Efficacy and safety of nivolumab combinations in patients with relapsed or refractory classical Hodgkin lymphoma

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Introduction

Therapy with immune checkpoint inhibitors had shown significant activity in patients with relapsed or refractory classical Hodgkin lymphoma (r/r cHL). However, disease relapse or progression is later observed in the majority of patients. One potential approach to enhance the effect of anti-PD1 therapy is a combination with chemotherapy and targeted therapy.

The aim of this analysis was to evaluate the safety and the efficacy of nivolumab (nivo) in combination(nivo) with bendamustine (benda), vinblastine (vin) and brentuximab vedotine (BV) in patients with relapsed r/r cHL after failure of nivo monotherapy.

Patients and methods

This analysis included 3 groups of adult patients. History and clinical status of the patients at the moment of combination therapy were summarized (Table 1) and evaluated according to LYRIC criteria. The first group (n=42) received nivo and benda. Patients were treated in a 28-day cycle for up to 3 cycles. Benda (90 mg/m^2) was infused on day 1.2, and nivo (3 mg/kg) on day 1 of the cycle. The second group (n=16) received nivo and vin. The patients were treated in a 14-day cycle for up to 3 cycles. Vin (10 mg/m^2) was infused on day 1, 2, and nivo (3 mg/kg), on day 1 of the cycle. The third group (n=11) received nivo and BV. Patients were treated in a 28-day cycle for up to 3 cycles. BV (1.8 mg/m^2) was infused on day 1, and nivo (3 mg/kg) was administered on day 1 and14 of the cycle. Toxicity was graded according to the NCI CTCAE (version 4.03). After treatment completion, the clinical responses were evaluated by PET-CT scan and assessed by investigators using LYRIC criteria.

Results

Median follow-up time for first group (nivo/benda) was 24 months (8-33) from the start of the combined treatment. Median OS was not reached, 40/42 (95%) of patients were alive at the time of analysis. Median PFS was 10.6 months (7-14) with 31% of patients alive and free of disease progression (Table 2). Adverse events (AE) during treatment were observed in 40 (95%) of patients. The most common AE were fatigue (74%), nausea (64%), dyspnea (38%). Grade 3-4 adverse events included of severe fatigue, leukopenia, thrombocytopenia, uveitis, colitis, pneumonia, infusion reaction in 1 case each. All cases of immune related AE resolved completely after treatment with glucocorticosteroids. Median follow-up time for second group (nivo/vin) was 13 months (7-16) from the start of combined treatment. All the patients were alive at the time of the follow-up evaluation. Median PFS was 10 months (1-16), 38% of patients free of disease progression. AE during treatment were observed in

Table 1. Clinical characteristics of the patients treated with nivolumab

	Nivo/benda	Nivo/vin	Nivo/BV
Number of patients	42	16	11
Median age	31 years (21-62)	31 years (21-60)	30 years (25-37)
Median number of previous therapy lines	6 (3-11)	7 (3-17)	7 (3-10)
Previous nivo monotherapy	39/42 (93%)	15/16 (93%)	10/11 (91%)
Median number of nivo infusions	18 (4-27)	13 (4-22)	15 (7-27)
Prior auto-HSCT	19/42 (45%)	5/16 (31%)	5/11 (45%)
Prior BV	22/42 (52%)	11/16 (69%)	8/11 (73%)
Prior Benda	24/42 (56%)	9/16 (56%)	7/11 (64%)
The status of the patients at the moment of combination therapy: PR IR SD PD	 10% 26% 10% 55%	 6% 6% 88%	 12% 88%

Note: PR, partial response; IR, indeterminate response; SD, stable disease; PD, disease progression

12 (75%) of patients. The most common AE were fatigue (63%), nausea (38%) and pruritus (38%). Grade 3-4 AE included of pneumonia in 1 case.

Median follow-up time for first group (nivo/bv) was 27 months (10-30) from the start of combined treatment. At the time of analysis 10/11 (91%) of patients were alive. Median PFS was 12 months (4-30), 45% of patients free of disease progression. AE during treatment were observed in 8 (73%) of patients. The most common AEs were creatinine increase (55%), nausea (27%), fatigue (18%). Grade 3-4 AE included 2 cases of anemia and thrombocytopenia, and leukopenia in 1 case.

Conclusions

The results of analysis demonstrate that the nivolumab combinations have promising activity in the treatment of r/r cHL with a manageable toxicity profile.

Keywords

Hodgkin's lymphoma, classical, PD-1, salvage treatment.

Table 2. Results of nivolumab-based therapy in Hodgkin's disease

	Nivo/benda	Nivo/vin	Nivo/BV
OS: CR PR	79% 33% 45%	56% 31% 25%	64% 36% 27%
IR	5(12%)	1(6%)	1(9%)
SD	1(2%)	3(19%)	3(27%)
PD	3 (7%)	3 (19%)	
Allo-HSCT after combinations	12	1	5

Note: OS, objective response; CR, complete response; PR, partial response; IR, indeterminate response; SD, stable disease; PD, disease progression.

Эффективность и безопасность комбинированных режимов с включением ниволумаба в терапии пациентов с рецидивирующей/рефрактерной классической лимфомой Ходжкина

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Введение

Терапия ингибиторами иммунных контрольных точек продемонстрировала высокую частоту ответов у пациентов с рецидивирующей/рефрактерной классической лимфомой Ходжкина (р/р кЛХ). Однако у большинства пациентов впоследствии наблюдается рецидив или прогрессирование заболевания. Возможным подходом к усилению эффекта анти-PD1-терапии является комбинация с химиотерапией и таргетной терапией. Целью данного анализа было оценить безопасность и эффективность комбинаций ниволумаба с бендамустином, винбластином и брентуксимабом ведотином у пациентов с р/р кЛХ.

Пациенты и методы

В исследование включено 3 группы пациентов, состояние которых на момент начала комбинированной терапии оценивалось по анамнезу, клиническим показателям и критериям LYRIC (Табл. 1). Пациенты первой группы (n=42) получали ниволумаб с бендамустином (ниво/бенда). Проводилось до 3 циклов комбинированной терапии: бендамустин (90 мг/м^2) вводили в день 1,2 и ниволумаб (3 мг/кг) в день 1 цикла. Пациенты второй группы (n=16) получали ниволумаб с винбластином (ниво/вин). Проводился 14-дневный цикл до 3 циклов: винбластин (10 мг/м^2) вводили в день 1,2 и ниволумаб (3 мг/кг) в день 1 цикла. Пациенты третьей группы (n=11) получали ниволумаб с брентуксимабом ведотином (ниво/бв). Проводился 28-дневный цикл до 3 циклов. Брентуксимаб ведотин (1,8 мг/м^2) вводили в день 1, и ниволумаб (3 мг/кг) в день 1, 14 цикла. Токсичность оценивали согласно с NCI CTCAE (версия 4.03). После завершения лечения ответы на терапию были оценены с помощью ПЭТ-КТ, согласно критериям LYRIC.

Результаты

Медиана наблюдения для первой группы (ниво/бенда) – 24 месяца (8-33) от начала комбинированной терапии. Медиана ОВ не достигнута, 40/42 (95%) пациентов были живы на момент анализа. Медиана БПВ – 10,6 (7-14), 31% не имеют прогрессии заболевания (Табл. 2). Нежелательные явления (НЯ) во время лечения наблюдались у 40 (95%) пациентов. Наиболее частыми НЯ были усталость (74%), тошнота (64%), одышка (38%).

НЯ 3-4 степени включали по одному случаю тяжелой слабости, лейкопении, тромбоцитопении, увеита, колита, пневмонии, инфузионной реакции.

Медиана наблюдения для второй группы (ниво/вин) – 13 месяцев (7-16). Все пациенты были живы на момент анализа. Медиана БПВ – 10 (1-16), 38% не имеют прогрессии заболевания. НЯ во время лечения наблюдались у 12 (75%) пациентов. Наиболее частыми НЯ были усталость (63%), тошнота (38%) и зуд (38%). Нежелательные явления 3-4 степени представлены одним случаем пневмонии.

Медиана наблюдения для третьей группы (ниво/бв) – 27 месяцев (10-30). На момент анализа 10/11 (91%) пациентов были живы. Медиана БПВ – 12 (4-30), 45% не имеют прогрессии заболевания. НЯ во время лечения наблюдались у 8 (73%) пациентов. Наиболее частыми НЯ были повышение креатинина (55%), тошнота (27%), слабость (18%). НЯ 3-4 степени включали по два случая анемии и тромбоцитопении, один случай лейкопении.

Выводы

Комбинированные режимы с включением ниволумаба могут быть перспективным подходом преодоления резистентности к монотерапии ниволумабом у пациентов с р/р кЛХ.

Ключевые слова

Лимфома Ходжкина, классическая, PD-1, терапия спасения.

The outcomes of second allo-HSCT in a cohort of 50 pediatric patients with high-risk hematological malignancies lacking response or without engraftment after the allo-HSCT

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the standard of treatment in high risk hematological malignancies. Nevertheless, the relapse rates range from 10% to 70%. There are no optimal treatment options of the disease recurrence after allo-HSCT. Possible therapeutic options include reinduction chemotherapy, immuadoptive therapy (DLI), targeted therapy, immunotherapy (CAR-T) and second allo-HSCT. The presented study presents a retrospective single-center experience of second allo-HSCT in patients (pts) with refractory hematological diseases or graft failure in high-risk patients. The aims of this study were to evaluate the efficiency and factors affecting the outcome after second allo-HSCT in children that relapsed or had a graft failure after first allo-HSCT.

Materials and methods

We analyzed clinical outcomes in 50 children after second allo-HSCT with hematological malignancies: ALL – 24 pts, AML – 15 pts, MPL/MDS – 11 pts. First allo-HSCT was performed in 1st clinical remission – 16 pts, in 2nd, 3nd and more remissions, in 18 pts; active disease, in 16 pts. Allo-HSCT was performed from MUD in 20 pts, MRD in 14 pts, haplo-donors in 14pts, singeneic – 2 pts. Condition regimen was MAC in 34 pts, RIC in 16 pts. Median age at the time of the first allo-HSCT was 5 y.o. (1-18), median remission duration after 1st allo-HSCT was 148 days (31-1084), median time between 1st and 2nd allo-HSCT was 7.3 month (1-48). Indications for the second allo-HSCT were relapse or progression of the disease in 36 pts, primary graft failure, in 11 pts, secondary graft rejection, in 2 pts, transplant hypofunction, in 1 case. Median age at second HSCT was 7 y.o. (1.0-20).The conditioning regimens prior to second allo-HSCT were RIC in 40 pts and MAC in 10 pts, included post-transplant cyclophosphamide on Days +3, +4 in 31 pts, ATG-based GVHD prophylaxis was used in 11 pts; combination Tx-based GVHD prophylaxis, in 38 pts; Sirolimus, in 31 pts, Cyclosporin A, in 7 pts; monothyerapy with calcineurin inhibitors, in 7 pts. The 2nd allo-HSCT was performed from haploidentical donors in 44 pts (3 pts with the same haploidentical donor, as at in 1st allo-HSCT). In other pts: MUD (without donor substitution), in 4 pts; MRD (without donor substitution), in 2 pts. Different kinds of therapy prior to second HSCT were performed in 38 pts, 12 pts were transplanted in aplasia (transplant rejection/hypofunction). FLAG/BFM was administred in 24 pts; target therapy (hypomethylating agents/monoclonal antibodies), in 7 pts, combination of chemotherapy and targeted drugs was used in 7 pts. There was no clinical response in 16 pts, 10 pts achieved remission and cytoreduction of blasts (<20% blasts) was achieved in 12 pts. Thirty-one pts underwent post-transplant therapy: immunoadoptive therapy (DLI), 9 pts; maintenance therapy/ HMA/MA, 13 pts; DLI + combined CT was performed in 9 pts.

Results

Forty-four patients achieved engraftment, with median neutrophil reconstitution time of 21 days (12-41). Clinical remission was achieved in 44 pts (88%). OS in the whole group was determined by Kaplan-Meier method as 48%; LFS was