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– ORIGINAL PAPERS –

Checkpoint Inhibitors Prior to Autologous Stem Cell Transplantation for Relapsed/ Refractory Hodgkin Lymphoma

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Abstract

Aim: *To present the evolution of our patients treated with checkpoint inhibitors before high-dose chemotherapy and autologous stem cell transplantation (ASCT) and to compare the results with data from the literature.*

Material and methods: *We evaluate 3 patients with relapsed/refractory Hodgkin's Lymphoma, who failed to achieve complete remission after 2 or more lines of salvage chemotherapy and were treated with anti PD1 inhibitors as a bridging therapy to autologous stem cell transplant. To evaluate the treatment response, we used PET CT scan before and 100 days after ASCT.*

Results: *In our study, heavily pre-treated and chemo-refractory patients had increased response rates to conditioning chemotherapy followed by ASCT given after exposure to immune-checkpoint inhibitors. All 3 patients remain in complete response at 14 months, 20 months and respectively 32 months of follow-up.*

Conclusions: *High-dose chemotherapy and ASCT can be curative for many patients with relapsed or refractory Hodgkin's Lymphoma (HL), but the outcome depends on disease status at ASCT. Patients who have chemorefractory disease, particularly those who fail more than 2 lines of salvage therapy, are considered poor candidates for ASCT. Checkpoint inhibitors are routinely employed in relapsed/refractory classical Hodgkin lymphoma. The results from our center are similar with those from several studies which have suggested that treatment with anti PD1 can sensitize previously chemorefractory HL patients to subsequent high-dose therapy and ASCT.*

Keywords: *Hodgkin lymphoma, checkpoint inhibitors, autologous stem cell transplantation.*

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Introduction

Hodgkin's lymphoma is one of the most common malignant conditions in adolescents and young adults. The majority of cases are cured through standard chemotherapy and/or radiotherapy, providing a favorable prognosis. However, a subset of patients experience refractory or relapsed disease and poses a great challenge for the clinician. In recent years immunotherapy,

particularly checkpoint inhibitors (CPi), has emerged as a promising strategy in the management of relapsed/refractory Hodgkins lymphoma (R/R HL)[1]. Checkpoint inhibitors are a class of immunotherapy drugs designed to block inhibitory signals in the immune system, allowing it to recognize and attack cancer cells more effectively. In HL, the programmed death-1 (PD-1) pathway is often exploited by cancer cells to evade immune detection. Pembrolizumab and Nivolumab, both PD-1 inhibitors, have shown remarkable efficacy in treating R/R HL. CPi have shown impressive efficacy, producing significant remission rates with manageable toxicities [2,3]. Nevertheless, long-term disease control cannot be guaranteed, and ultimately, most patients become resistant, leading to disease progression. Autologous stem cell transplantation remains a standard of care for eligible patients with R/R HL [5]. However, the optimal timing and sequencing of therapies, especially in the era of immunotherapy, have become critical considerations. Integrating checkpoint inhibitors into the treatment paradigm prior to ASCT offers several potential advantages. According to literature data, autologous hematopoietic stem cell transplantation performed after anti-PD1 therapy improves progression-free survival [4,5,6]. We aim to explore the evolving landscape of using checkpoint inhibitors as a bridge to autologous stem cell transplantation (ASCT) in patients with R/R HL. Here we report our center's experience in heavily pretreated HL patients undergoing ASCT as consolidation after CPi therapy.

Patients and Methods

We retrospectively investigated the effectiveness and safety of ASCT after CPi therapy (Pembrolizumab) in 3 patients with R/R HL. The patients were identified from the electronic database of our Institute. To be enrolled patients must have been refractory or relapsed after standard chemotherapy and they had received at least two cycles of single agent CPi before proceeding to ASCT. The diagnosis of HL was established from lymph node biopsies, in accordance with the 2008 World Health Organization classification [7]. Responses were assessed with positron emission tomography (PET) scan and computed tomography (CT) scan. Responses were classified according to the Lugano criteria [8,9]. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE version 5.0). Demographics and patient's characteristics were summarized by descriptive statistics.

Results

Three males with age at diagnoses of 17, 22 and 24 years were identified. According to Ann Arbor classification, two patients had stage III and one patient had stage IV; two patients had B symptoms and bulky disease was counted in one patient. The study patients were heavily pretreated with four to six prior therapies, including Brentuximab Vedotin (BV) in all patients. None of the 3 patients received ASCT before CPi. Patients were refractory to the first line of treatment (for two patients ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine and for one patient OEPA: vincristine, etoposide, prednisolone, doxorubicin). The treatment given immediately before CPi was GVD: gemcitabine, vinorelbine, pegylated liposomal doxorubicin (two patients) and BV as a single agent (one patient). All three patients were refractory to the last therapy before CPi (table 1). Patients received 6, 11 and respectively 24 cycles of CPi therapy (Pembrolizumab). The best response obtained with CPi was CR in one patient (figure 1) and PR in two patients. One patient developed grade 2 CTCAE colitis, necessitating corticosteroid therapy, while the other two patients exhibited grade 1 CTCAE cholestatic syndrome, as adverse events to CPi treatment. After 4, 11 and respectively 12 weeks from the last CPi administration, all 3 patients have received conditioning chemotherapy followed by ASCT. The disease status before ASCT was represented by one CR patient, two PR patients. All patients received LEAM (lomustine [CCNU], etoposide, aracytin, melphalan) as conditioning regimen. The hematological recovery was complete in all patients without any particular or unexpected adverse events (AE) or cumulative toxicity. Each patient had grade 3 hematological AE (febrile neutropenia). Grade ≤2 extra-hematological toxicities occurred in two patients, all quickly resolved: mucositis, diarrhea, nausea. One patient experienced severe orthostatic hypotension, which was resolved with corticosteroid treatment.

The post ASCT response was assessed with PET scan after 100 days from the HSC reinfusion; all three patients obtained a CR (two patients converted from PR status). The follow-up period is 14, 20 and 32 months, time in which no one patient had disease relap

Parameters	Frequency
Patients, n	3
Age, years	17, 22, 24
Males, n	3
Stage disease (ann Arbor), n III IV	 2 1
Refractory, n To first-line therapy To last line previous CPi	 3 3
Response to CPi, n CR PR	 1 2
Response to ASCT, n CR	 3

Table 1. Characteristics of patients. CPi- checkpoint inhibitors, CR- complete response, PR- partial response, ASCT- autologous hematopoietic stem cell transplantation.

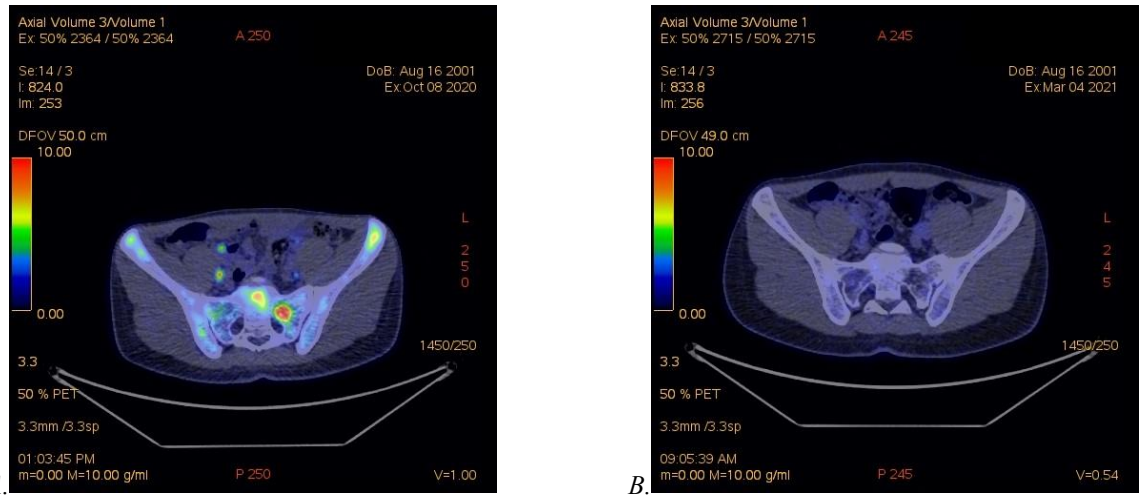

Figure 1. PET scan before (A) and after (B) Pembrolizumab therapy in one of the patients. PET- positron emission tomography.

Discussion

Given the lack of therapeutic options for patients with R/R HL until recently, the introduction of CPi can be considered a breakthrough regarding this subset of patients. Patients who fail to achieve a complete response after salvage chemotherapy are poor candidates for ASCT. In our country Pembrolizumab is reimbursed for patients refractory after two lines of chemotherapy or are considered to be ineligible for ASCT. The other, Nivolumab, can be administered only if the patients relapse after ASCT. In both scenarios the use of CPi improved the OS in patients with R/R HL treated in our center. Although until now there are no randomized trials to investigate the use and efficacy of CPi before ASCT, some case series reports have shown that it can be used with success in prolonging the survival of the R/R HL population. In our study we found that heavily pretreated patients have benefited from the use of Pembrolizumab.

One patient obtained complete response and the other two achieved only a PR based on the PET/CT scan performed before the transplantation. Even so all three of them proceeded to receive high-dose conditioning chemotherapy followed by ASCT. The disease assessment by PET/CT scan at 100-day post-transplantation procedure has shown the maintaining of CR for the first patient and moreover the conversion from PR to CR for the other two. There were no grade 3 or 4 extra-hematological adverse events reported during the treatment with Pembrolizumab or after the ASCT which shows that this sequential therapy can be used safely. In contrast there are reports that performing Allogeneic Stem Cell Transplantation after using CPi can increase the risk for severe veno-occlusive disease and grade IV GvHD [10,11]. All three patients are still in complete remission with the longest follow-up being 32 months. The conversion from PR to CR in two of our patients shows a paradigm shift meaning that autologous stem cell transplantation can be successfully used also in patients who were previously chemoresistant. Despite the small sample size, our study comes to confirm previous reports that ASCT can be used to consolidate and improve the response obtained with the use of Pembrolizumab. There is no consensus regarding the perfect timing to undergo the transplantation procedure for the patients receiving CPi and also further studies are necessary to shed light on the therapeutic attitude post ASCT – do you need to administer maintenance treatment and if so, for how long?

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Patient consent for publication
The patient provided their informed consent for the publication of the case details and any associated images. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Conflicts of interest
There are no conflicts of interest regarding this article.

References

1. Zhang, XY., Collins, G.P. Checkpoint Inhibitors and the Changing Face of the Relapsed/Refractory Classical Hodgkin Lymphoma Pathway. Curr Oncol Rep 24,1477–1488(2022). https://doi.org/10.1007/s11912-022-01292-2

2. Calabretta E, Guidetti A, Ricci F et al. Chemotherapy after PD-1 inhibitors in relapsed/refractory Hodgkin lymphoma: Outcomes and clonal evolution dynamics. Br J Haematol. 2022 Jul;198(1):82-92. doi: 10.1111/bjh.18183.

3. Carreau NA et al. Checkpoint Blockade Treatment May Sensitize Hodgkin Lymphoma to Subsequent Therapy. Oncologist. 2020 Oct;25(10):878-885. doi: 10.1634/theoncologist.2020-0167.

4. Reid W. Merryman et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. *Blood Adv* 2021; 5(6):1648–1659.doi: 10.1182/bloodadvances. 2020003556;

5. Broccoli, A. and Zinzani, P.L. (2019), The role of transplantation in Hodgkin lymphoma. Br J Haematol, 184: 93-104. https://doi.org/10.1111/bjh.15639;

6. Casadei B et al., Potential survival benefit for patients receiving autologous hematopoietic stem cell transplantation after checkpoint inhibitors for relapsed/refractory Hodgkin lymphoma: A real-life experience. Hematol Oncol. 2020 Dec;38(5):737-741. doi: 10.1002/hon.2803;.

7. Campo E et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117:5019-5032.

8. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-586.

9. Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128:2489-2496.

10. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell

transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood. 2017;129:1380-1388.

11. Ijaz A, Khan AYAY, Malik SU, et al. Significant risk of graft-versus-host disease with exposure to checkpoint inhibitors before and after allogeneic transplantation. Biol Blood Marrow Transpl. 2019;25:94-99.