A Case of Recurrence/Refractory Mediastinal Hodgkin's Lymphoma Relapsed After Allogeneic Hematopoietic Stem Cell Transplantation: Immunotherapy Brings Hope

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Abstract: Hodgkin lymphoma (HL), is a B-cell lymphoma. HL is a common hematological malignancy, mostly seen in young and middle-aged people. According to NCCN guidelines, common treatment options include ABVD, BEACOPP, Stanford V, etc. Most HL have a good prognosis and even can be cured. However, some Refractory / Recurrent (R/R) HL, continue to progress during treatment or even relapse after the completion of a complete chemotherapy course 3 months. At this time, the best treatment for R/R HL is high-dose chemotherapy / Autologous Hematopoietic Stem Cell Transplantation (HDC/HSCT). This paper reports a case of Recurrence/Refractory (R/R) mediastinal Hodgkin's lymphoma that relapsed after Allogeneic Hematopoietic Stem Cell Transplantation. After receiving a variety of treatments, including chemotherapy, radiotherapy, autologous hematopoietic stem cell transplantation and so on, no long-term sustained remission was achieved. Traditional chemotherapy regimen has not brought ideal therapeutic effect to patients, but the rapid development of immunotherapy in recent years has brought new hope to patients. Finally sustained remission was achieved under the treatment of Brentuximab Vedotin combined with PD-1 inhibitor. This paper combined with the literature reports and discussed the clinical characteristics, treatment process and related experience and thinking methods of immunotherapy related to PD-1 inhibitors in this refractory and easy-to-relapse case. To provide more clinical data for the application of immunotherapy in R/R HL.

Keywords: Hodgkin Lymphoma, Refractory / Recurrent, Brentuximab Vedotin, PD-1 Inhibitor, Immune

1. Introduction

Hodgkin lymphoma (HL), is a B-cell lymphoma. In the world, HL accounts for 13.6% of lymphoma. Most HL have a good prognosis and even can be cured [1]. However, some refractory / recurrent (R/R) HL, continue to progress during treatment or even relapse after the completion of a complete chemotherapy course 3 months [2]. At this time, the best treatment for R/R HL is high-dose chemotherapy / Autologous Hematopoietic Stem Cell Transplantation (HDC/HSCT) [3]. This paper reports a case of R/R HL that relapsed three months after Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT). After diagnosis, the patient used BEACOPP for 8 cycles, but completing the chemotherapy, the lymphoma relapsed on the 43rd day. Then came to hospital for Allo-HSCT, after acquired remission by using IGDV+ Brentuximab Vedotin (BV) chemotherapy regimens. However, it relapsed again in the second month after transplantation. At this time, there was no long-term sustained remission after using a variety of treatment regimens, including radiotherapy, chemotherapy and demethylation therapy. Finally, long-term sustained remission was achieved under the treatment of BV combined with Procedural death factors 1 (PD-1) inhibitors. This paper combined with the literature reports and discussed the clinical characteristics, treatment process and related experience and thinking methods of immunotherapy related to PD-1 inhibitors in this refractory and easy-to-relapse case. To provide more clinical data for the application of immunotherapy in R/R HL.
2. Case Report

An 18-year-old man was treated for "repeated cough and expectoration (duration not mentioned)" coughing a small amount of yellow sticky sputum, with chest tightness, skin itching, no systemic symptoms (fever, weight loss, night sweats). PET/CT showed multiple enlarged lymph nodes with increased metabolic activity in bilateral supraclavicular fossa, mediastinum and left internal breast area, and abnormal metabolic activity without observed in the other parts. Then mediastinal lymph nodes biopsy was performed, immunohistochemistry showed: LCA(+), CD30(+), CD15(+,partly), MUM1(+), CD3(-), CD5(-), CD7(-); ALK(-), EMA(-), PAX-5(+weakly), Oct-2(-), CD20(-), CD57(-), Granzyme--B(-), CD21(+, Follicular dendritic network).

The bone marrow examination without showed abnormality, the patient was diagnosed as HL mixed cell type, stage II A type. Within 16 months after definite diagnosis, remission was achieved after 8 courses of treatment with BEACOPP regimen. Forty-three days later, the patient was hospitalized again because of cough, expectoration and fever. PET/CT showed recurrence of lymphoma with invasion of both lungs. Right mediastinal lymph node and right upper lung nodule biopsy: IHC: LCA(-), CD20(-)CD30(+), CD15(+,partly), MUM-1(+), CD10(-), ALK(-), BcI-6(-), CD23(-), CD5(-), Pax8(-). After 3 courses of IGDV (Ifosfamide 3400 mg d1-2, 3450 mg d3-4,Gemcitabine 1400 mg d1, 1500 mg d4+Vindesine 37 mg d1+methylprednisolone 100 mg d1-4+Mesna 800 mg tid) Hodgkin regimen and 4 cycles of BV (100 mg). PET/CT showed that the lesions were significantly reduced and partially disappeared.

Then the patient came to our hospital for further treatment, re-evaluated the patient's condition, and diagnosed as HL (mixed cell HL, typical stage IV, group B, IPI score 3, ECOG 0). The primary disease recurred during regular chemotherapy, had the indicator of Allo-HSCT. The donor is his father, HLA match type 5/10, blood type A, after pretreatment (Busulfan 12 mg/Kg + fludarabine + Cyclophosphamide), Allo-HSCT was performed. Cyclosporine A (CsA) + Mycophenolate Mofetil (MMF) + high dose Cyclophosphamide (CY) was used to resist graft versus host disease (GVHD). The lymphoma relapsed again in the third month after transplantation. And then local radiotherapy was given to the primary mass and right hilar masses of remission lasted for 7 months.

During the 13th PD-1 inhibitor treatment, imaging showed that the lung and mediastinal lesions were enlarged than before, indicating disease’s activity. Increase the dose of PD-1 inhibitors, the patient received three times of immunotherapy with 80 mg PD-1 inhibitors and two cycles of chemotherapy + targeted therapy (gemcitabine 1000 mg / m² d1 + Vindesine sulfate 3 mg / m² d1 + 15 mg / m² d1 + BV 150 mg d8). Since then, the patient's condition is stable. Combined with previous treatment regimens, the patient is sensitive to BV treatment. So we have given four courses of BV (100 mg) to consolidation therapy, and after the third course of treatment, the patient achieved partial remission. However, progress during treatment showed that patients were no longer sensitive to BV.

According to the manual, we gradually adjusted the PD-1 dose. The final dose was increased to the manual recommended standard dose of 3 mg/kg, and the patient received remission. Up to now, the patient has been in the state of remission for a long time under the maintenance therapy of 3 mg/Kg PD-1 inhibitor.

3. Discussion

HL is a common hematological malignant tumor, which usually occurs in young and middle-aged people [6]. According to the NCCN guidelines, the common treatment schemes are ABVD, BEACOPP, StanfordV and so on [3]. Most patients will be in complete remission after initial treatment and achieve long-term disease control. However, there are still a small number of patients with recurrent attacks, and the progression of the disease eventually leads to death. This paper reports a case of R/R HL that relapses within a short period of time after transplantation.

After being diagnosed with HL at the age of 18, the patient experienced a variety of treatments, including bone marrow
transplantation, but all failed to achieve long-term remission. Then we tried immunotherapy including BV and PD-1 inhibitors. Despite progress during treatment, the patient eventually achieved long-term remission with the maintenance of standard doses of PD-1 inhibitors.

The traditional chemotherapy regimen does not get the ideal therapeutic effect on patient, but the rapid development of immunotherapy in recent years has brought new hope for patient. BV is a kind of antibody-drug coupling, which recognizes and binds tumor cells which expressing CD30+ through the combination of monoclonal antibodies and small molecular antineoplastic drugs, and then make chemical small molecular drugs enters tumor cells through endocytosis of cells. It can be used in combination with other chemotherapy drugs or alone in recurrent lymphoma after transplantation, it showed a good complete remission rate in II/III clinical trials [9]. The patient we reported received four cycles of BV before transplantation and responded well, so we treated the patient again in the event of recurrence after transplantation, but did not achieve the desired effect like past.

The above enlightens us to explore the reasons why follow-up BV treatment is ineffective. We often think that antigen down-regulation is a potential mechanism of drug resistance to antigen therapy. However, the resistance to BV in HL is not due to the decreased expression of CD30, but to the up-regulation of multiple drug resistance gene MDR1 and the emergence of cytotoxic drug monomethyl auristatin E (MMAE) resistance [10]. It was found that in the mouse model, the effect of BV on HL was restored after competitively inhibiting the expression of MDR1 [11]. Phase I trials that combined with BV and CsA were performed in 86% of patients with R/R HL insensitive to BV [11]. The results showed that the rates of ORR and CR were 75% and 42%, respectively [11]. However, the subsequent adverse reactions, such as myelosuppression, also greatly limit the clinical use. It is suggested that the simultaneous detection of the expression level of CD30 may play a better role in guiding the use of drugs when using BV.

PD-1 is the key immunosuppressive receptor for T cells to activate the second signal [12]. PD-1 inhibitors activate T cells to fight tumor by antagonizing the binding of PD-1 to the specific receptor PD-L1, and obtain a good response in solid tumors [12]. It has a good effect in hematological tumors, especially in patients with HL [13]. The role of PD-1 inhibitors as consolidation therapy in patients with Allo-HSCT is still controversial. As we all know, the GVL effect after transplantation is an important anti-tumor step, and the loss of GVL effect is considered to be one of the main causes of recurrence of metastatic diseases, which is also the most common cause of death and treatment failure after Allo-HSCT [14]. As early as in the study of leukemia, it has been found that recurrence after Allo-HSCT is related to the killing of tumor cells by PD-1-mediated loss of donor T cells, after down-regulating the expression of PD-1, it may restore the effect of GVL on recurrent AML [15]. Obviously, blocking the inhibitory effect of PD-1 on immune cells may be beneficial to patients after Allo-HSCT. However, as an immune checkpoint, PD-1/PD-L1 has not only disadvantages. PD-1/PD-L1 can significantly regulate the GVHD effect, and the interaction between PD-1 and PD-L1 can inhibit the graft-versus-host immune response mediated by Th1/Th17 [16, 17]. Therefore, how to balance the advantages and disadvantages of PD-1/PD-L1 blocking is a problem that we continue to pay close attention to. Both preclinical and clinical data suggest that the shorter interval between Allo-HCT and ICI treatment is associated with a higher risk of immune complexity [17]. We did not use PD-1 inhibitors for the first time, but 9 months after transplantation, which may be one of the reasons why the patients did not show serious adverse reactions.

At present, the recommended dose of lymphoma PD-1 inhibitor is 3 mg/Kg or 240 mg fixed dose. However, the results of pharmacokinetic analysis and clinical observation show that low dose PD-1 especially monoclonal antibody has potential curative effect on solid tumor [4, 18]. In additionally, it has been reported that R/R HL patients who have previously received Allo-HSCT or not, have significant responses to low dose nivolumab and pembrolizumab [5, 19]. To be on the safe side, the low-dose PD-1 inhibitor (40 mg) we used at first. After that, patients not only got a good response, but also without show serious adverse reactions, which provided a guarantee for gradually increasing the therapeutic dose of PD-1 inhibitor after the later progression of the disease. However, the patient inevitably progressed, until the dose of the PD-1 inhibitor was gradually increased to the recommended dose of 3 mg/kg in the instructions, the disease was controlled. Since then, the patient has been treated with PD-1 inhibitor and is still in the state of remission.

It has been found that, nivolumab (standard dose 240 mg) sequential N-AVD regimen has good efficacy and safety in newly diagnosed III-IV patients with advanced cHL and cHL adults with large fast masses or extranodal diseases [20]. It makes us wonder whether the initial use of large doses of PD-1 inhibitors can achieve early remission. Besides, although the current guidelines recommend that patients with high risk factors have little chance of recurrence after 1-2 years of maintenance therapy with PD-1 inhibitors [2, 3], for this patient, who has experienced early recurrence and poor response to many chemotherapeutic drugs and radiotherapy, even relapse after transplantation and BV resistance. The duration of PD-1 inhibitor maintenance treatment, how to prevent PD-1 inhibitor treatment resistance and select subsequently treatment options after drug resistance? Above, all is worth us to continue to think and explore the problem.

4. Conclusion

For patients with Hodgkin’s lymphoma who have undergone multiple conventional chemotherapy regimens but have not achieved desired therapeutic outcomes, the rapid development of immunotherapy has brought new hope to patients. However, for such patients with recurrence and progression of disease after transplantation, the dosage, timing and maintenance time of immunosuppressive drugs...
are still questions that we continue to study and explore.

Statement

The manuscript has been read and approved by all the authors.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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