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CLINICAL CASE REPORTS

THE USE OF IMMUNOTHERAPY FOR THE TREATMENT OF REFRACTORY FORMS OF HODGKIN LYMPHOMA IN REAL CLINICAL PRACTICE

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ABSTRACT

With a frequency of 2.2 cases per 100,000 population in Russia, Hodgkin's lymphoma (HL) is one of the most common malignant neoplasms in young people. In connection with the predominant spread of HL among young people, the issue of effective treatment of various forms of HL remains relevant. Currently, 70-90 % of patients with HL who have received standard chemotherapy or chemoradiotherapy have a long period of remission. However, 10 % of patients with progressive course, can`t achieve a response, and 30 % of patients subsequently recur. The standard approach of treating recurrent and/or refractory HL after initial treatment is “salvage therapy” followed by consolidation with high-dose chemotherapy and stem cell transplantation. Although there is a model for treating these patients, recent research has focused on improving the effectiveness and tolerability of rescue therapy. The use of anti-PD-1 drugs opens up new possibilities for the treatment of recurrent/refractory HL. The article describes the results of using checkpoint inhibitors for patients with a history of multi-course chemotherapy. Inhibitors of immune check points were supplemented in the 3rd and subsequent lines of ChT. A clinical case with immunotherapy supplementation in a patient with severe comorbidity is also presented.

Keywords:
Hodgkin lymphoma, immunotherapy, refractory, relapse, targeted therapy, clinical experience.

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ПРИМЕНЕНИЕ ИММУНОТЕРАПИИ ДЛЯ ЛЕЧЕНИЯ РЕФРАКТЕРНЫХ ФОРМ ЛИМФОМЫ ХОДЖКИНА В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ

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РЕЗЮМЕ

Лимфома Ходжкина – это В-клеточное злокачественное лимфопролиферативное заболевание. При частоте встречаемости 2,2 случая на 100 000 населения в России ЛХ является одним из наиболее встречающихся злокачественных новообразований у молодых людей. Заболевание возникает в любом возрасте, зачастую в интервале от 16 до 35 лет, среди заболевших большую часть составляют женщины. В связи с преимущественным распространением ЛХ среди молодежи вопрос эффективного лечения различных форм ЛХ остается актуальным. В настоящее время 70-90 % пациентов с ЛХ, получивших стандартную химиотерапию или химиолучевую терапию, имеют длительный период ремиссии. Однако у 10 % больных с прогрессирующим течением не удается добиться ответа, а 30 % больных впоследствии рецидивируют. Стандартным подходом в лечении рецидивирующей и/или рефрактерной ЛХ после первоначального лечения является «терапия спасения» с последующей консолидацией при помощи высокодозной химиотерапии и трансплантации стволовых клеток. Несмотря на то, что существует модель лечения таких пациентов, исследования последних лет направлены на повышение эффективности и переносимости терапии «спасения». Применение анти-PD-1 препаратов открывает новые возможности лечения рецидивирующих/рефрактерных ЛХ. В статье описаны результаты применения ингибиторов контрольных точек иммунитета у девятерых пациентов, имеющих в анамнезе многокурсовую химиотерапию. Ингибиторы контрольных точек иммунитета назначались при этом в 3 и последующих линиях ХТ. Приведен также клинический случай использования иммунотерапии у пациента с выраженной коморбидностью.

Ключевые слова:
лимфома Ходжкина, иммунотерапия, рефрактерность, рецидив, таргетная терапия, клинический опыт.

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RELEVANCE

Hodgkin's lymphoma (HL) is a B – cell malignant lymphoproliferative disease [1]. The incidence of HL a in Russia is 2.2 cases per 100,000 population per year, and the mortality rate reaches 0.61 cases per 100,000 population per year. The disease occurs at any age, but mainly in the range of 16-35 years, in this age group in Russia, women predominate among the patients [2]. Despite significant success in HL therapy, relapses occur in 10-15 % of patients with local and 20-49 % with generalized stages of the disease (depending on the factors of unfavorable prognosis and treatment). In 40-50 % of cases, relapses are registered within 12 months after the completion of initial polychemotherapy. Line 2 treatment allows achieving remission only in half of the patients [3]. Treatment of patients with relapses and refractory forms of HL remains an urgent problem at the present time. The advent of immunotherapy in the treatment of refractory and recurrent HL has dramatically changed the treatment options for such patients. Classic HL are unique in that they consist of a small number of Reed-Sternberg cells and a large number of dysfunctional reactive immunological cells that make up the majority of the tumor mass. Neoplastic Reed-Sternberg cells secrete various cytokines and chemokines to regulate the microenvironment and evade the immune response [4]. One of the pathways involved in T-cell functional disorders is the programmed cell death – 1 (PD-1) – PD-1 ligand signaling system. Tumor cells that express PD-1 engage the PD-1 receptor on T cells and inhibit cell activation and proliferation. PD-1 expression is markedly increased in tumor-infiltrating T cells of classical HL. This factor has made PD-1/PD-L1 a promising pathway for therapeutic targeted therapy with immune checkpoint inhibitors (CPIs) [5]. However, when CPI is treated, an unusual response to treatment may be observed. Thus, when using CPI, the clinical situation can develop in five main directions: reducing the size of existing foci without the appearance of new ones; long-term stabilization of the tumor size with its subsequent decrease in size; increasing the existing foci with the appearance of new foci; as well as 2 unique options: reducing the size of the tumor after its initial increase and reducing the size of some foci with the appearance of new ones [6]. At the same time, it is necessary to focus on the general well-being of the patient and continue the ongoing immunotherapy.

Clinical case review description

The patient considers himself ill since March 2015, when he first developed a cough, fever, and treated ARVI without effect. He was examined at the place of residence, an increase in ESR to 65 was revealed. In April 2015, he performed spiral computed tomography (SCT), which revealed: hyperplasia of the intra-thoracic lymph nodes (in the upper mediastinum, conglomerate up to 9.2 cm: retrocaval lymph nodes up to 2.3 cm, bifurcation up to 1.4 cm, anterior to the aorta up to 1.5 cm, bronchopulmonary on the right up to 1.4 cm, left 1.7 cm), subclavian on the left 2.0 cm, right 1.3 cm, axillary on the left 1.2 cm. A biopsy of the right neck lymph node was performed, histological conclusion: the morphological picture corresponds to HL; according to the results of the immunohistochemical study – "Hodgkin's lymphoma, nodular sclerosis". In May 2015, the patient had a myocardial infarction. From May to August, 4 courses of polychemotherapy (PCT) were conducted according to the BEACOPP scheme. In the control SCT, hyperplasia was observed – intra-thoracic lymph nodes in the mediastinum up to 6.4 cm. Incomplete remission was achieved. Then 2 more ChT courses were conducted according to the BEACOPP scheme (a total of 6 ChT courses).

Due to the persistent conglomerate of intrathoracic lymph nodes up to 6.4 cm, the PCT course was changed. In October-November 2015, 2 courses of ChemT were conducted under the MEPD scheme. In March 2016, a course of radiation therapy was performed, with a total dose of 37G on the area of the supraclavicular and subclavian lymph nodes. Complete remission was achieved.

In March 2018, the patient's condition began to deteriorate – there was a fever, weakness. He independently applied to the RNIOI in May 2018, where SCT showed hyperplasia of the upper mediastinal lymph nodes up to 4.8 cm. In May 2018, a video-assisted thoracoscopic biopsy was performed on the right side with the histological conclusion "Hodgkin's lymphoma". The condition is regarded as the first late relapse-activation of the intra-thoracic lymph nodes, stage 2B.

By the decision of the council recommended to conduct anti-relapse courses of ChT. From June to August 2018, 4 anti-relapse PCT courses were conducted under the BEACOPP scheme. In September, he performed SCT of the chest organs, which showed lung tissue without pathology, and fibrous tissue in the upper mediastinum. Complete remission was achieved. In September, the 5th anti-relapse course was conducted under the BEACOPP scheme. It is recommended to perform a PET-CT scan.

The patient did not follow the recommendations for further examination to determine the tactics of further treatment, and appeared with signs of early relapse No. 2. PET-CT was performed only in March 2019: in the right supraclavicular region, a drain focus of pathologically increased accumulation of radiopharmaceutical therapy (RPT) with dimensions of 17 × 18 × 25 mm is determined; in the jugular region with a spread to the right half of the upper floor of the mediastinum, a focus with dimensions of 43 × 43 × 47 mm. Signs of metabolic activity in the right supraclavicular region and mediastinum, 5 points according to Deauville. The condition is regarded as a second early relapse.

From March to July 2019, 4 courses of anti-relapse ChT were conducted according to the GPD-21 scheme. In August 2019, he performed a PET-CT scan: a picture of a tumor conglomerate of the upper mediastinum with dimensions up to 60x55x37mm, a conglomerate of supraclavicular lymph nodes on the right, a parasternal nodular formation of the anterior chest on the right, single axillary lymph nodes (left axillary node 6x5 mm), axillary lymph nodes up to 12 mm, lymph nodes of the right side of the neck with hyperfixation of RPT 5 points according to Deauville. The condition is regarded as continuously progressive, and therefore the patient is recommended to undergo immunotherapy. From October 2019 to February 2020, 7 courses of nivolumab were conducted.

In April 2020, he performed a PET-CT scan, which showed a decrease in the size of single cervical-supraclavicular lymph nodes on the right (up to 8 mm) with an increase in their metabolic activity, 5 points for Deauville; a decrease in the size of the tumor conglomerate in the upper mediastinum (40.5 × 29 mm), 5 points for Deauville; a decrease in the size of the parasternal lymph node on the right and the axillary lymph node on the left with the absence of pathological hyperfixation of RF. It is recommended to continue therapy until the disease progresses, or until unacceptable toxicity occurs.

DISCUSSION

The table 1 shows retrospective data on 9 patients with refractory HL who received and continued the treatment in the Department of Oncohematology of the National Medical Research Centre for Oncology of the Ministry of Health of Russia. Of all patients: 6 patients (66.6 %) initially had stage IV of the disease, 2 patients had stage II (22.2 %), 1 patient initially had stage I (11.1 %). B-symptoms were observed in the majority of patients (88.8 %). Morphological variants of HL were nodular sclerosis in 7 patients (77.7 %), mixed-cell variant in 2 patients (22.2 %). 6 patients (66.6 %) had concomitant pathology in the form of chronic heart disease. The first-line therapy was mainly the BEACOPP scheme – in 5 patients (55.5 %), which is due to the prevalence of the process. Four patients (44.4 %) who received first-line treatment received remote radiotherapy. The response in the form of partial remission was noted in 4 patients (44.4 %), initially resistant in 3 patients (33.3 %), in 2 patients, according to control examinations, an uncertain complete remission of the disease was registered, but less than 6 months later, these patients had an early relapse. According to the literature data, preference in first-line therapy for localized stages of the process should be given to the ABVD scheme followed by radiation therapy, which gives satisfactory results with a 10-year progression-free survival of 87 % [7]. Early assessment of the response by PET-CT after two ABVD cycles can significantly reduce the toxicity of therapy [8]. For common stages of the disease and the presence of risk factors, the BEACOPP scheme is currently used [1]. However, in the era of PET-CT, more and more research is devoted to finding the optimal balance between the response to therapy and the intensity of treatment. The HD15 test can serve as an example showing that 6 BEACOPP-escalated cycles are equally effective and at the same time less toxic compared to the previous standard consisting of 8

such cycles [9]. All patients received 2-line therapy from 2 to 14 courses. The most common regimens of 2-line therapy were DHAP, MINE, GDP-21, as well as bendamustine therapy in a single mode. Three (33.3 %) patients managed to achieve stabilization after the 2-line therapy, but less than 6 months later they experienced a progression of the process. All cases are considered to be refractory to standard chemotherapy, and patients are recommended to continue treatment with immunotherapy.

During therapy, stabilization of the process was achieved in 7 patients (77.7 %), no adverse events were noted. The median duration of treatment was 4 months (range 1-7). Autotransplantation of stem cells was performed in 1 patient after 8 injections of the drug, the remaining patients continue immunotherapy with nivolumab. In 1 patient, after 14 injections of the drug nivolumab, the progression of the process was noted (after 7 months of treatment with the drug), at the moment the patient receives anti-relapse courses of CT. Interruptions in taking doses of the drug were registered in 1 patient, the duration of the delay in the dose of the drug was 3 weeks. The choice of the BeGeV regimen in combi-

Table 1. Patient taking Nivolumab as a therapy

№	Patient 1, 47 years	Patient 2, 40 years	Patient 3 24 years	Patient 4 51 years	Patient 5, 37 years
D	Hodgkin's lymphoma, nodular sclerosis, with lesions of the cervical-supraclavicular, axillary, intra-thoracic l/n, v/lobar bronchus on the right st IVB (2018)	Hodgkin's lymphoma, nodular sclerosis with lesions of the cervical l/n on both sides, axillary l/n st IIB (2017)	Hodgkin's lymphoma, nodular sclerosis with lesions of the cervical-supraclavicular axillary, intra-thoracic retroperitoneal l/n, lung st IV B (2019)	Hodgkin's lymphoma, nodular sclerosis, lesion of intra-thoracic l/n, retroperitoneal l/n of the breast, pleura with IVB (2006)	Hodgkin's lymphoma, nodular sclerosis, lesion of the cervical-supraclavicular subclavian l/n on 2 sides, axillary l/n on the left, in/thoracic l/n, soft tissues of the chest wall st IVB (2015)
1st line therapy	6 courses BEACOPP[1]	8 courses BEACOPP[2]	8 courses BEACOPP[1]	5 courses ABVD[3], 1 course BEACOPP2, DRT 36G, 6 courses BEACOPP[2], 4 courses COPP[4]	8 courses BEACOPP[2], 2 courses MEPD[5], DRT SLD 37 G
Response	PR	PR	Resistant flow	PR	APR (2018) Early relapse (2019)
2nd line therapy	2 courses ICE[6], 2 courses DHAP[7]	2 courses GemOx[8], 4 courses MINE[9], 2 courses of bendamustine	2 courses DHAP[7]	6 courses GDP-21[10], 4 courses MINE[9], 4 courses bendamustin	5 courses BEACOPP[2], 4 courses GDP-21[10]
Response	Progression after stabilisation	Refractive flow	Progression after stabilisation	Progression after stabilisation	Refractive Flow
CPI	Nivolumab therapy 8 administrations	Nivolumab therapy 2 administrations	Nivolumab therapy 11 administrations	Nivolumab therapy 6 administrations	Nivolumab therapy 12 administrations
Effects	Stabilisation	Stabilisation	PR	Stabilisation	Stabilisation
AE	No AE	No AE	No AE	No AE	No AE
Current time	auto-THSC	Observation	Observation	Observation	Observation

nation with brentuximab-vedotin as an anti-relapse course after progression against the background of nivolumab therapy is not accidental. According to the literature data, the BeGeV scheme shows good results in the treatment of refractory forms of HL with a complete response of 75 % and a total response rate of 83 % [10]. The successful use of brentuximab-vedotin in the treatment of refractory and recurrent (r/r) forms of HL is also confirmed in many clinical studies. This drug was the first approved for the treatment of such a cohort of patients. This is based on the results of a phase II study in patients with p/r HL after auto-THSC or 2 lines of prior therapy. Patients received brentuximab-vedotin at a dose of 1.8 mg/kg every 3 weeks with an overall response rate of 75 % [11]. Its use in combination with chemotherapeutic regimens, such as DHAP, ICE, etc., is also being actively studied [10].

The effectiveness of nivolumab has been evaluated in many clinical trials. According to the literature [12], the response when taking this drug can be achieved in 70 % of patients, the frequency of partial remissions was 34 %, complete remissions-36 %, stabilization of the process in 8 % of patients. In our

Table 1. Patient taking Nivolumab as a therapy

№	Patient 6, 28 years	Patient 7, 22 years	Patient 8, 50 years	Patient 9, 36 years
D	Hodgkin's lymphoma, mixed-cell variant, with lesions of the cervical-supraclavicular axillary, inguinal, intra-thoracic retroperitoneal l/n, left lung, st IVB (2015)	Hodgkin's lymphom, mixed-cell variant with lesion of the cervical-supraclavicular l/n on the right st I B (2015)	Hodgkin's lymphoma, nodular sclerosis NSII, with lesions of the supraclavicular axillary intra-thoracic l/n, sternum, st IVB (2018)	Hodgkin's lymphoma, nodular sclerosis involving the cervical-supraclavicular, axillary, and intra-thoracic l/n. st. IIA (2010)
1st line therapy	8 courses BEACOPP[2]	7 courses BEACOPP[2] DRT SLD 30 G	6 courses ABVD[3]	5 courses BEACOPP[2] DRT SLD 36 G
Response	APR (2016) Early relapse (2016)	Resistant flow	Resistant flow	PR
2nd line therapy	4 courses DHAP[7], 2 courses ViGEPP[11], 6 courses bendamustin, DRT 36 G	6 courses GDP-21[10], 2 courses ICE[6], 2 courses GemOx[8]	3 courses MINE[9]	5 courses ICE[6], 1 courses BEAM[12], Auto-THSC, 1 course BEACOPP esc.[13], 10 course GDP-21[10]
Response	Refractive flow	Refractive flow	Refractive flow	Refractive flow
CPI	Nivolumab therapy 12 administrations	Nivolumab therapy 3 administrations	Nivolumab therapy 14 administrations	Nivolumab therapy 12 administrations
Effects	Stabilisation	Stabilisation	Progression	Stabilisation
AE	No AE	No AE	No AE	No AE
Current time	Observation	Observation	Anti-relapse courses: BeGeV+ brentuximab vedotin	Observation

work, stabilization was observed in 77.7 %, partial remission in 11 %, it is necessary to take into account the lines of therapy, in our work, nivolumab was prescribed to patients of the 3rd and subsequent lines. The differences in results seem to be related to a small sample of patients and differences in the duration of treatment. It is also necessary to take into account that the article provides data on the routine use of the drug. And the literature describes the results of clinical trials in which there are certain criteria for the selection of patients, the duration of follow-up.

CONCLUSIONS

Thus, this clinical observation confirms the validity of the use of immunotherapy in refractory forms of HL after 3 or more lines of systemic therapy, including patients with severe comorbidity and a long history of the disease. In addition, our clinical experience allows us to conclude that earlier use of PD-1 inhibitors in patients with an established refractory course of HL for the possibility of using the option of autologous stem cell transplantation to achieve a long-term response.

Authors contribution:
Kamaeva I.A., Lysenko I.B., Nikolaeva N.V. – research concept and design, text writing, material processing.
Lysenko I.B., Nikolaeva N.V. – scientific editing.
Kamaeva I.A., Pushkareva T.F., Kapuza E.A. – technical editing, bibliography design, preparation of illustrations.
Kamaeva I.A., Gaisultanova Ya.S., Velichko A.V. – data collection, analysis, and interpretation.

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