Interim analysis of effectiveness and safety of Nivolumab 40 mg in relapsed/refractory Hodgkin lymphoma

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Introduction

Aim of the study was to determine effectiveness and safety of therapy with Nivolumab 40 mg in patients with relapsed/refractory Hodgkin lymphoma.

Materials and methods

Intermediate analysis included 14 patients with relapsed/refractory Hodgkin lymphoma who were treated with nivolumab 40 mg once per 14 days until disease progression/unacceptable toxicity. Response was assessed by PET/CT using LYRIC criteria every 3 month (6 cycles). The safety was estimated by registration adverse effects according to NCI CTCAE 4.03.

Results

Median follow-up time was 10 months. Median number of treatment cycles with nivolumab was 17 (12-22). Median dose of drug was 0,56 mg/kg (0.4-0.91 mg/kg). 9 patients (64.3%) achieved an objective response, 5 (35.7%) a complete response (CR), and 4 patients (28.6%) a partial response. 4 patients (28.6%) had intermediate response as their best response. Two (14.3%) patients had progressive disease (at the moment of 12th and 18th cycles). Ten (71.4%) patients had adverse effects (AE). Grade ¾ AE were reported in 3 (21%) patients and included an anemia, arthritis and hepatitis. In general, the treatment was well tolerated and the toxicity profile was similar to the previously published data.

Conclusion

According to the intermediate analysis, the structure of the response to therapy in patients treated with nivolumab 40 mg was comparable to patients treated with nivolumab in standard dose (3 mg/kg). The distribution of frequency, time of occurence and structure of adverse events was also similar to the standard therapy group. In conclusion, our data indicates that nivolumab 40 mg can be an effective and safety treatment option for R/R HL patients, but it's nessesary to continue the study to obtain the final results.

Keywords

Hodgkin lymphoma, nivolumab, immunotherapy, PD1 inhibitors, relapsed lymphoma, refractory lymphoma.

Промежуточный анализ эффективности и безопасности терапии ниволумабом в дозе 40 мг в лечении рецидивирующей и рефрактерной лимфомы Ходжкина

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Введение

Целью работы была оценка эффективности и безопасности терапии ниволумабом в дозе 40 мг у пациентов с рецидивирующей/рефрактерной лимфомой Ходжкина.

Материалы и методы

В промежуточный анализ были включены 14 пациентов с рецидивирующей/рефрактерной лимфомой Ходжкина. Ниволумаб в дозе 40 мг вводился 1 раз в 2 недели до прогрессирования заболевания или развития тяжелых нежелательных явлений. Каждые 3 месяца (6 введений) производилась оценка ответа на терапию при использовании критериев LYRIC по данным ПЭТ/КТ, а также оценка наличия нежелательных явлений на терапию в соответствии с критериями NCI CTCAE 4.03.

Результаты

Медиана наблюдения составила 10 месяцев. Медиана введений ниволумаба 17 (12-22). Медиана дозы препарата составила 0,56 мг/кг (0,4-0,91 мг/кг). Объективный ответ был получен у 9 (64,3%) пациентов, полный ответ у 5 (35,7%) и частичный ответ у 4 (28,6%) пациентов. Неопределенный ответ установлен у 4 (28,6%) пациентов. За время наблюдения у 2 (14,3%) пациентов было зафиксировано прогрессирование заболевания (после

12 и 18 введений). Нежелательные явления любой степени тяжести были представлены у 10 (71,4%) пациентов, при этом 3/4 степени тяжести только у 3 (21%), в виде анемии, артрита и гепатита. В целом, терапия хорошо переносилась пациентами, а профиль токсичности был сопоставим с ранее опубликованными данными.

Заключение

По данным промежуточного анализа, структура ответа на терапию у пациентов, получавших ниволумаб в дозе 40 мг, сопоставима с пациентами, получавшими препарат в полной дозе (3 мг/кг). Распределение частоты встречаемости, времени появления и вариантов нежелательных явлений также схожи с группой пациентов, получающих стандартную терапию. Таким образом, можно предположить, что данный режим дозирования будет эффективен и безопасен у пациентов с рецидивирующей/рефрактерной лимфомой Ходжкина, однако необходимо продолжить исследование для получения заключительных результатов.

Ключевые слова

Лимфома Ходжкина, ниволумаб, иммунотерапия, PD1-ингибиторы, рецидивирующие лимфомы, резистентные лимфомы.

Cytogenetic evolution in acute leukemia at relapse after allogeneic hematopoietic cell transplantation: association with regimen conditioning and effect on survival

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Introduction

The aim of this study was to characterize patterns of cytogenetic changes in patients with acute leukemia who relapsed after allo-HSCT, to assess the effect of cytogenetic evolution upon survival; and to elucidate associations of cytogenetic evolution with conditioning regimen.

Materials and methods

Our study included seventy-three patients (35 females and 38 males, at the age of 0.8 to 60 years) diagnosed with acute myeloblastic leukemia (AML) or acute lymphoblastic leukemia (ALL) who underwent allo-HSCT at our University from 2009 to 2016. The bone marrow karyotypic changes in posttransplant relapse (PTR) were compared with those observed before allo-HSCT. Median time from transplant to relapse was 87 days (range, 18 to 1280). Myeloablative conditioning and reduced intensity conditioning was performed in 39 (53%) and 34 (47%) patients, respectively.

Results

Karyotypic changes at PTR were noted in 29 AML patients (71%) and 23 ALL patients (72%). The cytogenetic changes were divided into five following groups: a) clonal evolution of karyotype at PTR (n=30); b) clonal regression (n=1); c) new unrelated clones (n=5); d) clonal evolution of karyotype, combined with clonal regression (n=15); and e) changing of normal karyotype into abnormal at PTR (n=1). Moreover, two or more cytogenetic subclones were detected in 6 (8%) patients before allo-HSCT and in 24 (33%) patients at PTR ($p<0.0002$). Eight different ways of subclone formation has been identified. Acquisition of 3 or more new chromosomal abnormalities was the most frequent cytogenetic change, followed by acquisition of both unbalanced abnormalities and aneuploidy. The common losses in AML patients were 1q, 2q, 3q 5q, 7q, 9q, 11p, 13q, 14q, 17p, and 20q, whereas gains concerned 1q, 11q 13q, 15q, and 21q. The common losses in ALL patients were 1p, 8p, 11p, 11q, 17p, whereas the gains concerned 1q, 8q, 18p, 18q, 21q, and Xp. In the group with cytogenetic evolution at PTR, myeloablative conditioning was used more often ($p=0.01$). Cytogenetic clonal evolution frequently occurred in an unfavorable pre-transplant group with complex chromosome aberrations (3 and more per metaphase) ($p=0.02$). Overall survival after HSCT and survival after PTR were shortened in the group of patients with karyotype changes in PTR (38% vs. 17%, $p=0.03$ and 41% vs. 6%, $p=0.006$, respectively) as well as in the group of patients with two or more abnormal cytogenetic clones in PTR (31% vs. 9%; $p=0.04$ only for OS). The emergence of a new unrelated clone was associated with decreasing of survival after PTR (17% vs. 0%, $p=0.04$).

Conclusion

We have revealed evidence for a significant impact of cytogenetic evolution to clinical progression in acute leukemia treated with allo-HSCT.

Keywords

Acute leukemia, posttransplant relapse, cytogenetic evolution, conditioning regimen, outcomes.