Review Article

Treatments targeting Hodgkin's lymphoma microenvironment—a review of immune checkpoint inhibitors

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Abstract: Hodgkin lymphoma (HL) is still considered a rare cancer, which originates from B lymphocytes in lymphoid tissues. About 90% of patients with early disease and 70% of patients with advance disease achieve long term complete remission. In relapsed/refractory disease, high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) is only effective in 50% of the cases. In classical Hodgkin's lymphoma (cHL), Hodgkin Reed-Sternberg cells (HRS) exploit programmed death-1 (PD-1) pathway, which allow for increase in the abundance of PD-1 ligands, PD-L1 and PD-L2. Even though classical HL responds well to a combination of chemotherapy and radiation, a number of patients relapse and become refractory to standard therapy. Recently the FDA approved nivolumab, a PD-1 blocking antibody in patients with classical HL, who have relapsed after ASCT and post transplantation brentuximab vedotin (BV). This review article aims to understand the efficacy of novel immune checkpoint inhibitors and to further assess the future of HL in the context of immunotherapy with nivolumab and pembrolizumab.

Keywords: Hodgkin's lymphoma (HL); immune checkpoint inhibitor; nivolumab; pembrolizumab

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Introduction

Standard chemotherapy regimen produces disease free survival in about 80-85% of HL patients (1). A small but significant percentage of the population experiences relapsed/refractory disease. Within this population, mortality rate is as high as 70%, even in patients achieving complete response (CR) after high dose chemotherapy (HDC) followed by ASCT and receiving maintenance therapy (2). Even with brentuximab vedotin (BV) as maintenance therapy post ASCT, overall survival was not significantly improved (3). There are many mechanisms that make these cells refractory to standard chemotherapy and radiotherapy. This survival may be based on the theory of Cancer Stem Cells (CSC). These quiescent cells consist of a tumor promoting population, which are particularly resistant to chemotherapy and radiotherapy (4). Resistant minimal residual disease and compromised immunity could attribute to relapse as well.

Of particular research interest is the HL microenvironment. Upon histologic review, it has been determined that neoplastic cells constitute <1% of the tumor microenvironment; the rest being occupied by inflammatory cells. This microenvironment, which includes T cells, has shown to enhance tumor growth. Cytokines and chemokines are key to providing this secure and stimulating environment of HRS. Primarily CD-4 positive T cells (Th2 helper and T regulatory phenotype) are recruited by this environment, which suppress the activation of CD-8 positive cytotoxic T lymphocytes and other immune cells (5,6). This disproportion of Th1/Th2 allows for the tumor cells and its microenvironment to thrive and escape immune surveillance.

The purpose of this review article is to provide an overview of the clinical trials conducted in the realm of targeting tumor microenvironment- particularly immune checkpoint inhibitors-nivolumab and pembrolizumab.

Relapse after BV

For patients who are refractory or have relapsed after multi-agent chemotherapy and radiotherapy, the subsequent line of therapy is autologous stem cell transplant (ASCT) and HDC. Approximately 50% of the patients that experience primary relapse respond to HDC and ASCT. Patients who relapse after ASCT are now offered BV, a monoclonal antibody against CD30 linked to a microtubule inhibitor (monomethyl auristatin E) (7). This antibody drug conjugate binds to CD30 on HRS cells, which is how it potentiates its action. In a phase I, open label, multicenter dose escalation study by Younes *et al*., response in terms of complete remission was seen in 35% of HL patients, 73% of whom were status post ASCT. The median duration of the response was 9.5 months (8). Cheah *et al*. demonstrated poor prognosis of patients with disease progression after BV therapy. Among patients who received BV as single agent, overall response rate (ORR) was 56%. The median progression free survival (PFS) was 3.5 months. Additionally, regardless of the choice of post BV therapy, patients did not remain in remission after 18 months of initiation of therapy (9). Overall, in the past 5 years, the median overall survival of patients who received BV post ASCT and HDC, is 22.4 months. The median PFS with treatments post relapse from BV is 3.5 months (10). It seems apparent that the disease control after treatment with BV is short lived and there are no standardized treatment options that exist for patients who have failed both ASCT and BV. Although, in a recent publication, Chen *et al*, demonstrated a small but significant and durable response to BV. Nine out of 102 patients in their study achieved CR with long-term results, exceeding 5 years, with single agent BV therapy and no additional therapy thereafter. These results are from phase 2 trial of BV in relapsed/refractory HL in patients who failed HSCT (11).

Based on the AETHERA trial, the Food and Drug Administration (FDA) had approved BV as consolidative and maintenance therapy post ASCT in cHL at risk or relapse or progression. Even though the 2 year PFS was improved to 63% in treatment group and 51% in placebo, the overall survival was unchanged. In the 5 year follow up of this trial, the estimated 5 year survival rate was 41% (12). Hence, only a small percentage of patients are actually cured with BV, even post-ASCT relapse.

Therefore the need for other targets of immune modulation of the HRS microenvironment is pressing.

T cell exhaustion

Immune checkpoint pathways are important to prevent autoimmunity and to create tolerance against self-antigens. The immune system does this by tight regulation of interactions between various receptors and the ligands related to immune cells, namely T lymphocytes. Tumor cells, such as HRS exploit this checkpoint system to evade anti-tumor immune response (3). One such checkpoint pathway is the PD-1 and PD-L1 and PD-L2 pathway, which is also responsible for T cell exhaustion.

Normal T cells expressed and secreted cytokines act as survival factors and stimulate malignant cells to express PD-L1 on their surface (3). Additionally HRS themselves secrete type 2 helper T chemokines and cytokines to attract immune cells such as T lymphocytes, macrophages, eosinophils to their microenvironment (8). This ligand then interacts with the peritumoral T lymphocytes in the microenvironment of cHL cells and causes immune dysfunction and tumor tolerance. It should be noted that PD-L1 is also present on the surface of normal tissue, and this is the pathway through which immune response against self-antigens is prevented (13).

The genes for PD-L1 and PD-L2 ligand have been found to be amplified in the nodular sclerosing subtype of cHL, on chromosome 9p24.1.

PD-L1 and PD-L2 expression on tumor cells

The ligands for PD-1, PD-L1 and PD-L2 are upregulated in the tumor environment of HL. The Janus kinases (JAK) phosphorylate signal transducer and activator of transcription (STAT) proteins, through which the intracellular effect of cytokines, such as interferon is mediated (3). Additionally, this also leads to production of downstream interferon targets, such as PD-L1 and major histocompatibility complex class I (MHC) (10). As it is known, MHC is important for antigen recognition by CD8 cytotoxic T cells. Chromosome 9p24.1 also possesses the genes for JAK-2 and demonstrates gene-dose dependent JAK-STAT activity, which further induces PD-L1 transcription. This leads to over expression of PD-L1 and PD-L2 in HRS cells. Additionally, Epstein-Barr virus

(EBV) infection also increases expression of these ligands in EBV positive Hodgkin's lymphoma (HL). This presumed dependence of HL on PD-1 immune checkpoint pathway, has been target for the novel therapies via nivolumab and pembrolizumab (14).

Phase I and II trials for nivolumab

In May 2016, the U. S. FDA granted approval to nivolumab for the treatment of patients with classical Hodgkin's lymphoma (cHL) that has relapsed or progressed after ASCT and post BV treatment.

Nivolumab is a fully human immunoglobulin G4 (IgG4) antibody, which binds to human programmed death-1 (PD-1) receptor and blocks its interaction with its ligands (PD-L1 or PD-L2). This alleviates the immune suppressive effects that are normally present on T cells in order to prevent autoimmunity against self-antigens in the setting of chronic antigen exposure (7,15).

In phase 1b trial of nivolumab for advanced cHL patients, a total of 23 patients were treated with nivolumab at a dose of 3 mg/kg on week 1, week 4 and every 2 weeks. Patients were selected based on histologic confirmation of relapsed or refractory HL. Fifteen (65%) patients had received four or more prior therapies, out of which 78% had failed ASCT and BV therapy. The efficacy was assessed based on computed tomography (CT) and 18F-fluorodeoxy-glucose-positron-emission tomography (PET). Four patients (17%) received CR, 16 patients (70%) received partial response (PR), with an ORR of 87%. Three (13%) of patients had stable disease. PFS at 24 weeks was 86% (7). No grade 4 adverse drug effects were seen in the studied population. Encouraging results from the phase I trial, prompted further investigation of nivolumab with a phase 2 trial.

In the phase I trial, HRS cells in all evaluable tumor samples demonstrated copy number alterations in chromosome 9p24.1, which translated to an increase in PD-L1 and PD-L2.

The phase II trial of nivolumab was a single-arm multicenter, multicohort, non-comparative study in which patients were enrolled from 34 hospitals and academic centers throughout Europe and North America.

The cohort reported in the study by Younes *et al*., included patients who had failed both ASCT and subsequent BV and had recurrent cHL. Inclusion criteria included receiving BV. Patients who had been treated with BV before ASCT were excluded. An MRI and PET scan was assessed at baseline. MRI was evaluated every 8 weeks for the first year and then every 16 weeks until week 97 and then every 26 weeks beyond that until disease progression or initiation of allogeneic/autologous stem-cell transplantation. Pet scan was performed at 17 and 25 weeks after baseline. Complete remission was assessed by a negative PET scan as evaluated by independent radiological review committee (IRRC).

The patient population had been heavily treated with a median of four previous lines of therapy. Based on IRRC results, 66% or 53 patients received ORR out of 80 patients. Seven patients received CR and 46 or 58% of patients received PR. All but one patient had at least 50% tumor reduction from baseline. Median time to first objective response was 2.1 months per IRRC. The median IRRC assessed duration of objective response was 7.8 months. Out of 43 patients who had no previous response to BV, 31 had achieved IRRC- assessed response to nivolumab. At 12 months the median PFS was 10.0 months.

Seventy-one (89%) of the patients had drug-related AEs with 17 patients experiencing grade 3 and 3 patients experiencing grade 4 events. Two patients experienced drug related pneumonitis. Other grade 3/4 hematological abnormalities included decreased lymphocyte count in 15 patients, Neutropenia in 5 patients. Overall the safety profile of nivolumab was acceptable with minimal severe AE. Additionally response to nivolumab was seen in most of the patients who did not initially respond to BV. In all evaluable specimens of biopsies, HRS cells had copy number alterations of chromosome 9p24.1 and increased PD-L1 expression (16).

Phase I trial with pembrolizumab

Like nivolumab, pembrolizumab is a humanized monoclonal IgG4 with activity against PD-1. It has demonstrated clinical effectiveness in solid tumors like melanoma and non-small cell lung cancer (15).

Pembrolizumab was evaluated in the multicohort, open label, phase Ib study for cHL in 31 patients. Patient selection criteria included confirmed diagnosis of cHL with relapsed or refractory disease. Patients had to have relapsed after, be ineligible for or refused ASCT. Previous BV treatment was another requirement. Exclusion criteria included active or past autoimmune disease, CNS involvement of the malignancy, interstitial lung disease, second malignancy or HIV infection (15).

Patients received intravenous doses of pembrolizumab, 10 mg/kg every 2 weeks. Response was assessed through CT and PET scans after 12 weeks of initial treatment and

then every 8 weeks thereafter. The primary end point was to assess complete remission rate (CRR). Main secondary end points were safety, ORR and duration of response.

Five (16%) of the 31 patients achieved CR and 15 patients (48%) achieved a PR. The ORR was 65%. Seven patients had stable disease and four patients had progressive disease (PD). Overall 28 patients had tumor size reduction, which indicated tumor burden reduction. The median follow-up for surviving patients was 17.6 months. Seventy-four percent of the patients stopped treatment after data lock date. Two patients due to adverse effects (AEs), 3 due to undergoing allogeneic stem cell transplantation, 1 due to switching therapy, 1 due to CR and 1 due to consent withdrawal. Amongst the 20 patients who had CR or PR, 70% had a response duration of ≥24 weeks. The PFS at 52 weeks for these 20 patients was 46% (15).

The major AEs were reported in 30 of 31 patients. The most common was hypothyroidism (16%). Only 3 patients (10%) experienced pneumonitis. Five patients experienced grade 3 AEs related to pembrolizumab: colitis, increased AST and ALT levels, nephrotic syndrome, joint swelling, back pain and axillary pain. There were no grade 4 AEs and no deaths related to the drug (15).

More on the horizon

Adoptive transfer of genetically modified T cells has been another immune modulated approach towards specific antitumor activity. Previously cytotoxic T cells raised against specific EBV proteins have shown CR in EBV positive cHL patients. But 70% of HL is EBV negative. Cruz *et al*., demonstrated novel adoptive T cell therapies in this patient population by targeting cancer/testis antigen (CTA), which are selectively present on HRS cells. Specifically MAGE-A4, an HL-associated CTA was targeted in their study. The expression of this antigen was enhanced using epigenetic modification via decitabine, a DNA methyltransferase inhibitor. MAGE-A4 specific T cells were raised in donor and HL patients. Although this study was on an extremely small scale, it demonstrated the synergistic effect of using epigenetic modification with immune modulation. This combination needs further investigation in future trials to evaluate durable results in relapsed/refractory HL patients (17).

Furthermore, studies including Chimeric Antigen Receptor have already shown promising results in other B cell malignancies and prompt investigation in cHL patients as well. Reconstructing T cell receptors in this way further increases T-cell specificity to tumor specific antigens in a human leukocyte antigen-independent manner (18).

Conclusions

For patients with relapsed and refractory cHL, there are still no standardized treatments to address the unmet need of disease progression (6). Immune checkpoint inhibitors like nivolumab and pembrolizumab have provided a pathway towards novel approaches to battle the biology that HRS cells present. The biology of HRS cells and their overexpression of PD-1 and PD-2 ligands allows for these drugs to utilize innate immune system, to attack relapsed disease. Looking at the future, the goal is to initiate these medications earlier in the course of the disease, in conjunction with existing chemotherapeutic agents. Additionally, more research is required into looking at these medications and their therapeutic benefit in conjunction with existing regimens.

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