VIA MEDICA

CASE REPORT

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Nivolumab therapy for refractory and relapsed Hodgkin's lymphoma — case report

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ABSTRACT

A case of a 34-year-old male patient was described with increased sweating, itching of the skin without accompanying skin lesions, and a dry cough. Numerous enlarged nodes in the chest and hypodense centres in the spleen were visualised in the CT imaging. Based on lymph node biopsy, Hodgkin's lymphoma (HL) nodular sclerosis type was diagnosed. After ABVD (doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2), chemotherapy, and radiotherapy complete remission was achieved. Two months after treatment completion the disease relapsed. Six courses of chemotherapy DHAP (cisplatin 100 mg/m^2 on day 1, cytarabine 2000 mg/m^2 every 12 hours on day 2, dexamethasone 40 mg on day 1–4) were followed by high-dose chemotherapy BEAM (carmustine 300 mg/m^2, etoposide 400–800 mg/m^2, cytarabine 800–1600 mg/m^2, and melphalan 140 mg/m^2) supported with autologous transplantation of haemopoietic stem cells (ASCT). Through numerous relapses of the disease, the patient received many lines of chemotherapy and immunotherapy, including IGEV (ifosfamide 2000 mg/m^2 on day 1–4, gemcitabine 800 mg/m^2 on day 1–4, vinorelbine 20 mg/m^2 on day 1), brentuximab vedotin 1.8 mg/m^2 (BV), CNOP (cyclophosphamide 750 mg/m^2, mitoxantrone 10 mg/m^2, vincristine 1.4 mg/m^2, dexamethasone 20 mg), chlorambucil 12 mg daily for 14 days with a seven-day break + prednisone chronically in a dose of 40 mg daily, and TBS (thalidomide 100 mg per day chronically, bendamustine 90 mg/m^2 on day 1–2, methylprednisolone 1000 mg/day on day 1–3). We decided to introduce an immunotherapy with nivolumab, the anti-PD1 antibody, achieving a significant clinical response. This case report presents nivolumab as an effective treatment in refractory and relapsed HL.

Key words: Hodgkin lymphoma, nivolumab, anti-PD1 antibody

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Introduction

Hodgkin lymphoma (HL) is neoplastic disease derived from B lymphocytes. It is one of the most common cancers in young adults (15–35 years old), accounting for about 15% of all lymphoma cases. The prognosis is usually good; however, some patients fail to achieve permanent complete remission (CR) after first-line treatment due to disease recurrences or primary chemoresistance. The prerequisite to obtain a cure is well-planned first-line treatment and treatment intensification among patients refractory to basic treatment.

Case report

In February 2014 a 34-year-old male patient sought a family doctor's advice due to increased sweating and increased pruritus without accompanying skin lesions. Due to the lack of improvement after symptomatic treatment and the appearance of a dry, exhausting cough, a chest X-ray was performed, which revealed enlarged lymph node bundles. The patient was referred to the Białystok Oncology Centre.

The computed tomography (CT) of the chest revealed massively enlarged mediastinal lymph nodes: upper right paratracheal, paratracheal on both sides,

at the aortic arch and in the aortopulmonary window, subcarinal, paraesophageal, in both pulmonary hilus, at the right diaphragm crus, and enlarged lymph nodes in both supraclavicular fossa. In addition, the lymph nodes under gastric cardia and around the celiac trunk were visible. In thoracic part of the spleen visible in chest CT small hypodense lesions were described. A mediastinoscopy with lymph node biopsy was performed, based on which HL was diagnosed, grade III B, nodular sclerosis type, CD15+, CD30+. PET-CT scan was not performed before treatment. Between March and November 2014, the patient received eight ABVD chemotherapy courses and between December 2014 and January 2015 supplementary radiotherapy at a dose of 36 Gy in 18 fractions with use of photons X 6 MeV and 15 MeV. After this treatment CR was achieved, as determined based on PET-CT — metabolic activity of the mediastinal and abdominal lymph nodes below the vascular background — grade 2 in the Deauville scale.

Two months after completion of radiotherapy, subfebrile conditions and pruritus recurred. The PET-CT examination confirmed the relapse — metabolically active lymph nodes on both sides of the diaphragm and focal lesions in the spleen.

After consultation with the Oncology Centre-Institute (CO-I) in Warsaw, the patient was qualified to chemotherapy intensification and ASCT. Six courses of DHAP chemotherapy were given, after which a complete metabolic response was described in PET-CT. The patient received high-dose chemotherapy BEAM (5–9.12.2015), and on 11.12.2015 ASCT was performed. The post-transplantation period was without complications.

In March 2016 the next relapse of the disease was diagnosed in the form of nodular lesions in the lung parenchyma — the most active on borderline of segments 1/2 and 3 of the left lung and enlarged lymph nodes in the abdominal cavity — restaging according to PET-CT — grade IV. The patient was qualified for salvage chemotherapy according to IGEV protocol. The first course was complicated by profound anaemia requiring transfusion of five units of red cell concentrate and febrile neutropaenia, despite the use of primary prophylaxis with granulocyte colony stimulating factor (G-CSF).

In echocardiographic examination performed during the third-line treatment a reduced ejection fraction and hypokinesis of septum and apex were revealed. After introduction of beta blocker, angiotensin converting enzyme (ACE) inhibitor, and diuretic the heart failure symptoms disappeared. Due to increased parameters of renal functions the patient required a forced diuresis. After two IGEV courses the patient was qualified for BV treatment, and from August 2016 to January 2017 received eight courses. Gradually increasing peripheral polyneuropathy was observed during treatment. Allogeneic stem cell transplantation (alloSCT) was planned but was not performed due to lack of a matching donor.

In a PET-CT study performed on 08.02.2017 another recurrence of lymphoma in lymph nodes below the diaphragm was diagnosed — increased glucose metabolism in lymph nodes at hepatic hilum and aortocaval lymph nodes at L2–L3 level — restaging according to PET-CT — II degree. The patient was then hospitalised at the Department of Oncological and Cardiac Diagnostics of CO-I in Warsaw, where on 24.01.2017 he received the first CNOP course with palliative intent. Due to long-lasting haematological complications after the first CNOP course starting from April chemotherapy was changed to chlorambucil with prednisone to alleviate general symptoms, mainly pruritus. The treatment resulted in increasing cytopaenia, but it was not possible to get relief from general symptoms. The patient was referred to the regional oncological centre — the Department of Clinical Oncology and Haematology in Biała Podlaska, for palliative treatment.

Due to disease progression — lymph node bundles at hepatic hilum and around the renal vessels in abdominal ultrasound, increased pruritus and dry cough with good overall condition and no significant organ damage — the patient was qualified for treatment with bendamustine, thalidomide, and high doses of methylprednisolone (TBS). Between 24 and 28 May 2017 and 29 June and 3 July 2017 two courses of TBS chemotherapy were given. This next, sixth line of treatment did not give significant clinical improvement aside from the minimal reduction in pruritus, but it also did not cause serious complications.

Since 3 August 2017 nivolumab was used at a dose of 3 mg/kg body weight IV every two weeks, thanks to the funds obtained from the support of the Bogdani Family Haematology Foundation and the Siepomaga website. After the first drug administration the patient required hospitalisation due to non-immunological pneumonia and the need to transfuse two units of red cell concentrates due to symptomatic grade II anaemia. General symptoms resolved about 14 days after inclusion of nivolumab.

In control PET-CT performed after four administrations of the drug (27.09.2018), as compared to the study from 08.02.2017 the morphological and metabolic regression of nodal lesions was documented — grade 2 in Deauville scale. In the mediastinum, the lymph nodes were visible at the aortic arch, bilateral paratracheal, and subcarinal, without increased marker acquisition. No enlarged lymph nodes were seen in pulmonary hilus or at hepatic hilum. Extraperitoneally enlarged paraaortic and aorto-jejunal lymph nodes have been described.

Currently, the patient is still during immunotherapy, as of February 2018 he has received 12 administrations of nivolumab. There has been no recurrence of general symptoms, cytopaenias have resolved in the peripheral blood, and peripheral neuropathy has decreased.

After eight administrations of the drug articular pain appeared, mainly in the knee, elbow, and metacarpophalangeal and carpal joints. The pain was symmetrical, the strongest after getting out of bed, and decreased after physical activity. Due to the possibility of autoimmune joint disease, anti-citrullinated protein antibodies (result: < 0.50 U/mL), antinuclear antibodies, and anticytoplasmic ANP2 antibodies were determined; only antibodies against smooth muscle in the titre of 1:100 (IIF method) was confirmed.

In the control PET-CT scans performed on 29.01.2018, there were no metabolically active lymph nodes of lymphoproliferative nature, as in the examination from September 2017. Only residual nodal lesions on both sides of the diaphragm are described without increased metabolism — grade 2 in the Deauville scale.

Discussion

Although HL is a malignant disease with good prognosis, in 10% patients with early stage and 25–30% of patients with advanced stages, it is not possible to achieve permanent complete remission after first-line treatment. The main cause of failure is relapse, and in 5% of patients a primary chemoresistance [1]. The standard management in relapsed/refractory patients is second-line salvage chemotherapy and high-dose chemotherapy with ASCT. The most commonly used are protocols based on cisplatin/carboplatin: DHAP, ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), and on gemcitabine: IGEV, GVD (gemcitabine, vinorelbine, pegylated doxorubicin), and GDP (gemcitabine, dexamethasone, cisplatin). The effectiveness of the above schemes is presented in the following Table 1.

The choice of second-line treatment depends on the centre's experience, the clinical status of the patient, the presence of comorbidities, and previously used therapy. If the patient does not achieve a partial response (PR) after two courses, the protocol should be changed. In the case of response after 2–4 cycles of salvage therapy the patient should be qualified to high-dose chemotherapy, most often according to the BEAM scheme with ASCT [8].

In the case of relapse after ASCT, the treatment of choice is BV or, if not previously used, bendamustine. After obtaining CR allogeneic transplantation or patient's qualification for clinical trials with anti-PD1 antibodies should be considered [9].

BV and bendamustine monotherapy showed an activity in patients with recurrent and/or resistant HL [10]. Their combination resulted in an ORR and CR ratio of 67% and 19%, respectively [11]. In the second study, in which BV and bendamustine were used in patients with primary refractory HL or after the first relapse, the percentages of ORR and CR were 93% and 74%, respectively [12].

There are also several reports on the use of thalidomide in patients with relapsed and refractory HL. In one of the small studies, patients with relapse after ASCT received thalidomide in combination with vinblastine. Four out of 11 patients achieved PR, and two patients had disease stabilisation (SD). Baseline B symptoms were present in four patients and completely resolved during treatment in two patients. Five patients had disease progression within three months of treatment initiation [13].

The ability of Reed-Sternberg cells (R-S) to inhibit the immune system's response gave a new impetus to design studies on the effectiveness of drugs affecting immune checkpoints in patients with HL.

Nivolumab is a human monoclonal antibody from the G4 immunoglobulin class that binds to programmed death receptor-1 (PD-1) and blocks its interaction with PD-L1 and PD-L2 ligands. Nivolumab enhances the T-cell response, including anti-tumour responses, by blocking the attachment of PD-L1 and PD-L2 ligands to the PD-1 receptor, which in turn leads to a reduction

Table 1. The effectiveness of chemotherapy regimens

	Patients (n)	Overall response rate (ORR)%	Complete response rate (CR)%
ASHAP [2]	56	70	34
DHAP [3]	102	89	21
ICE [4]	65	85	26
IGEV [5]	91	81	54
GVD [6]	91	70	19
GDP [7]	34	62	10

in tumour growth [14]. R-S cells in classical HL form are characterised by genetic changes at the 9p24.1 locus, which lead to PD-L1 and PD-L2 overexpression, and the HL microenvironment is dominated by extensive, mixed, inflammatory cell infiltration. Nivolumab as a PD-1 blocking antibody gives a high response rates in patients with recurrent and refractory classic HL with an acceptable safety profile [15].

In 2016, the American Food and Drug Administration (FDA) approved the use of nivolumab in the treatment of patients with classic HL, who had a relapse or progression after ASCT and post-transplantation use of BV. The decision was based on the analysis of data from the CheckMate 205 and CheckMate 039 trials [16]. In phase I of the CheckMate 039 study concerning 23 patients with recurrent or refractory HL, ORR was 87%, CR was recorded in four patients, and PR in 16 patients. The remaining three patients had SD. The phase II CheckMate 205 study included 80 patients with classic HL, who received ASCT and BV. ORR was 66%, and CR and PR rates were, respectively, 9 and 58%. The estimated median duration of response was 8.7 months [16]. After a longer follow-up period, the median duration of response was extended to 13.1 months. The 12-month progression-free survival (PFS) was 54.6%, and the 12-month overall survival (OS) was 94.9% [17].

In Japan, a phase 2 trial launched in March 2015 examined the efficacy and safety of nivolumab in 17 Japanese patients with refractory/relapsing HL previously treated with BV. ORR was 81.3%, with CR and PR in four and nine patients, respectively. OS and PFS after six months were 100% and 60.0%, respectively. The most frequent adverse events were fever (41.2%), pruritus (35.3%), rash (35.3%), and hypothyroidism (29.4%). Four patients (23.5%) experienced grade 3 or 4 adverse reactions [18].

A total of 82 patients participated in studies conducted in 24 centres in Turkey, who received an average of 5–7 lines of chemotherapy. 70% of them were after ASCT, and 77% of them were after treatment with BV. After 12 weeks of treatment with nivolumab, the response was achieved in 64% of patients and 26% of patients achieved CR. During the study 41 patients remained on treatment with nivolumab [19].

Adverse events reported during nivolumab treatment may include decreased lymphocyte and platelet counts, pruritus, rash, diarrhoea, increased serum lipids levels, myelodysplastic syndrome, and immunological side effects, such as pancreatitis, pneumonia, stomatitis, or colitis. More unusual side effects include immunological hepatitis, pituitary inflammation, or thyroiditis. The severity of side effects can be reduced with glucocorticoids [20].

In a phase II clinical trial on nivolumab treatment in patients with relapsed/refractory HL, the most common adverse events were fatigue (25%), infusion-related reactions (20%), and rash (16%). The most frequent adverse events of grade 3 or 4 were neutropaenia (5%), and the most common complication of any grade was fever (4%) [14].

In the patient described in this publication, shortly after the first administration of nivolumab, pneumonia occurred, and two units of red cell concentration had to be transfused. These complications have not been repeated during further course of treatment, so it is difficult to determine whether they were drug-related or resulted from previously used chemotherapy.

In conclusion, clinical studies with nivolumab have shown that it is an effective treatment option for patients with recurrent or refractory classic HL previously treated with BV, which is confirmed by long-lasting remissions after nivolumab monotherapy and persistent PR even in patients who have been intensively pre-treated with chemotherapy. Adverse events associated with nivolumab include immune-related complications and infusion-related reactions, but they are well-tolerated, allowing treatment continuation. The presented case confirms the efficacy of nivolumab therapy, where after two months of treatment it was possible to achieve metabolic and morphological regression of nodal lesions and resolution of general symptoms, as well as maintaining these effects after another four months of treatment.

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