Cellular Therapy and Transplantation (CTT). Vol. 8, No. 4, 2019
doi: 10.18620/ctt-1866-8836-2019-8-4-41-48
Submitted: 27 October 2019, accepted: 06 December 2019

Nivolumab in pediatric Hodgkin's lymphoma

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Citation: Kozlov AV, Kazantzev IV, Iukhta TV et al. Nivolumab in pediatric Hodgkin's lymphoma. Cell Ther Transplant 2019; 8(4): 41-48.

Summary

Immune checkpoint inhibitors (ICIs) are rather efficient in classical Hodgkin's lymphoma (cHL). Pembrolizumab (pembro) is approved in children and demonstrates high response rates with acceptable toxicity. The role of nivolumab (nivo) in pediatric cHL is only to be elucidated. The aim of the presented study was to assess safety and efficiency of nivo in this age group with relapsed or refractory (R-R) cHL. Twenty-one pediatric heavily pre-treated patients 9-18 years old received nivo-based therapy. Overall response was registered in 86% (complete response – 57% and partial response – 29%). Three-year overall survival (OS) and progression free survival (PFS) were 95% and 29%, respectively. Only 1 clinically significant adverse effect (AE) of nivo was registered in the study (autoimmune thyroiditis). We did not observe any unacceptable toxicity of nivo.

Keywords

Children, Hodgkin's lymphoma, relapsed, refractory, nivolumab.

Introduction

Discovery and clinical success of ICIs entered a new era in oncology. The 2018 Nobel Prize in Medicine was awarded to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation". The principal role of immune system in tumor control was understood long ago. Earlier researchers mostly explored the opportunities to activate the immune system by stimulation of effector cells ("pressing gas pedal"). James P. Allison and Tasuku Honjo demonstrated that inhibition of checkpoints ("releasing the brake pedal") may effectively upregulate the immune system.

The ICIs demonstrate substantial efficiency in cHL. Pembrolizumab was approved for the treatment of children with cHL, but the role of other ICIs in pediatrics should only to be elucidated. Despite impressive progress in oncology, the children with refractory or resistant (R-R) cHL still demonstrate suboptimal prognosis if ≥3 lines of therapies have to be used [1]. This group of R-R cHL patients needs new approaches in management, and ICIs are among the most promising candidate drugs. The discovery of CIs introduced principally novel approach to cancer cure. This may convert cancer to one of chronic diseases [2].

The principal feature of immunity is the ability to differ between autoantigens and alloantigens. But the immune system is not ideal and regularly makes mistakes. These errors are often mild and non-significant but sometimes may lead to serious consequences such as oncological, autoimmune or infectious diseases. Studying molecular mechanisms of antigen procession, presentation, co-stimulation and inhibition is crucial for the treatment of patients with tumors.

PD-1 (programmed cell death-1) gene was discovered during the research of cell apoptosis [3]. It took a long journey to understand the function of PD-1 [2]. In terms of physiological role (immune inhibition) the definition of PD-1 is relatively correct, due to fundamental position of apoptosis in tolerance. But, in general, the term PD-1 does not precisely reflect the function of the protein.

Structurally PD-1 is a transmembrane protein and its interaction with ligands (PD-L1 or PD-L2) results in activation of PD-1/PD-L pathway [4, 5]. This effect leads to downregulation of autoreactive T cells and upregulation of T regulatory cells [6]. Development of autoimmune disorders in the model of PD-1 knockout mice proved significance of the pathway for adequate immune regulation [7]. Excessive PD-1 expression due to continuous antigen stimulation results in T-cell exhaustion and tolerance [8]. This mechanism may be realized in tumors.

PD-1 and ligands are expressed constitutive or inducibly on many tissues. PD-1 is expressed on immune cells (T-helpers, cytotoxic T-lymphocytes, natural killers, B cells, monocytes and dendritic cells) [9]. PD-L1 has extensive distribution throughout the body while PD-L2 is only present on macrophages and dendritic cells. PD-L1 can be expressed on non-hematological structures, such as endothelial cells, fibroblasts, mucous, pancreatic islet cells, astrocytes, neurons, trophoblasts, retina, heart, placenta, skeletal muscle, lung and kidney [10, 11]. Presence of PD-1 on endothelial cells may play an important role in the prevention of T cell migration into tissues and establishment of blood-organ immunological barriers [12]. Both PD-1 and PD-L1 are present on T cells, B-cells, macrophages and dendritic cells. These cells possess bimodal opportunity to regulate and to be regulated by the pathway. Some tumors also have PD-L1 on its surface, and it allows them to be "invisible" to immune system [13]. The expression of PD-1 and ligands is controlled by cytokines. For example, interferon 1 and tumor necrosis factor-α stimulate PD-L1 expression. Theoretically, combining these drugs with inducers of PD-1/PD-L1 may improve the efficiency of ICIs.

Nivo and pembro are PD-1 blocking antibodies that have been approved by the U.S. Food and Drug Administration for the treatment of cHL and some solid tumors. They were also registered in Russian Federation for the management of adult patients (nivo and pembro) and children with cHL (pembro). In the majority of cHL patients, ICIs induce durable clinical response. Complete or partial recovery of tumor immune control results in significant attenuation of disease progression. Amplification of 9p24.1 and subsequent overexpression of PD-L1 seems to be the characteristic feature of HL-specific Reed-Sternberg cells [14]. It explains high efficiency of ICIs in cHL. However, most HL patients relapse after treatment with ICIs. Therefore, it is important to improve the results by shifting to combination therapy, incorporation of ICIs earlier in treatment and consolidation with HSCT [15]. We are only in the beginning of CIs era, and appropriate schemes and schedules are only to be discovered. For example, lower dosage of nivolumab could be comparable to standard dosage of 3 mg/kg biweekly [16].

The aim of our work was to assess safety and effectiveness of nivo in childhood R-R cHL.

Patients and methods

Twenty-one children and adolescents with R-R Hodgkin's lymphoma (HL) received nivo-based therapy in Raisa Gorbacheva Memorial Research Institute of Children Oncology, Hematology and Transplantation, Pavlov First St. Petersburg State Medical University (see Table 1 for patient´s characteristics). Median age was 16 years (9 to 18). Histological forms of HL were as follows: nodular sclerosis was diagnosed in 15 patients (71%); mixed cellularity cHL, 4 cases (19%), lymphocyte-rich cHL, 1 (5%) and nodular lymphocyte predominant Hodgkin's lymphoma, 1 (5%). At the onset of the disease, the early-stage favorable status was diagnosed in 4 patients (19%); early-stage unfavorable or advanced disease was diagnosed in 17 cases (81%). B-symptoms were documented in 12 patients (67%). Bulky disease (>7 cm) and extranodal lesions were registered in 12 (57%) and 14 (67%) children, respectively. The disease was refractory in 9 cases (43%), whereas resistant or multiple relapses occurred in 12 patients (57%).

Median number of previous therapy lines was 4 (2-7) with radiation therapy in 14 patients (67%), and autologous HSCT in 6 cases (29%). Prior to nivo therapy, 16 children (76%) had progression; 3 (14%), stabilization, and 2 (10%), partial remission according to Lugano criteria [17]. All the patients received nivo in an outpatient setting. Monotherapy was used in 13 (62%) and combination with other drugs in 8 (38%). In 5 children, combination therapy was indicated, based on opinion of attended physician. In 3 cases, other drugs were added after slow clinical response to the first nivo infusions, aiming to achieve faster clinical improvement. Treatment schedule consisted of 3 mg/kg of nivo biweekly in 11 (52%) or 40 mg of nivo biweekly in 10 (48%). Combinations of nivo with following drugs were used: brentuximab vedotin 1.8 mg/kg triweekly (n=4) with median of 5 cycles (4-7), bendamustine 180 mg/m^2 triweekly (n=3) with median of 5 cycles (5-7) and gemcitabine 1000 mg/m^2 №5 weekly (n=1). Median number of nivo cycles was 9 (2-28). Response to treatment was evaluated by the LYRIC criteria [18]. They represent modified Lugano recommendations, with the addition of indeterminate response (IR). This category describes possible pseudo-progression and allows to continue ICIs hoping for further best response without discontinuation of treatment in the patients with progressive disease according to previous criterial algorithms. After nivo-based treatment, 8 patients (38%) received auto- or allogeneic hematopoietic stem cell transplantation (HSCT). Conditioning regimen in autologous HSCT (n=4) was BeEAM (bendamustine, etoposide, cytarabine and melphalan). Haploidentical donors were employed in two allo-HSCTs, and two matched related siblings were used in two other cases. The conditioning regimen in allogeneic HSCT consisted of bendamustine 360 mg/m^2 and Fludarabine 150 mg/m^2. Graft-versus-host disease prophylaxis was based on posttransplant cyclophosphamide and calcineurin inhibitors. Radiation therapy was applied to consolidate the effect of nivo in 2 cases (10%). Eleven patients (52%) did not receive any consolidation treatment.

Results

Clinical response to nivo-based therapy was assessed in 21 patients (100%). Efficiency of treatment is shown in Table 2. Overall response (ORR) was registered in 18 children (86%); CR, in 12 cases (57%); PR, in 6 patients (29%) and IR, in 3 cases (14%). Among the patients with IR, two children

Table 1. Patient´s characteristics (n=21)

HL	Age	Stage	Prior therapy	R/R	Mono/Comb	Nivo (n)	Response to nivo	Follow-up	Status
NSCHL	16	IIA	ABVD, BEACOPP+RT, DHAP, ChVPP, GDP, BV, vinblastin	rel	mono	24	CR	1137	alive, remission
NSCHL	16	IIA	BEACOPP, DHAP, auto-HSCT	rel	comb	12	PR	162	alive, remission
NSCHL	15	IVA	OEPA/COPDAC, IEP/ABVD, DHAP, BV+bendamustine	ref	comb	12	IR	391	alive, progression
NSCHL	16	IIIB	BEACOPP+RT, ICE, auto-HSCT, bendamustine	ref	comb	8	CR	478	alive, remission
NSCHL	18	IIIB	OPPA/COPP+RT, IEP, GemVin, DHAP, BV+bendamustine	ref	mono	9	CR	382	alive, progression
NSCHL	18	IVB	OEPA/COPDAC+RT, IGEV, BV+bendamustine, auto-HSCT	ref	mono	6	CR	91	alive, remission
MCCHL	17	IIB	OEPA/COPDAC+RT, IEP/ABVD, auto-HSCT, BV	ref	mono	5	CR	237	alive, remission
MCCHL	17	IIA	BEACOPP, DHAP	mr	mono	6	PR	105	alive, remission
NSCHL	13	IIA	BEACOP, DHAP, auto-HSCT, GemOx	ref	mono	6	CR	993	alive, remission
NSCHL	17	IIIB	OEPA/COPDAC+RT, DHAP, IEP/ABVD, bendamustine, BV	rel	mono	10	PR	954	alive, remission
NSCHL	16	IIB	DAL/GPOH+RT, DHAP, IEP	rel	mono	11	PR	305	alive, progression
NSCHL	16	IIIB	COPP, ABVD, DHAP, BV+bendamustine	rel	comb	2	PR	65	dead, progression
NLPHL	11	IIIB	OEPA/COPDAC, IEP/ABVD, DHAP, BV	mr	mono	12	CR	827	alive, remission
NSCHL	17	IVB	OEPA/COPDAC, ICE+RT, IGEV, BV	ref	mono	10	CR	535	alive, remission
NSCHL	10	IIIB	OEPA/COPDAC+RT, IEP/ABVD, BEACOPP, IGEV	ref	comb	4	PR	47	alive, remission
NSCHL	14	IIB	OEPA, ABVD, VIGEPP, IEP, BV	ref	mono	12	IR	933	alive, progression
MCCHL	18	IIIA	DAL-HD-90+RT, CEMP, MIV, bendamustine, BV	mr	mono	15	CR	447	alive, progression
LRCHL	16	IVB	BEACOPP, DHAP, BV	ref	comb	7	CR	318	alive, remission
NSCHL	9	IVB	BEACOPP, COPP/ABV, DHAP, BV, GemOx	ref	comb	28	CR	902	alive, progression
MCCHL	13	IIA	OEPA/COPDAC+RT, OEPA/BEACOPD, MIV, bendamustine	rel	comb	7	CR	606	alive, remission
NSCHL	15	IVB	OEPA/COPDAC, DHAP, BV	ref	comb	3	IR	355	alive, remission

Abbreviations: NSCHL (nodular sclerosis classical Hodgkin lymphoma), MCCHL (mixed cellularity classical Hodgkin lymphoma), NLPHL (nodular lymphocyte predominant Hodgkin's lymphoma), LRCHL (lymphocyte-rich classical Hodgkin lymphoma), OEPA/COPDAC (vincristine, etoposide, prednisolone, doxorubicin/cyclophosphamide, vincristine, prednisolone, dacarbazine), RT (radiotherapy), BEACOPP (bleomycin, etoposide, cytarabine, cyclophosphamide, vincristine, prednisolone, procarbazine), GDP (gemcitabine, dexamethasone, cisplatin), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), DHAP (dexamethasone, cisplatin, cytarabine), ChVPP (chlorbutine, vinblastine, prednisolone, procarbazine), IEP/ABVD (ifosfamide, etoposide, prednisolone/doxorubicin, bleomycin, vinblastine, dacarbazine), VIGEPP (vinorelbine, gemcitabine, procarbazine, prednisolone), auto-HSCT (autologous hematopoietic stem cell transplantation), GemOx (gemcitabine, oxaliplatin), ICE (ifosfamide, carboplatin, etoposide), OPPA/COPP (vincristine, prednisolone, procarbazine, doxorubicin/cyclophosphamide, vincristine, prednisolone, procarbazine), IEP (ifosfamide, etoposide, prednisolone), IGEV (ifosfamide, gemcitabine, vinorelbine), COPP (cyclophosphamide, vincristine, prednisolone, procarbazine), CEMP (cyclophosphamide, etoposide, mitoxantron, prednisolone), COPP/ABV (cyclophosphamide, vincristine, prednisolone, procarbazine/doxorubicin, bleomycin, vinblastine), BV (brentuximab vedotin), rel (relapse), ref (refractory), mr (multiple relapses), mono/comb (monotherapy/combination therapy), R/R (relapsed/refractory), CR (complete response), PR (partial response), IR (indeterminate response), N/A – not applicable.

relapsed, and one patient is now in remission with the follow-up of 355 days. Monotherapy resulted in ORR of 92% (12 patients); CR, in 62% (8), and PR, in 30% of cases (4). Combination therapy demonstrated similar effectiveness, i.e., ORR, 6 (75%); CR, 4; (50%); PR, 2 (25%).

The three-year OS rates comprised 95%. PFS rates at 1, 2 and 3 years were 69%, 58% and 29%, respectively (Fig. 1A and 1B). Median OS was not reached. With median follow-up of 391 days (47-1137), twenty patients (95%) were alive, and 14 (67%) remained in remission state. Median PFS was 24 months. Consolidation with HSCT (auto- or allo-) resulted in 3-year PFS of 75% (Fig. 2). Only 1 patient died in early posttransplant period due to infectious complications.

The general scheme of nivo-based therapy (mono- *vs* combined treatment), cHL stage (early *vs* advanced), tumor size (bulky+ *vs* bulky-), B symptoms, extranodal lesions, number of prior chemotherapy lines, preceding autoHSCT, number of nivo infusions (10 *vs* >10, see Fig. 3), and complications of therapy did not affect OS and PFS (p>0.1).

In the monotherapy group, complications of nivo were revealed in one adolescent (7.7%). This patient developed autoimmune thyroiditis which required hormone replacement therapy. It didn't lead to discontinuation of the drug. In combination therapy group, 2 patients (25%) developed transient cytopenias that could not be attributed solely to nivo and were probably associated with cytostatics.

Table 2. Efficiency of Nivolumab-based therapy

Clinical response degree	All patients (n=21)	Monotherapy (n=13)	Combination (n=8)	p
Overall response	86%	92%	75%	0.3
Complete response	57%	62%	50%	NS
Partial response	29%	30%	25%	
Indeterminate response	14%	8%	25%	

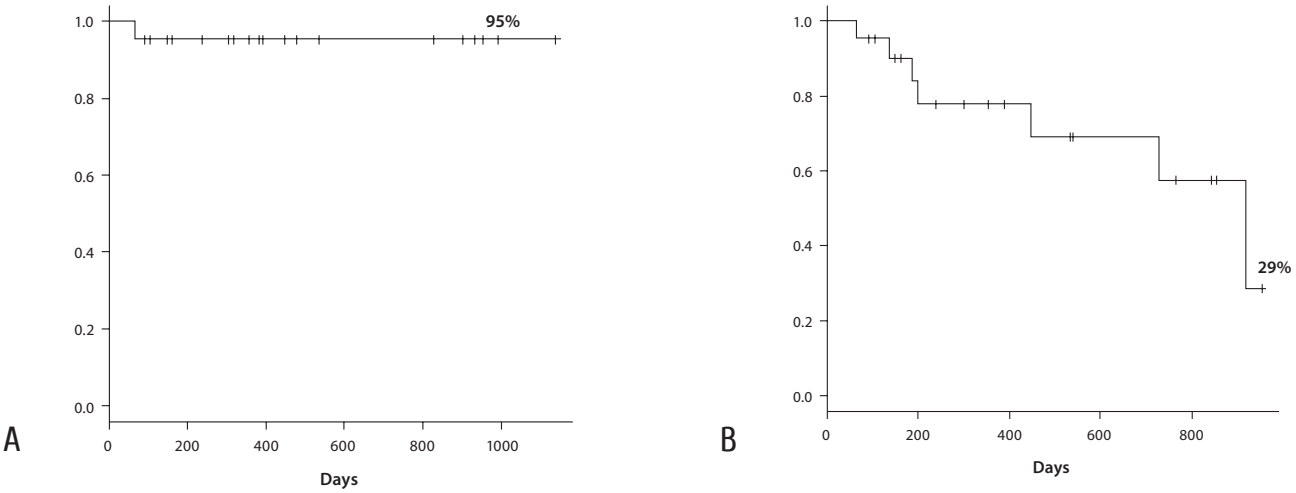

Figure 1. Overall survival (A) and progression-free survival (B) of the patients treated with nivolumab (n=21)

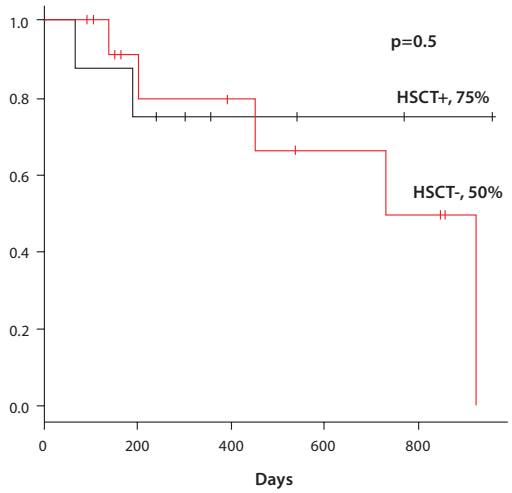

Figure 2. Progression-free survival curves with HSCT *vs* without following HSCT in the patients treated with nivolumab

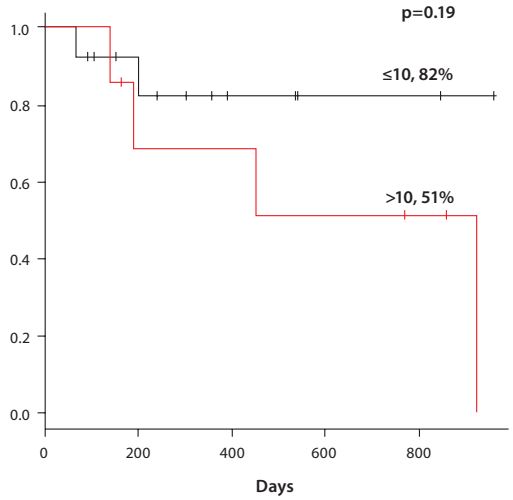

Figure 3. Progression-free survival curves among the patients treated with nivolumab (≤10 *vs* >10 infusions).

Discussion

ICIs have demonstrated high efficiency and acceptable safety profile both in adults and children in large cohorts of patients (Tables 3 and 4). Administration of ICIs in adult R-R HL results in overall response (ORR) of 64-82%, with 2-year PFS of approximately 30%-58.5% [1, 19]. The largest pediatric trial with pembro included 125 children. This study clearly demonstrated safety of ICIs in children. Only 7 (6%) had clinically significant adverse effects (grade 3-5). One patient (0.8%) with renal carcinoma experienced pembro-associated pulmonary edema and died.

No major interferences on the developing immune system were observed [20]. Another important trial included children with R-R cHL treated with combination of nivo and brentuximab vedotin. Drug-related complications were registered in 32% (grade 3-4) with neutropenia among the most common. Immune-mediated adverse effects were only grade 1-2 and included rash, hypersensitivity, infusion-related reactions and did not result in discontinuation of therapy [21].

In general, the results of the present study concerning nivo-based therapy in pediatric R-R cHL are in concordance with previously published data in adults and children [22]. Higher rates of CR in children and adolescents (57%) compared to adults (15-36%) may be associated with the differences of response evaluation in these studies, may represent a unique feature of pediatric sensitivity to ICIs or may be explained by limited patient number in the study [23, 24]. Despite similar ORR in mono- and combined therapy arms, the data from other investigators strongly support the opinion that additional drugs improve the effects of nivo [25, 26].

Suboptimal 3-year PFS of 29% in this heavily pretreated group (median number of prior lines – 4) replicates earlier data of CIs administration in adults and children [1, 20]. It is important to note that PFS rates at 1 and 2 years in our study are similar or higher than in above mentioned works and steadily decrease with time. It seems that PFS after nivo does not tend to reach plateau with time.

High ORR (86%) after nivo in R-R cHL solves a challenge of remission induction and bridging to HSCT that is now

Table 3. Efficiency of immune checkpoint inhibitors in adult cHL

Authors	Checkpoint inhibitor	Median number of prior lines	Number of patients	ORR (CR + PR), %	Bridge to HSCT, %, comments	PFS%	Median PFS, months
Armand P et al., 2018	Nivolumab	4	243	69 (16+53)	18% (allo)	Approx. 30% (at 2 years)	14.7
Chen R et al., 2017	Pembrolizumab	4	210	69 (22.4+46.6)	7% (auto and allo)	63.4% (at 9 months)	N/A
Herrera AF et al., 2018	Nivolumab + Brentuximab vedotin	1	62	82 (61+21)	66% (auto)	89% (at 6 months)	NR
Ansell S et al., 2016	Nivolumab + Ipilimumab	4	31	74 (19+55)	N/A	N/A	N/A
Lepik KV et al., 2018	Nivolumab	5	101	64 (31.6+32.7)	N/A	40.6% (at 2 years)	17.9
Santoro A et al., 2017	Nivolumab	4	133	68 (15-53)	23% (auto and allo)	61.4 (at 1 year)	N/A
Ferhanoglu B et al., 2019	Nivolumab	5	87	70 (36+34)	15% (auto and allo)	58.5% (at 2 years)	2-31

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; HSCT, hematopoietic stem cell transplantation; PFS, progression-free survival; N/A, not applicable

Table 4. Efficiency of immune checkpoint inhibitors in pediatric cohorts

Authors	Checkpoint inhibitor	Total number of pts (n), comments	ORR in all tumors (CR + PR),%	ORR in HL (CR + PR),%	PFS in HL, %	Median PFS in HL, months
Geoerger B et al., 2018	Pembrolizumab	125 (melanoma, solid tumors, NHL, HL – 10)	5.2	60 (10+50)	56.3 (at 1 year)	12.2
Kelly KM et al., 2019	Nivolumab + Brentuximab vedotin	31 (HL- 31)	81 (58+23)	81 (58+23)	N/A	N/A

Abbreviations: HL, Hodgkin's lymphoma; NHL, non- Hodgkin's lymphoma; ORR, overall response rate; CR, complete response; PR, partial response

possible in the majority of children. There is an opinion of principal opportunity of ICIs to cure cHL but declining PFS curve argues it, and longer follow-up is needed to draw firm conclusion. Dissociation between high 3-year OS and low PFS marks a very characteristic feature of ICIs therapy in cHL that repairs immune tumor control and improves somatic status of a patient even in active disease. Slow subclinical progression probably is driven by other non-immune mechanisms of tumor escape. Median PFS in children and adolescents in our study is 24 months and well correlates with data in other publications [20]. Longer median PFS may be explained by combination of nivo with other drugs in 38%. The positive effects of nivo significantly prolong life expectancy with good quality of life. Consolidation of nivo-induced remission with HSCT (auto or allo) results in 3-year PFS of 75%. HSCT is a potential option to improve cure rates after ICIs.

There is no established consensus opinion when to proceed with HSCT after ICIs, and what type of HSCT should be chosen. Allogeneic HSCT may be preferable, due to presumed sensitivity of the patients to immunotherapy. But autologous HSCT still may be effective in chemorefractory cases, since a recovery of chemosensitivity after ICIs treatment is hypothesized [27]. There are investigators that use both allo-HSCT and auto-HSCT to consolidate the ICIs effect [22, 24]. At the same time, an impressively high 3-year OS rate (95%) after nivo in our study, even in patients with progression, questions the need for transplantation at all [28]. Extensive follow-up is required to understand how long this clinical stabilization of cHL will continue in the majority of patients. In other words, can cHL be "cured" with morphologically and visibly obvious tumor, and if these patients may have a near-normal life expectancy similar to heathy people? This proposal seems more fantastic than real, and a longer follow-up is needed to see whether such observations will appear. Despite theoretical importance, the classical prognostic factors did not affect OS and PFS in our study. It may be explained by the domination of chemoresistance in our patients that minimizes the role of all other factors. Higher number of nivo cycles also did not improve outcome in our study. It emphasizes the challenging unsolved problem of optimal nivo treatment duration. Hypothetically, earlier consolidation with HSCT can minimize nivo-associated complications without loss of efficiency.

Only one clinically significant AE of nivo therapy was registered in the study, i.e., autoimmune thyroiditis which is a typical complication of the drug. Other characteristic autoimmune AEs were not encountered, probably due to limited patient number. All children and adolescents received nivo in outpatient setting, thus reflecting high tolerability and technical simplicity of treatment.

Conclusion

Nivo-based therapy is effective in the majority of children and adolescents with R-R cHL. In heavily pretreated patients, long-term PFS remains suboptimal, despite excellent OS levels. Consolidation with HSCT after nivo results in 75% PFS at 3 years and should be considered in the majority of patients. Nivo-based therapy is relatively safe with only one clinically significant adverse effect (autoimmune thyroiditis) observed in our study. Nivo is technically simple and well tolerable treatment that is administered in an outpatient setting.

Conflict of interest

None declared.

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Применение ниволумаба у детей с лимфомой Ходжкина

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Резюме

Ингибиторы контрольных точек показали высокую эффективность в лечении классической лимфомы Ходжкина (кЛХ). Пембролизумаб одобрен для применения у детей. Назначение данного препарата приводит к высокой частоте ответа на терапию и является относительно безопасным. Роль ниволумаба у детей с кЛХ еще только предстоит определить. Целями представленной работы были оценка эффективности и оценка побочных эффектов у детей с рецидивирующим и рефрактерным течением кЛХ. Терапия на основе ниволумаба была проведена у 21-го предлеченного пациента (9-18 лет) с кЛХ. Общий ответ отмечался у 86 % (полный ответ – 57% и частичный ответ – 29%). Трехлетняя общая выживаемость и выживаемость без прогрессирования составили 95% и 29%, соответственно. Отмечалось только одно клинически значимое осложнение ниволумаба (аутоиммунный тиреоидит). Не было зарегистрировано тяжелых побочных явлений проводимой терапии.

Ключевые слова

Лимфома Ходжкина, рецидивирующая, рефрактерное течение, дети, ниволумаб.