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Autologous hematopoietic stem cell transplantation after immune checkpoint inhibitor therapy in pediatric relapsed/refractory Hodgkin lymphoma

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Summary

Effective treatment of relapsed/refractory Hodgkin lymphoma (r/r HL) in children is still a challenge, especially in case of failure after several therapy lines. The present study demonstrates high effectiveness of auto-HSCT in heavily pretreated children with HL after immune checkpoint inhibitor (ICIs) therapy. Overall 16 children with r/r HL received auto-HSCT after ICIs with OS and PFS of 93.8% and 73.1%, respectively (median follow-up, 1.3 years). The transplantation procedure was generally well tolerated, with only one death (6.3%) due to sepsis. Thus, auto-HSCT after ICIs is a promising option in pediatric r/r HL but longer follow-up is mandatory to draw valid conclusions.

Keywords

Hodgkin lymphoma, relapsed/refractory, immune checkpoint inhibitors, hematopoietic stem cell transplantation, autologous.

Introduction

Nowadays, Hodgkin's lymphoma (HL) is a highly curable disease with estimated 5-year survival rates greater than 90% after treatment with chemotherapy alone or combined with radiotherapy (RT) in pediatric patients [1]. Nonetheless refractory disease or relapse are the therapeutic challenge for treating physicians. [2]. The standard of care for relapsed or refractory (r/r) HL in pediatrics is a risk-adapted approach using high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT). However, the treatment landscape has evolved with the advent of several novel agents, particularly with immune checkpoint inhibitors (ICIs) that have shown their efficacy in r/r pediatric cHL [3].

The mechanism of ICIs action is based on blocking PD-1 receptors on tumor cells. 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. This effect leads to downregulation of autoreactive T cells and upregulation of T regulatory cells [4]. The presence of PD-L1 on tumor cells makes them "invisible" to the immune system and thus allows the tumor to avoid an immune response. ICIs block the above-described pathways, which makes it possible for a human body to develop an immune antitumor response again.

Pembrolizumab (pembro) is approved in Russian Federation for children with r/r HL and demonstrates appropriate response rates with acceptable toxicity, but experience of other

ICIs is limited in children [5]. As for nivolumab (nivo), our previous data demonstrated its efficacy and relative safety in a small group of pediatric patients with HL [6].

Although ICIs alone are effective in most patients, low progression-free survival (PFS) underlines the importance of remission consolidation. Auto-HSCT demonstrated efficiency and safety in adults for consolidation of remission after ICIs in pilot studies [7]. There are few studies on the role of the auto-HSCT after ICIs in children with r/r HL [8, 9]. Compared to allogeneic HSCT, this approach seems to be more alluring as it is associated with a lower non-relapse mortality (NRM). Overall, to avoid the double-refractory HL or relapse/progression in children with r/r HL it is important to improve the results by shifting to combination therapy, early incorporation of ICIs in treatment and consolidation with auto-HSCT. The present study demonstrates single center experience of auto-HSCT after ICIs in pediatric r/r HL.

Patients and methods

The study included 16 patients with r/r HL that received auto-HSCT after the ICIs therapy in the period of time from 2017 to 2022 (Table 1). There were 81% males and 19% females. Median age was 16 years old. All but one patient with non-classical HL were diagnosed with nodular sclerosis classical HL. Bulky disease and extranodal lesions were diagnosed in 8 (67%) and 9 (75%) children, respectively.

To confirm the r/r status, second-look biopsies were carried out in 11 patients (69%). Refractoriness was established in 63% (n=10) of patients in case of progression of HL during first-line therapy or relapse within the first 3 months after the end of treatment. Early relapse (disease recurrence in the first 12 months after the start of therapy) was diagnosed in 5 patients (31%) and late relapse in 1 (6%).

Median number of therapy lines before auto-HSCT was 4 (3-8). ICIs were used to induce remission before auto-HSCT in all patients. Nivo was administered in 15 (94%) children at a fixed dose of 40 mg (n=9, 56%) or 3 mg/kg (n=6, 38%). Pembro (2 mg/kg triweekly) was used in four patients (25%), among them three (75%) had a history of previous nivo failure. Nivo alone was used bi- and tri-weekly in combination therapy. ICIs alone were started in all patients but later switched to combinational therapy (ICIs + other drugs) in

Table 1. Treatment regimens and clinical outcomes in the patients with r/r Hodgkin lymphoma

n	Age	Prior therapy to auto-HSCT	ICI (number of cycles), (n)	Status prior to auto-HSCT	Follow-up, years	Status
1	17	EuroNet+RT, BEACOPP, ICE, nivo	6	PD	2.4	alive, remission
2	15	EuroNet, IGEV, BB, nivo	9	CR	1.4	alive, remission
3	17	EuroNet, IEP/ABVD, DHAP, BB, nivo, nivo+gemcitabine, ChVPP	15	CR	4	alive, progression
4	17	BEACOPP, ICE, nivo	4	PR	1.3	alive, remission
5	17	EuroNet, DHAP+BV, BB, IGEV+nivo, pembro, nivo+bendamustine	14	PR	0.7	alive, remission
6	7	DBVE, ICE, BV, nivo	5	PR	1.3	alive, remission
7	16	BEACOPP+COPP/ABVD, DHAP, BV, BV+nivo	2	CR	0.04	dead, NRM
8	16	EuroNet, ICE, nivo	3	PR	0.9	alive, remission
9	12	EuroNet, IEP/ABVD, BV, DHAP, nivo, nivo+bendamustine	13	CR	5.3	alive, remission
10	14	EuroNet, IEP/ABVD, nivo	4	CR	1.3	alive, remission
11	16	ViGEPP, IEP/ABVD, ICE, BV, nivo, nivo+benda+RT, pembro, pembro+gemcitabine	6	PR	2.3	alive, progression
12	11	BEACOPP+COPP/ABV, DHAP, BV, GemOX, nivo, nivo+benda, pembro	31	CR	3.3	alive, remission
13	14	BEACOPP, ICE, nivo, nivo+benda	3	PR	0.5	alive, remission
14	16	EuroNet, ICE, pembro	4	PR	1.8	alive, remission
15	16	EuroNet, DHAP, nivo+BV	5	PR	4.3	alive, remission
16	12	EuroNet, ICE, nivo, nivo+benda	7	PR	0.3	alive, remission

Notes: BV, brentuximab vedotin; BB, brentuximab vedotin+bendamustine; ICE, ifosfamide, etoposide, carboplatin; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; DHAP, dexamethasone, cytarabine, cisplatin; ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; COPDAC, cyclophosphamide, oncovin, prednisone, dacarbazine; COPP, cyclophosphamide, oncovin, prednisone, procarbazine; CR, complete response; PR, partial response; PD, progression of the disease. The day of auto-HSCT was admitted as the start of observation; NRM, non-relapse mortality

9 patients (56%) due to incomplete response. ICIs were combined with bendamustine 90 mg/m^2 on days 1 and 2 (n=5) of 21-day cycle, gemcitabine 1000 mg on days 1 and 8 (n=2) of 21-day cycle and brentuximab vedotin 1.8 mg/kg (n=2) on day 1 of 21-day cycle. Median number of ICIs infusions was 5 (3-18) and median number of combinational therapy cycles was 3 (2-6). The response before auto-HSCT was evaluated by PET-CT using the Lugano criteria: complete remission (n=6, 38%), partial response (n=9, 56%), progression (n=1, 6%). Median interval between diagnosis and auto-HSCT was 1.6 years (0.5-3).

The conditioning regimens included BeEAM (bendamustine 320 mg/m^2, etoposide 800 mg/m^2, cytarabine 1600 mg/m^2, melphalan 140 mg/m^2) in all patients (94%, n=15) but one. This exclusive patient received FluBenda (fludarabine 90 mg/m^2, bendamustine 390 mg/m^2) regimen for allogeneic HSCT followed by graft failure and further reinfusion of autologous hematopoietic stem cells. Doses in conditioning regimen were reduced up to 10%-30% in 6 patients due to heavy pretreatment (n=4, >5 lines of prior therapy) and concomitant illness (n=2). The graft source was peripheral blood stem cells (PBSC) in 75% of patients (n=12) and bone marrow (BM) in 25% (n=4). Median number of infused CD34+/kg cells was 3 (2-10). Radiotherapy after auto-HSCT was administered in 8 (50%) patients (median dose 30 Gy).

Statistical analysis was performed using Easy R software. The main objectives of the study were overall survival (OS) and progression-free survival (PFS), which were calculated by Kaplan-Meier method. Survival curves were compared by means of logrank test. Non-relapse mortality (NRM) and cumulative incidence of relapse (CIR) were analyzed with regard to competing events. Adverse events (AE) were assessed according to Common Terminology Criteria for Adverse Events 5.0 (CTCAE).

Results

With a median follow up of 1.3 years (0.3-5.3) after auto-HSCT only 1 patient died in the early posttransplant period due to infectious complications (sepsis). Among survivors 13 patients (87%) remain in complete remission. Three-year OS and PFS were 93.8% (95%Cl: 63.2-99.1) and 79.1% (95%Cl: 47.9-92.8), respectively (Fig. 1A and 1B). Median OS and PFS were not achieved. NRM and CIR were 6.3% (95%CI: 0.4-24.7) and 13.9% (95%CI: 2.3-35.9), respectively (Fig. 2).

Such factors as disease stage (early *vs* advanced), B symptoms, bulky disease, extranodal involvement, type of first line (EuroNet-PHL *vs* BEACOPP) and second line therapy (IEP/ABVD *vs* ICE/DHAP), disease course (refractory *vs* relapse), second look biopsy, number of previous therapy lines (3 *vs* ≥4), number of ICI lines (<5 *vs* ≥5), type of ICI-based therapy (mono- *vs* combined), disease status prior to auto-HSCT (CR *vs* PR), dose reduction in conditioning regimen, number of infused CD34+ cells and RT after auto-HSCT did not affect the OS and PFS rates (p>0.27). Only male gender was associated with improved OS (p=0.037).

Severe transient cytopenia was observed in all patients after auto-HSCT. Mucositis developed in the majority of patients

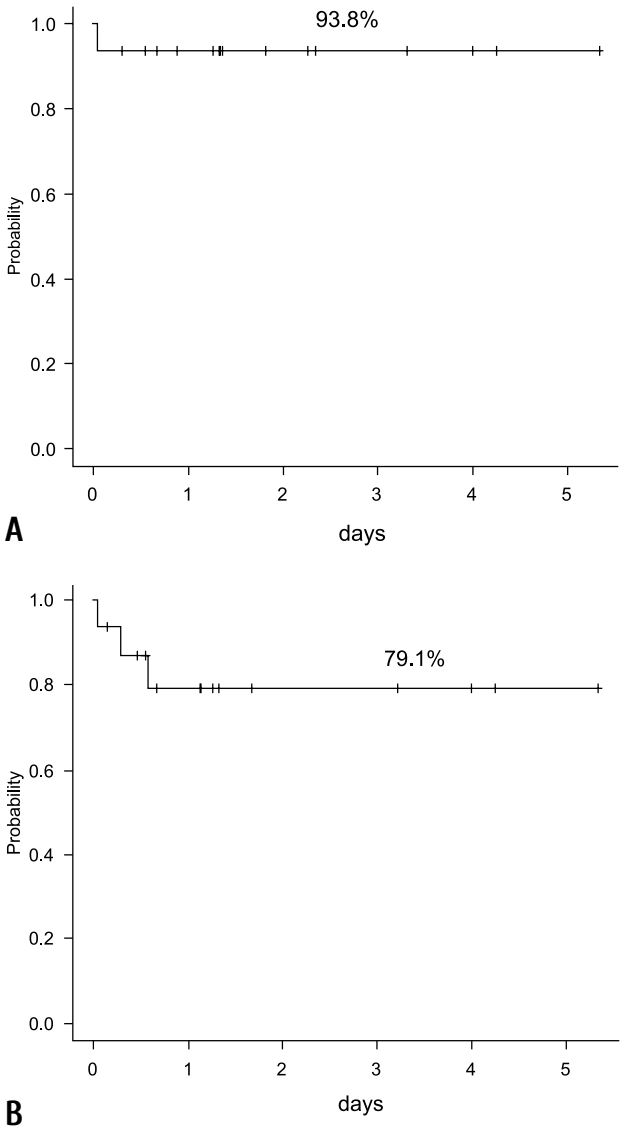

Figure 1. Overall survival (A) and progression-free survival (B) in the r/r Hodgkin lymphoma group

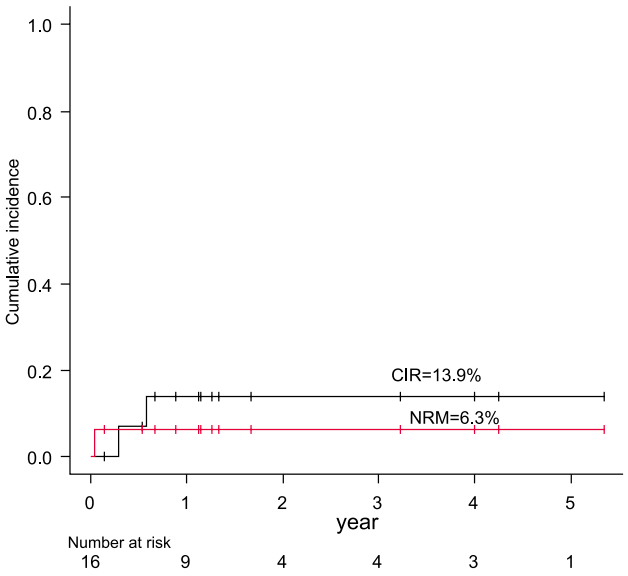

Figure 2. Non-relapse mortality and cumulative incidence of relapse in the studied patient group

(n=12, 75%). Among them grade 4, grade 3, grade 2 and grade 1 mucositis were diagnosed in 1 (8.3%), 5 (41.7%), 4 (33.3%) and 2 (16.7%) patients, respectively. Febrile neutropenia occurred in 9 children (75%). Bacterial infectious complications in posttransplant period included pneumonia (n=3, 25%) and catheter-associated infection (n=1, 8.3%). Three patients (25%) had clinically significant uncommon for auto-HSCT complications: pseudomembranous colitis (n=1, 8.3%), bronchiolitis (n=1, 8.3%) and vasculitis (n=1, 8.3%).

In two patients (16.7%) with relapse after auto-HSCT further antilyphoma therapy was initiated than consisted of nivolumab (n=1, 8.3%) and ICE chemotherapy (n=1, 8.3%).

Discussion

Auto-HSCT is a standard treatment for remission consolidation in pediatric r/r HL after second line chemotherapy [10]. Outcome of children with refractory and early relapsed HL is poor without auto-HSCT [11]. Meanwhile children with late relapses demonstrate relatively favorable outcome after second line chemotherapy alone. This risk-adapted treatment strategy should be used in children with r/r HL [12, 13]. The goal of such approach is to reduce incidence of long-term side effects [14]. Little is known on the role of auto-HSCT in children with r/r HL after ICIs. This approach seems attractive due to ability to achieve remission in the majority of patients with HL after ICIs while subsequent auto-HSCT has a theoretical potential to prevent relapse. ICIs are important milestone in the management of HL but still only approximately 10%-15% of patients can be cured in monotherapy [15]. Status prior to auto-HSCT is a crucial prognostic factor [16]. ICIs-based therapy increases the number of patients in CR prior to transplantation; another benefit of ICIs is a possible resensitization to chemotherapy in r/r HL [17].

Present study demonstrates retrospective single centre experience on auto-HSCT after ICIs in pediatric r/r HL. The data in children on this issue are limited to few publications with promising short-term results [8, 9]. Similar outcome was reported in adults recently [7, 18]. There is an ongoing dispute on the best treatment approach after ICIs (allo-HSCT *vs* auto-HSCT). To our opinion auto-HSCT is preferable due to lower NRM while allo-HSCT should be reserved for further therapy.

Overall ICIs are usually administered at least for 6 months or longer up to disease progression or unacceptable toxicity [19]. In our study we used short course of ICIs (median of 5 infusions) with the intent to proceed to auto-HSCT at the moment of best response and to reduce potential side effects of long-term ICIs exposure. The same strategy with several ICIs courses prior to auto-HSCT was adopted by other investigators as well [7, 8].

Nivo was administered at fixed dose of 40 mg in nine patients (56%) in our study. Lepik et al. used this reduced fixed dose of nivo with similar results compared to standard dose (3 mg/kg) in adults [20]. The rationale for this was an attempt to decrease possible side effects without the loss of efficacy. ICIs in combination with other antilymphoma drugs demonstrate higher efficacy compared to monotherapy [21, 22]. Our institute previously showed that combination of nivolumab and bendamustine may regain tumor control in patients with r/r HL after nivolumab monotherapy failure [20]. Nine children in our study received ICIs in combination with other drugs due to inadequate response to monotherapy. Data on combination of ICIs with other drugs in pediatric r/r HL are limited to several reports [8]. Conditioning regimen used in the study (BeEAM) is a standard approach for auto-HSCT in HL in our institute though BEAM (carmustine-based) conditioning regimen is more common approach worldwide. We demonstrated previously similar effectiveness of BeEAM and BEAM conditioning regiments for pediatric r/r HL [23].

As patients were heavily pretreated (median number of prior therapies – 4) OS (93.8%) and PFS (76.4%) obtained in our study should be regarded as satisfactory. High PFS after auto-HSCT compares favorably with historical data on ICIs alone and is in concordance with studies in children and adults on auto-HSCT after ICIs [6, 8, 9, 24]. But relatively short follow-up (median 1.3 years) as in other studies precludes valid conclusions and longer observation period is mandatory. Merryman RW et al. demonstrated similar results in heavily pretreated adults with r/r HL after ICIs and auto-HSCT (18-months OS 91%, PFS 86%) [19]. NRM (6.3%) was comparable to data published for auto-HSCT bridged with standard chemotherapy [25].

Among analyzed factors only male gender was associated with improved survival. To our opinion this fact should be regarded as random though some authors demonstrated previously possible association of gender and outcome in HL [26]. Similar survival in children with CR and PR prior to auto-HSCT and in children with different number of therapy lines (3 *vs* ≥4) supports the hypothesis that ICIs can resentitize to chemotherapy. The same results were previously demonstrated by investigators from USA in adults. These researchers also showed that lack of response to anti-PD-1 therapy, receipt of intervening salvage therapy, and advanced age were all significant predictors of inferior PFS on univariate analysis in a larger cohort (n=78) of adult patients after ICIs-based therapy and auto-HSCT [18]. Cytopenia, mucositis and febrile neutropenia were the three most common complications as had been expected. Unusual complications (vasculitis and bronchiolitis) could probably at least partially be driven by prior exposure to ICIs as immune component could not be ruled out. Though the largest up to date published study on auto-HSCT after ICIs-based therapy in children and young adults (n=43) did not describe any uncommon complications in posttransplant period; autoimmune adverse effects in our study probably were not associated with auto-HSCT and were related to recent ICIs exposure [8]. Complications of ICIs therapy can emerge months or years after the end of treatment [19]. Overall ICIs are well tolerated and can be administered in outpatient setting but one should be aware of rare life-threatening autoimmune complications in children [3, 5].

Conclusion

To summarize, the therapy with ICIs followed by auto-HSCT in children is a promising treatment for r/r HL with a rela-

tively low risk of complications and high PFS rate. However, additional cases and longer follow-up are required to draw valid conclusions.

Conflict of interest

None declared.

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Аутологичная трансплантация гемопоэтических стволовых клеток после терапии ингибиторами иммунных контрольных точек при рецидифирующей/рефрактерной лимфоме Ходжкина у детей

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Резюме

Лечение рецидивирующей/рефрактерной лимфомы Ходжкина (р/р ЛХ) у детей все еще является до конца не решенной проблемой, особенно у пациентов с несколькими линиями терапии в анамнезе. В рамках данной работы была показана высокая эффективность ауто-ТГСК у предлеченных пациентов детского возраста после применения ингибиторов иммунных контрольных точек (ИКТ). Всего ауто-ТГСК после ИКТ была проведена у 16 детей с р/р ЛХ, при этом общая выживаемость и выживаемость без прогрессирования составили 93,8% и 73,1% соответственно (медиана наблюдения – 1,3 года). Был зарегистрирован один летальный случай (6,3%) из-за сепсиса в раннем посттрансплантационном периоде. Таким образом, ауто-ТГСК после терапии ИКТ представляет собой перспективный метод терапии у детей с р/р ЛХ, однако необходим более длительный период наблюдения, чтобы сделать более обоснованные выводы.

Ключевые слова

Лимфома Ходжкина, рецидивирующая/рефрактерная, ингибиторы контрольных точек, трансплантация гемопоэтических стволовых клеток, аутологичная.