymphoma). Classical HL includes the following histological variants: a variant with nodular sclerosis (type I and II), a mixed-cell variant, a classic variant with a large number of lymphocytes and a rare variant with lymphoid depletion (morphological and immunohistochemical diagnostics of various variants of HL). In addition to determining the type of HL and the histological variant of cHL, the stage of the disease should be determined for each patient, and the risk group for cHL should also be determined [4].

Evolution of therapy

The history of therapy begins at the turn of the XIX and XX centuries. then for X-ray and gamma radiation were applied to the foci. In the 1940s, chloromethine, a derivative of mustard gas, began to be used as cytostatics.

Then they began to use: vinblastine, cyclophosphamide, vincristine, methotrexate, procarbazine, chlorambucil in monotherapy and in various combinations, as well as in combination with radiation therapy. However, all these options did not give a significant therapeutic effect. Until 1964, at the US National Cancer Institute in Bethesda, V. De Vita proposed using the MOPP scheme a combination of chloromethine, vincristine, procarbazine in combination with glucocorticosteroids, which led to a cure in more than 50 % of cases. When using this scheme, 77 % – 4-year overall survival (OS) were obtained [5]. In 1973 the protocol of combined chemotherapy according to the ABVD scheme included adriamycin, bleomycin, vinblastine and dacarbazine proved to be more effective in comparison with the MOPP scheme, the overall survival after 5 years was 82 % [6]. This therapy remained the standard of treatment until 1998, when the Stanford V protocol was approved, which included combined chemotherapy with doxorubicin, vincristine, mechloretamine, vinblastine, bleomycin, etoposide and prednisone [7]. This 12-week chemotherapy regimen was followed by consolidating radiotherapy to the primary lesion. The Stanford Protocol did not give better results in comparison with ABVD chemotherapy in relation to OS, but this treatment really increased the effectiveness of treatment [8]. Five years later, the German Hodgkin's Lymphoma Group presented the BEACOPP scheme, consisting of a combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, a scheme that was later improved by increasing the doses of drugs. This allowed the majority of patients with advanced stages to have a high percentage of a complete cure of the disease. When comparing ABVD with escalated BEACOPP, the latter had a significant advantage in terms of

better progression-free survival (PFS) and allowed to achieve a 5-year overall survival in more than 94 % of patients, but it is often accompanied by hematological toxicity of III–IV degree [9]. At the same time, in patients with early stages of the disease, the ABVD +/- radiation therapy chemotherapy regimen remains the gold standard of treatment, which allows achieving an 8-year overall survival rate of about 95 %, but the emergence of new drug therapy options in the form of targeted drugs reduces the number and intensity of adverse events.

In the last few years, various targeted drugs for the treatment of HL have been investigated, of which the most promising results have been shown by the anti-CD30-antibody conjugate- brentuximab vedotin – is an antibody-drug substance conjugate (ADSC), which delivers an antitumor substance to CD30-positive tumor cells, which leads to their apoptosis and death [10]. Brentuximab vedotin monotherapy has been investigated as an induction therapy and as a consolidating treatment after high-dose chemotherapy and autologous stem cell transplantation. In a one-cent study conducted at Memorial Sloan Kettering Cancer Center in New York, 45 patients with recurrent HL received weekly infusions of brentuximab vedotin at a dose of 1.2 mg/kg over two 4-week cycles. Patients with a PET-negative result switched to further therapy and subsequent stem cell transplantation, while patients with a PET-positive result continued treatment with two cycles of CT according to the ICE scheme (ifosfamide, carboplatin, etoposide). The two-year event-free survival of these patients was 92 % and, thus, is comparable to the two-year event-free survival of patients with a PET-negative result after ICE chemotherapy (91 %) [11]. Taking into account the results of a multicenter study, brentuximab vedotin before high-dose chemotherapy and transplantation shows good results in about 1/3 of patients with HL with relapse of the disease after 1-line treatment. A study was conducted to evaluate the effectiveness of brentuximab vedotin in combination with chemotherapy for newly diagnosed HL. A multicenter study from the USA included 30 patients with an early unfavorable stage of the disease [12]. The study treatment consisted of four courses of brentuximab vedotin (1.2 mg/kg every two weeks) in combination with doxorubicin, vinblastine and dacarbazine, followed by radiation therapy in the affected areas with a dose of 30 Gy. Intermediate PET was performed after 2 and 4 CT cycles. Metabolic remission after 2 and 4 cycles of treatment was observed in 93 % of patients. Due to its high efficacy, this drug is included in clinical recommendations [12].

A study was conducted, which included patients with classical HL with a relapse or refractory course of the disease, in which the effect of lenalidomide was evaluated (inhibits the proliferation of certain malignant hematopoietic cells, enhances immunity mediated by T-lymphocytes and natural killer cells (NK cells), increases the number of NK (T cells), suppresses angiogenesis, blocking migration and the adhesion of endothelial cells and the formation of microvessels, increases the production of fetal hemoglobin CD34+ by hematopoietic stem cells and inhibits the production of proinflammatory cytokines) at doses of 25 mg/day for 1–21 days with cycles of 28 days. Patients received the drug before the progression or occurrence of unacceptable toxicity. 38 patients who received an average of 4 courses of previous chemotherapy courses were studied, of which the percentage of refractory patients was (55 %) and 87 % of them who had previously received high-dose chemotherapy. The overall response rate was 19 %. Among the phenomena of undesirable toxicity: hematological toxicity of 3–4 degrees: neutropenia (47 %), anemia (29 %) and thrombopenia (18 %). All this indicates the presence of the desired effect of lenalidomide therapy in relation to HL, which needs to be studied further [13]. At the moment, it is not included in the clinical recommendations.

A study was conducted on the use of a targeted drug mTOR inhibitor (everolimus is an inhibitor of the transmission of proliferative impulse in cells. The blockade of this signal leads to the arrest of cell division at the G1 stage of the cell cycle), with the use of everolimus at a dose of 10 mg/day in 19 patients with refractory or recurrent HL, while 84 % of them had autoHSCT transplantation, the overall response was 47 %, 8 patients had a partial response, and only one patient had a complete response. The average time to disease progression was 7.2 months [14]. In another study, 37 patients on the same treatment received an overall response of 35 %. Stabilization of the process was observed in 27 %, survival without progression was 7.2 months. Treatment was accompanied by hematological toxicity of 3–4 degrees: thrombocytopenia – 38 %, fatigue – 43 %, neutropenia – 8 % and anemia – 8 %. As in the case of other previously described studies, it is reported that there is a good

response to treatment in patients who have received treatment. This allows us to think that everolimus may have a clinically significant role in recurrent or refractory HL. In addition, there is evidence of its possible synergism with other RAF inhibitors [15]. It is not included in the clinical recommendations.

A study was also conducted to study the use of nivolumab in patients with HL. Checkpoint drug therapy is a new word in the treatment of cancer patients, nivolumab is a human monoclonal antibody that blocks the interaction between the programmed death receptor (PD-1) and its ligands. The study obtained encouraging results – 87 % of patients managed to achieve a complete response to treatment, and this treatment has an acceptable toxicity profile. This study included patients who failed to undergo chemotherapy followed by bone marrow transplantation and therapy with brentuximab vedotin [16]. Based on the results obtained, several studies were launched using anti-PD-1 drugs. In 2020, the results of a 5-year follow-up of a multicomponent study called CheckMate 205 were published. The study included 243 patients with HL who had a relapse of the disease after 1 line of CT with subsequent autotransplantation of stem cells and treatment with brentuximab vedotin. The average duration of treatment was 14 months. The overall response rate was 71 %, and the full response rate was 21 %. The median PFS was 15 months. The frequency of OV after 2 and 5 years was 87 % and 71 %, and the frequency of PFS was 37 % and 18 %, respectively. This 5-year CheckMate 205 analysis demonstrated favorable survival and confirmed the high efficacy and safety of nivolumab [17]. After the studies conducted with the use of immune checkpoint drugs, the European Medical Agency approved nivolumab and pembrolizumab in a single mode for the treatment of patients with HL, but in the Russian Federation, to date, only nivolumab has been registered. Anti-PD-1 have shown significant activity in patients with recurrent/refractory HL, and they also have an acceptable toxicity profile with side effects that are usually treatable [18].

The results of a study using the drug anti-CD30 CAR by T cells in adult patients with HL were published, currently this type of treatment is actively used only in pediatric hematology. Anti-CD30 is a promising target for immunotherapy in Hodgkin's lymphoma. The use of autologous anti-CD30 CAR T-cells in Hodgkin's lymphoma was studied in 41 patients in two different centers, the complete response rate was 59 %. Unfortunately, after 1 year, PFS was only 36 %, and the one-year overall survival rate was 94 % [19]. This method of treatment allows patients with a resistant course of the disease to achieve a positive effect; however, CAR T-cell therapy is associated with extremely severe adverse events in the form of cytokine release syndrome, which must be taken into account when planning this type of treatment.

CONCLUSION

Taking into account the interest of the world community in studying this group of lymphoproliferative diseases, this review gives an idea of modern changes in the process of diagnosis and treatment tactics in this cohort of patients. Despite the fact that patients suffering from Hodgkin's lymphoma have the possibility of a complete cure from the disease, at the moment a large percentage of refractory or recurrent course remains after first-line therapy and even after subsequent transplantation of autologous stem cells. Relapse of the disease after high-dose chemotherapy and autologous stem cell transplantation remains the main cause of death in patients with recurrent or resistant Hodgkin's lymphomas. But the new treatment options that have appeared make it possible to improve progression-free survival and overall survival. Many of them are undergoing clinical trials and demonstrating efficacy, but it is too early to say whether all of these drugs will contribute to increased survival more than the standard treatments we use for these patients. Nevertheless, long-term observation and further research are necessary for final conclusions.

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Samaneva N. Yu. – idea, writing the article;
Lysenko I. B. – scientific guidance;
Nikolaeva N. V. – scientific text editing;
Kapuza E. A. – collecting the material;
Kamaeva I. A. – scientific text editing;
Gaysultanova Ya. S. – collection of the material;
Tishina A. V. – collecting the material;
Pushkareva T. F. – collecting the material.