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Novel agents in the treatment of Hodgkin lymphoma: Biological basis and clinical results

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ABSTRACT

Hodgkin Lymphoma (HL) is a lymphoproliferative disorder of B cells that commonly has a favorable prognosis when treated with either combination chemotherapy and radiation therapy, or chemotherapy alone. However, the prognosis for patients who relapse, or have evidence for refractory disease, is poor and new treatments are needed for patients with progressive disease. HL has a unique tumor microenvironment consisting of a predominance of inflammatory cells and a minority of malignant Hodgkin and Reed-Sternberg (HRS) cells. This unique biology provides an opportunity for novel therapy approaches that either specifically target the malignant HRS cell or target the inflammatory tumor microenvironment. New therapies including antibody drug conjugates targeting CD30, small molecule inhibitors that inhibit critical cell signaling pathways, monoclonal antibodies that block immune checkpoints, or agents that modulate the immune microenvironment have all recently been tested in HL with significant clinical activity. Multiple clinical trials are currently ongoing testing these agents in the relapsed and refractory setting but also in earlier phases of therapy often in combination with more standard treatment.

1. Introduction

Hodgkin lymphoma (HL) is a rare disease that accounts for approximately 9,000 new patients each year [1]. This population represents approximately 12% of all of the patients with lymphoma seen in the United States annually. HL has two distinct subtypes, classical HL and nodular lymphocyte-predominant HL. Classical HL includes four histologic subtypes: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL [2]. Most patients diagnosed with HL respond well to initial treatment resulting in an approximately 75% cure rate. A subset of the patients are either resistant to initial therapy or relapse after initial treatment, requiring additional therapy typically in the form of second-line regimens with autologous stem cell transplantation. For those patients who progress after autologous stem cell transplantation, the outcome is poor. Novel therapies are clearly needed for patients with relapsed and refractory disease. Furthermore, novel treatments are also needed for patients with newly diagnosed HL to improve the cure rate while reducing treatment-related toxicity.

2. Biological targets in HL

HL has a unique histological appearance with a very small number of malignant Hodgkin and Reed-Sternberg (HRS) cells present among an overwhelming number of reactive and inflammatory cellular infiltrate [3]. The inflammatory infiltrate includes T cells, histiocytes, eosinophils, B cells, and plasma cells that appear to have been attracted to by a network of cytokines and chemokines that are secreted by the malignant HRS cells [4]. These cytokines include thymus and activation regulated chemokine (TARC/CCL17), interleukin (IL)-6, IL-13, or soluble IL-2 receptor [5,6]. The intratumoral immune cells that have been attracted by these cytokines appear to provide survival and growth support to the HRS cells. While many cells present in the tumor appear to be immune effector cells, these cells appear unable to effectively eradicate the tumor or mount an effective anti-tumor immune response. While initial studies suggested that intratumoral T cells have a TH2 phenotype, recent data suggest that they may in fact be TH1 cells. This is due to an abundant expression of TH1-associated TBET seen on gene expression profiling, while TH2-associated GATA3 was seen at substantially lower levels [7]. Despite the presence of TH1 cells in the tumor, these cells do not appear to efficiently target the malignant clone.

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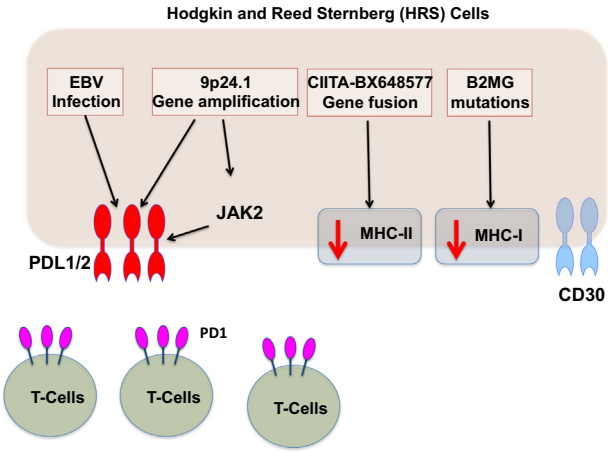

Fig. 1. Regulation of PD-L1 and PD-L2 expression in Hodgkin lymphoma.

A potential reason for the lack of an effective anti-tumor immune response may be increased signaling through program death 1 (PD1). PD1 is physiologically expressed on activated T cells, and PD1 signaling has been shown to suppress T-cell function. HRS cells express high levels of the PD1 ligands (PD-L1 and PD-L2), which is linked to genetic amplification at the PD-L1 and PD-L2 locus on chromosome 9p24.1. Epstein-Barr virus (EBV) infection, which is commonly seen in HL, may also account for increased expression of the PD1 ligands [8]. Furthermore, the genetic alterations on chromosome 9p24.1results in activation of JAK-STAT signaling, further increasing the expression of PD-L1 and PD-L2 (Fig. 1).

An additional tumor-associated factor that has been associated with a poor outcome includes the presence of increased numbers of tumor-associated macrophages. Previous studies have reported that increased numbers of $CD163^+$ macrophages are present in HL and this is associated with a poorer outcome and a decreased overall survival [9]. Further immune factors that have been associated with patient outcome include increased levels of circulating serum cytokines and increase monocytes in the peripheral blood that skews the absolute lymphocyte to monocyte count ratio [6,10]. Both of these factors may be associated with the proficiency of the patient's immune response. All of these features confirm the fact that the active immune microenvironment and inadequate immune response seen in HL represent potential targets for novel therapies.

Furthermore, the unique expression of CD30 on the malignant HRS cells is an additional therapeutic opportunity [11,12]. CD30 is not typically expressed on normal human tissue under physiologic conditions. CD30 is predominantly expressed on thymocytes during thymus development and occasionally on pancreatic exocrine cells as well as cells in the uterus and endometrium during pregnancy. Some activated T cells can also transiently express CD30. This restricted expression of CD30 makes CD30 a target to specifically treat HRS cells present in HL.

3. Novel therapies in HL

Due to the unique composition of lymph nodes in HL, new treatments have been developed that either directly target HRS cells, target cells in the inflammatory infiltrate, or reverse the suppressed immune response. Many of the agents discussed below have showed promising clinical activity in patients with HL; particularly in those who have progressed after standard initial therapy and subsequent salvage autologous stem cell transplantation.

3.1. Brentuximab vedotin

Brentuximab vedotin is an antibody drug conjugate that specifically targets CD30. Initial clinical trials included significant numbers of HL patients due to the selective expression of CD30 on the HRS cell. In the initial phase I trial, patients received brentuximab vedotin on a three weekly schedule. The initial studies showed objective responses in 17 patients with HL, 11 of who had a complete response to treatment [13]. Of the 12 patients with HL who were treated at the maximum tolerated dose, an overall response rate of 50% was observed. A subsequent pivotal phase II trial was performed to confirm these results. Brentuximab vedotin was given to patients with relapsed and refractory HL, all of whom had progressed after a previous autologous stem cell transplant [14]. In 102 patients treated on this trial, the overall response rate was 75%; 34% of the patients had a complete response to treatment. The median progression-free survival for all patients was 5.6 months; however, the median duration of response for those attaining a complete response to treatment was 20.5 months. Subsequent long-term follow-up of patients on this trial confirmed the durability of the responses [15]. Of the 34 patients who had a complete response to treatment initially, 16 (47%) remained in remission without evidence of progression at a median follow-up of 53.3 months.

Based on these encouraging results, brentuximab vedotin has been incorporated into combination treatment approaches. An initial clinical trial combined brentuximab vedotin with standard ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) as initial treatment for patients with advanced stage HL [16]. The initial cohort of patients showed that brentuximab vedotin when combined with bleomycin in the ABVD regimen resulted in significant pulmonary toxicity and the study was subsequently revised to combine brentuximab vedotin with AVD (bleomycin omitted). The maximum tolerated dose of brentuximab vedotin in combination with this chemotherapy regimen was found to be 1.2 mg/kg. The study showed that the combined approach was highly effective with complete responses seen in 96% of the patients treated. Due to these very promising clinical responses, a comparative frontline randomized trial is being conducted and accrual to the study has been completed. In this trial, AVD chemotherapy plus brentuximab vedotin is being compared to standard ABVD chemotherapy and the results of this study are now awaited.

3.2. Anti-PD1 antibodies

PD1 signaling regulates the immune response by decreasing T-cell activation and suppressing T-cell proliferation and cytokine production. In the tumor microenvironment in HL, expression of the PD1 ligands including PD-L1 and PD-L2 is significantly increased with very high expression of PD-L1 and PD-L2 on HRS cells. The expression of PD-L1 and PD-L2 inhibits the intratumoral T-cell response that may be directed at the malignant cell. Overexpression of PD-L1 and PD-L2 are due to copy number gains at chromosome 9p24.1 resulting in overexpression of the PD1 ligands. Furthermore, as mentioned above, incorporation of EBV virus into the malignant cell genome can result in upregulation of PD-L1. The PD1/PD1 ligand axis provides a unique target for therapy in HL. Two recent clinical trials that have blocked the PD1/PD-L1/PD-L2 interaction have been reported and both have shown remarkable clinical results. In the clinical trial using nivolumab in relapsed and refractory HL patients, 23 patients received 3 mg/kg of nivolumab every 2 weeks [17]. The majority of patients in the trial had previously undergone an autologous stem cell transplant and most had also received brentuximab vedotin. In this group of heavily pretreated patients an overall response rate