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Treatment of Hodgkin lymphoma relapse after autologous hematopoietic cell transplantation

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Abstract

Despite the high response rate to first-line treatment, approximately 10% of patients with Hodgkin lymphoma (HL) develop primary resistance to chemotherapy, and 10–30% of patients experience relapse. Today, salvage chemotherapy with subsequent autologous stem cell transplantation (ASCT) remains the standard of care for those patients with relapsed/refractory HL (RRHL). Treating patients with HL who relapse following ASCT continues to be a difficult clinical challenge. For many years, allogeneic hematopoietic stem cell transplantation was the only therapeutic option in this patient population. The last decade has brought new treatment options for RRHL patients with immunotherapy, including: brentuximab vedotin anti-CD30 monoclonal antibody, or the checkpoint inhibitors nivolumab and pembrolizumab, or advanced immune therapies such as bispecific antibodies, or chimeric antigen receptor T-cell therapy.

Key words: Hodgkin lymphoma, brentuximab vedotin, nivolumab, autologous stem cell transplantation, allogeneic stem cell transplantation

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Introduction

Hodgkin lymphoma (HL) accounts for approximately 10% of all diagnosed lymphoproliferative disorders [1]. Most patients with HL achieve disease remission after first-line chemotherapy, but c.5–10% of patients remain refractory to treatment, while 10–30% of patients are found to have rapid relapse of the disease (RRHL) [2].

The standard of care for patients with RRHL continues to be salvage chemotherapy with subsequent autologous stem cell transplantation (ASCT) [3, 4]. However, more than 50% of patients undergoing ASCT are found to have disease progression or relapse. Over the years, multivariate prognostic models have been developed to assess survival probabilities in RRHL patients undergoing ASCT. Poor prognostic factors include: relapse <12 months after the completion of first-line treatment, primary refractory disease, the number of prior lines of therapy, time from diagnosis to ASCT, extra-nodal disease, cancer stage, anemia, and the presence of B cell symptoms at relapse [5–7].

Chemosensitivity prior to ASCT is crucial in the patient population with primary refractory HL. A study by Moskowitz et al. [8] found a difference in 10-year overall survival (OS) of 66% vs. 17% in patients who were chemosensitive compared to chemoresistant prior to ASCT. Similarly, Sirohi et al. [9] demonstrated the significance of the depth of response to therapy before ASCT, highlighting the 10-year OS of 72% for patients who achieved complete remission (CR), 54% for patients who achieved partial remission (PR), and only 11% for patients who were chemoresistant [9]. Treatment of relapse after ASCT in patients with HL remains a major clinical challenge, with allogeneic stem cell transplantation being the only therapeutic option in this patient population [10].

Encouragingly, the 2010s brought new treatment options for RRHL patients through immunotherapy including

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BV anti-CD30 monoclonal antibody, or the immune checkpoint inhibitors nivolumab and pembrolizumab, or advanced immune therapies such as chimeric antigen receptor T-cell (CAR-T), or bispecific antibody therapy.

Today, immunotherapy is a promising and increasingly popular treatment option for cancer patients. The genome of cancer cells contains numerous mutations and epigenetic modifications that lead to the generation of immune tolerance and inhibition of the anti-tumor immune response. Therefore, the goal of immunotherapy is to break down immune tolerance of cancer cells and develop optimal immune responses to the tumorigenic process. This review summarizes the current therapeutic options in the HL patient population with relapse following ASCT.

Brentuximab vedotin

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody that was approved in 2011 by both the Food and Drug Administration and the European Medical Agency for the treatment of patients with HL who relapse after ASCT, or those who have not responded after two lines of therapy and are not eligible for ASCT. Results of phase II clinical trials demonstrated the efficacy and safety of BV therapy in 102 patients with RRHL following ASCT. Encouragingly, the overall response rate (ORR) was 75%. 34% of patients achieved metabolic complete remission (mCR) [11], and the 5-year OS and progression-free survival (PFS) were 41% and 22%, respectively [12]. BV therapy has also been shown to play an important role in first-line treatment in combination with standard chemotherapy options [13–15].

Consolidation treatment is used in lymphoma patients to maintain and strengthen the response to therapy. Optimal consolidation treatment should have a low toxicity that will not affect hematopoietic recovery after ASCT. The efficacy of BV for patients with high-risk HL in the early consolidation phase following ASCT was demonstrated in the phase III AETHERA trial. Patients who were included in this study had at least one of the following risk factors: primary refractory HL (no CR after first-line treatment), relapse of HL <12 months after completion of therapy, or an extra-nodal disease location [16]. The 5-year PFS in the group receiving BV was 59% compared to 41% in untreated patients [17].

The results of the AETHERA trial contributed to the revision of both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network guidelines for the management of post-ASCT HL patients. According to the ESMO, consolidation with BV after ASCT is recommended in patients with at least one of the following: primary refractory HL, disease relapse <12 months after treatment completion, or extra-nodal disease. Consolidation treatment with BV after ASCT is not recommended in cases of prior BV resistance [18]. Retreatment with BV in patients with HL and in patients with anaplastic large cell lymphoma resulted in an ORR of 60% with an mCR rate of c.30%, with a median response time of 9.5 months [19].

Checkpoint inhibitors

Immune disorders that stimulate Reed-Sternberg cells to overproliferate play a significant role in the pathogenesis of HL. The amplification of chromosome 9 (9p24.1) has been shown to lead to dysregulation of PD-1 ligand and JAK2 kinase [20]. The PD-1 receptor is expressed on activated T and B lymphocytes, NK/T cells, and monocytes as a result of antigen binding by the T or B cell receptor (TCR or BCR). The primary function of PD-1 is to inhibit the activity of T cells and reduce their effector functions, by inhibiting the production of IFN-gamma, IL-2 and TNF-alpha. The presence of PD-1 ligands on Reed–Sternberg cells and tumor-associated macrophages, as well as the expression of PD-1 receptors on T cells, suggest a significant suppression of T cells due to PD-1/PD-L1/PD-L2 interactions, and justifies the use of a PD-1 blockade in the treatment of cancer. As a therapeutic measure, PD-1 inhibitors will block the attachment of PD-L1 and PD-L2 ligands to the PD-1 receptor, thereby enhancing the T-cell anti-tumor response [21].

Nivolumab and pembrolizumab are two anti-PD-1 antibodies that have been approved for RRHL therapy. In a phase II clinical trial, nivolumab was used in HL patients after failed ASCT and BV treatment. The study population included 80 patients, with a median four different treatments (range 3–15), and an average of 16 nivolumab cycles that resulted in a PFS of 76.9% and OS of 98.7% at 6-month follow-up. The reasons for discontinuation of nivolumab therapy were: disease progression (16% of patients), stem cell allotransplantation (6%), and autotransplantation in 1% [22]. In the phase II CHECKMATE 205 trial, which included 243 patients with RRHL, nivolumab was used in three patient groups: patients not treated with BV, patients treated with BV after ASCT, and patients in whom BV was used before and after ASCT. The ORR in the entire study group was 69%, with an mCR of approximately 16%, and a one-year OS of 92% [23]. Following this successful trial, a subsequent analysis of the CHECKMATE 205 trial results confirmed the efficacy and safety of nivolumab therapy in patients with RRHL. After 18 months of follow-up, the 12-month OS was 98%, while the 31-month follow-up showed a median PFS of 15 months and OS rates of 86–90%, depending on the study group [24].

The phase III KEYNOTE-204 trial evaluated pembrolizumab versus BV in RRHL patients. PFS was 13.2 months for pembrolizumab and 8.3 months for BV. This study achieved an objective response rate of 65.6% in the pembrolizumab group and 54.2% in the BV group [25].

Currently, there are numerous trials investigating concomitant immunotherapy in patients with RRHL. The treatment of BV with nivolumab resulted in an ORR of 95% and an mCR of 65% [26]. Adding ipilimumab, an anti-CTLA-4 antibody, to BV and nivolumab resulted in ORR in 95% and mCR in 84% of cases. However, triple immunotherapy is not currently recommended due to potential grade 3 immunological complications [27].

Allogeneic hematopoietic stem cell transplantation in era of new drugs

Allotransplantation of hematopoietic stem cells continues to play a role in the therapy of patients with multidrug-resistant HL. Historical analyses have shown that patients with HL who received myeloablative treatments had a 50% non-relapse mortality (NRM) rate, although the use of reduced intensity conditioning regimens significantly reduced NRM and prolonged both PFS and OS [28, 29]. However, even with the introduction of novel targeted molecules such as BV and PD-1 inhibitors which facilitate long-term remissions, there is still a group of patients for whom allo-HSCT is the only therapeutic option. Interestingly, novel drugs such as nivolumab and pembrolizumab used before and after allotransplantation may actually increase complications, with PD-1 inhibitors shown to increase the risk of veno-occlusive liver disease and graft-versus-host disease (GvHD) when administered shortly before allotransplantation. Moreover, the risk of acute GvHD is higher in patients who receive PD-1 inhibitors after allotransplantation [30, 31].

As yet, the optimal time between the discontinuation of PD-1 inhibitors and the execution of allo-HSCT has not been determined, and there is still discussion around whether a patient who achieves CR, or at least PR, after PD-1 inhibitor therapy should receive consolidation treatment with allo-HSCT. Six weeks appears to be a safe period after the discontinuation of PD-1 inhibitor therapy. The authors of the recommendations also address the situation of using PD-1 inhibitors after allo-HSCT in the case of relapsed disease. In this patient population, a reduced-dose PD-1 inhibitors therapy is recommended [32]. Post-transplant cyclophosphamide as GvHD prophylaxis is recommended in HL patients undergoing haploidentical stem cell transplantation [33].

New therapies in RRHL

CAR-T therapy

CAR-T therapy is a novel, advanced genetic engineering technology that represents a new therapeutic option for patients with RRHL. In a phase I/II clinical trial with 22 RRHL patients after multiple lines of treatment, 53% of patients achieved CR within six weeks following CAR-T administration. However, cytokine release syndrome (CRS) developed in four patients during the trial (three with grade 1 disease and one with grade 2 disease) [34]. In another phase I/II trial, when CD30. CAR-T therapy was preceded by lymphocyte depletion with fludarabine, ORR was achieved in 72% of RRHL patients, with a CR rate of 59%. Most patients in the study population had been previously treated with ASCT, BV, and PD-1 inhibitors, with a one-year PFS of 36% [35]. Again, CRS was observed in 24% of patients from this trial, most commonly at grade 1. In patients who show progression after CAR-T treatment, retreatment with PD-1 inhibitors has been implemented with fairly good results [36]. Current research is evaluating CAR-T therapy based on the co-expression of CD30 and CCR4 (CD30.CCR4.CAR-T) [37]. Finally, CAR-T therapy that targets latent membrane proteins 1 and 2 (LMP1 and LMP2) has also shown encouraging results, with an ORR of 62% and a CR of 52% in patients with refractory lymphoma [38].

JAK2 inhibitors

A common disorder in HL is amplification of chromosome 9p24 that leads to dysregulation of the JAK2 signaling cascade, and contributes to abnormal cell proliferation [39]. Therefore, JAK2 inhibition has emerged as another potential target for therapy in the RRHL patient population. The JAK1/2 inhibitor ruxolitinib was used in a phase II trial in patients with RRHL, although the resulting ORR was 9.4%, response duration was only 7.7 months, and the PFS was 3.5 months [40]. It has therefore been concluded that ruxolitinib monotherapy has no benefit for patients with RRHL. It is possible that the use of JAK1/2 inhibitors in combination with other treatment options will allow for better therapeutic outcomes.

Novel antibodies

Camidanlumab tiserine is an anti-CD25 antibody conjugated with cytotoxic agent pyrrolobenzodiazepine. In a phase II study, this antibody was administered to 51 heavily pretreated HL patients with a median seven previous lines of therapy including BV and PD-1 inhibitors. ORR and CR rates were 83% and 38.3% respectively.

A bispecific, tetravalent AFM13 antibody directed against CD30 and CD16 antigens is undergoing phase I trials. Its mechanism of action is based on activating NK cells through the CD16 antigen and on Reed–Sternberg cells through the CD30 antigen. In a phase Ib trial, AFM13 was used in combination with pembrolizumab in patients with RRHL not previously treated with PD-1 inhibitors. The ORR in the study group was 87% and the CR was 39%, making this a promising therapeutic option in need of further development [41].

BTK inhibitors

The use of Bruton's tyrosine kinase (BTK) inhibitors in patients with RRHL is also the subject of clinical trials. The literature reports a therapeutic effect of ibrutinib in patients

with RRHL after allo-HSCT [42]. Ibrutinib in monotherapy, as well as in combination with BV or nivolumab, is the subject of phase II trials.

Conclusion

In recent years, the therapeutic approach to patients with RRHL has changed with the introduction of new molecules using immunological mechanisms of action. The ASCT procedure is still the primary treatment for RRHL, but with new therapeutic tools such as BV, many patients are achieving optimal response prior to hematopoietic stem cell transplantation.

Moreover, consolidation therapy after ASCT significantly improves outcomes in patients with high-risk HL. Advanced genetic engineering technologies such as CAR-T, or novel bispecific antibodies with a complex mechanism of immune action, provide a potential therapeutic option for multidrug-resistant patients after ASCT and allo-HSCT, but there is a need for further development.

Author's contributions

Equal contribution in design of the article and preparing manuscript.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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