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Emergence of Novel Agents for Treatment of Hodgkin Lymphoma

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Abstract

cHL patients are generally classified in 1 of 3 groups: early-stage favorable, early-stage unfavorable or advanced-stage disease. Prognostication in advanced-stage patients is defined by the IPS. Patients with low-risk IPS are treated with 6 cycles of standard ABVD, whereas high-risk patients are initially treated with the more intensive German-derived regimen, escalated BEACOPP. Treatment may be further refined through PET-adapted therapy. The optimal chemotherapy for advanced stage HL can be endlessly debated. Based on recent study results, two classes of drugs stand out as highly active in advanced HL: antibody-drug conjugates (BV) and programmed death 1 inhibitors (Nivolumab). There are abundant salvage therapy options for patients with R/R HL. The choice of salvage chemotherapy therapy is becoming increasingly difficult in the era of novel agents.

Abbreviations: cHL: Classical Hodgkin lymphoma; IPS: International Prognostic Score; EBV: Epstein Barr Virus; H/RS: Hodgkin and Reed Sternberg; ASCT: autologous stem cell transplantation; BV: Brentuximab-Vedotin; PD-1: Programmed Death 1; MMAE: Monomethyl Auristatin E; CAR-T: Chimeric Antigen Receptor-modified T cell; GVHD: Graft-Versus-Host Disease; HL: Hodgkin lymphoma; PD-L1: Programmed Death Receptor Ligand 1; PD-L2: Programmed Death Receptor Ligand 2; R/R: Relapsed/Refractory; TARC: Thymus And Activation-Regulated Chemokine; TME: Tumor Microenvironment

Introduction

cHL accounts for about 10% of all lymphomas, with approximately 9000 new cases in the United States in 2013 and 1200 deaths [1]. cHL is derived from germinal center B cells [2]. Its pathogenesis remains poorly understood [3]. Molecular alterations involved in cHD development are only partially known [4] due to rarity of tumor cells (HRS- cells) in the lymph node [2]. Tumor immune evasion through PD-1 augmentation appears to play a major role in the oncogenesis of cHL [5].

Hodgkin and Reed Sternberg (HRS) cells

H/RS cells are large CD30+ tumor-infiltrating cells that are derived from germinal center B cells and lack immunoglobulin expression [3]. They usually constitute <5% of an extensive ineffective inflammatory/ immune micro-environment [5]. Despite this extensive polymorphous inflammatory infiltrate, there is poor antitumor immune response to neoplastic HRS cells [5]. H/RS cells are highly interactive with this microenvironment through direct cell contacts and production of various cytokines and chemokines [3]. HRS cells demonstrate high expression of the immunoregulatory glycan-binding protein and galectin-1 resulting in a type 2 T-helper cell and T-regulatory cell skewed tumor micro-environment [5]. H/RS cells may escape apoptosis within germinal center due to alteration of apoptosis regulators expression [3]. Genetic alterations in NFκB pathway and the imbalance of T regulatory and TH17 lymphocytes has been recognized as critical pathogenetic mechanism involved in immune escape and blockade of apoptosis in Reed-Sternberg cells [4].

Advanced-stage disease

Advanced-stage disease refers to patients with Ann Arbor stage III/IV disease and patients with high-risk stage II disease. Prognostication in advanced-stage patients is defined by the IPS. Patients with an IPS greater than or equal to 3 have inferior treatment outcomes and identified as potentially requiring more intensive therapy [6]. cHL is a highly curable lymphoma and about 80% of patients can be cured with modern treatment strategies [3]. Refractory cHL represent 5 to 10% of cHL [3] and are more frequent in patients with advanced HL [1]. Many of these patients have a poor overall survival of 26% at 5 years [3]. A better biological characterization of primary refractory patients might allow the use of targeted therapeutic strategies earlier during the course of the disease [3]. Relapse after first-line treatment occurs in 25-30 % of cHD patients [7].

Secondary therapy only cures approximately 50% of patients with no reliable biomarkers to identify the patients in which the salvage treatment regimen fails [7]. The current standard care for R/R cHD is salvage chemotherapy followed by high dose chemotherapy and ASCT [1]. At the present time, there is a range of chemotherapy-based and novel-agent-based salvage options that can lead to excellent overall response rate and complete response rates [1].

Suggested predictors of response to therapy

Understanding cHL associated immunosuppression and the immune reconstitution after treatment may be the key to develop new prognostic factors and treatment strategies [8]. A correlation between markers of cell activation and/or differentiation, cell cycle and apoptosis deregulation, EBV detection in the neoplastic H/RS cells and the clinical outcome of cHL patients have been reported [3]. CD20 expression in H/RS cells is significantly higher in responders compared to refractory cHL. CD20 resembles a Ca2+ ion channel and is involved in signal transduction for B-cell differentiation and proliferation. An increase of Ca2+ permeability in H/RS cells along with chemotherapy and/or radiotherapy could decrease apoptotic resistance or even activate programmed cell death [3].

a. Serum levels of soluble CD30 and some interleukins might provide additional prognostic information to the clinical models [3].

b. Chan et al. [7] develop a novel model based on the TME gene expression profile of relapsed patients that have superior predictive properties for response to ASCT.

c. The measurement of the serum chemokine TARC could help identifying patients who may require new drugs like BV or nivolumab or pembrolizumab before ASCT, in order to achieve a durable remission [9].

Novel agents

A large number of novel agents have been approved and being investigated for HL treatment. Many of these agents have shown durable responses with improved safety profiles [10]. Based on recent study results, two classes of drugs stand out as highly active in advanced HL: antibody-drug conjugates (BV) and PD-1 inhibitors (Nivolumab) [11].

Brentuximab Vedotin (Anti-CD30)

BV is an antibody-drug conjugates that selectively target CD30 on the surface of the malignant HL cells to achieve its therapeutic effect [10] with minimal collateral damage to normal tissue [11]. In cHL, CD30 expression is highly expressed on Reed-Sternberg cells with normal limited expression on activated B and T cells only [10]. BV consists of a chimeric monoclonal antibody against human CD30 coupled to the antimicrotubule agent MMAE using a peptide linker. BV binds CD30 on the surface of the malignant HL cells and after being internalized, it releases MMAE which prevents tubulin polymerization, a protein essential for cell division, causing cell cycle arrest and apoptosis [11]. BV was approved by the FDA for treatment of HL patients who has failed either ASCT or two other chemotherapy regimens and are not eligible for transplant [10]. The incorporation of BV either as a single agent or as part of salvage therapy for R/R HL patients regimen is appealing.

Two strategies have evolved to study BV as part of salvage therapy for R/R HL patients: sequential administration of BV with chemotherapy and combined chemo-immunotherapy [12]. BV can be used as a salvage option in prior BV responders [1]. As a single agent, BV is used at a dose of 1.8 mg/kg (up to 180 mg) intravenously every 3 weeks up to 16 cycles, disease progression, or unacceptable toxicity. BV is generally well tolerated [11] and has improved the outcomes of cHL patients [13]. The PET-negative rate after 2 to 4 doses of single agent BV is 30% to 40% in heavily pretreated patients. However, many eventually become refractory to BV. Duration and depth of response are important, as patients are often young and otherwise healthy [13]. BV is under study as part of front-line therapy [1].

It may be difficult to interpret data on BV-based second-line regimens in which patients were naïve to BV. Introduction of BV into second-line therapy allow its use as a bridge to ASCT with fewer side effects than conventional chemotherapy [1]. Post-ASCT consolidation with BV should be reserved for patients with multiple risk factors because the adverse effects are significant (namely, neuropathy) [12]. Cumulative peripheral neuropathy is the leading cause of drug discontinuation in some clinical trials. It may be severe (up to 31% at least grade 2) [11]. Sensory neuropathy is more commonly seen (42%) than motor neuropathy (11%). Median time to onset of neuropathy was about 12 weeks. Some improvement of symptoms (of at least one grade) was experienced in 80% of patients with drug discontinuation but complete resolution was observed in only half of the cases [11]. Other uncommon serious adverse events are progressive multifocal leukoencephalopathy and pancreatitis. The incidence of febrile neutropenia was extremely low [11].

Nivolumab (humanized immunoglobulin gamma-4 kappa anti-PD-1 receptor monoclonal antibody)

Under physiological conditions, PD-1 pathway activation via PD-L1 and PD-L2 engagement limits T-cell-mediated immune responses [13]. In cHL, recurrent amplification of 9q24.1 locus increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, on the tumor cell surface [14] and promote their induction through increase JAK-STAT signaling. JAK2 locus is also located on chromosome 9p24.1 [13]. In addition, latent EBV infection may contribute to increase PD-L1 and PD-L2 expression in EBV-positive HL (around 40% of cHL cases) [5]. The increased PD-L1 and PD-L2 expression by Reed-Sternberg cells may enable them to evade immune surveillance [13]. Disrupting the PD-1:PD-L1/2 axis by nivolumab overcome the immune tolerance induced by cancer cells, thereby releasing the immune system

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for an effective anti-cancer response [11]. Nivolumab received accelerated FDA approval in May 2016 for treatment of R/R cHL progressing after ASCT and BV treatment [15].

Nivolumab produces durable responses, even in heavily pre-treated patients with standard cytotoxic agents [13]. Nivolumab was associated with an overall response rate of 87% and a rate of progression-free survival of 86% at 24 weeks [16]. The most common adverse effects of this class are dermatologic (rash and pruritus), metabolic (lipid changes, hyperglycemia, hypoalbuminemia, and electrolyte imbalances), hematologic (anemia and lymphopenia), gastrointestinal (changes in bowel habits and nausea/vomiting), respiratory (cough and dyspnea), fatigue, abnormal liver enzymes, and arthralgia [10]. Adverse events were mainly of grade 1 or 2 [16]. Immune related adverse effects are the result of the immune-stimulatory effects of these drugs. They are uncommon but have pleomorphic presentations.

Potentially affected organs are the lungs (pneumonitis), the endocrine system (hypophysitis, thyroiditis, and adrenal insufficiency), the skin (toxic epidermal necrolysis), and the gastrointestinal tract (colitis and pancreatitis). These events can progress rapidly to cause significant morbidity or even death. Treatment must be individualized, hold therapy (for mild cases) and systemic steroids (for moderate to severe cases). Invasive testing (i.e. bronchoscopies and colonoscopies) are often needed to rule out infection or tumor progression. Caution is advised with utilization of this class in patients with a documented history of poorly controlled autoimmune disorders or for patients who have failed allogeneic SCT and have active GVHD [10].

Future therapy

The identification of new biomarkers in HL may provide potential targets for the development of new treatment agents. HRS cells display simultaneous activation of different cell-survival pathways, including NF-κB, JAK/STAT, PIP3K/AKT/mTOR, NOTCH and RAF/MEK/ERK [17]. In recent years, new agents have been developed and tested in HL with encouraging results [11].

CAR-T therapy

This involves genetically re-engineering the patient's effector immune cells (T cells) to recognize and eliminate tumor cells via modifications to the T cell receptor. Preclinical models demonstrate encouraging activity if the same principle has been applied to target CD30 –expressed on the surface of HL cells [11].

Small molecule inhibitors of cell signaling (PI3K δ inhibitor and JAK2 kinase inhibitor)

The JAK-STAT and PI3K pathways play an important role in the survival of RS cells and are deregulated in cHL. The combination of agents targeting these pathways may have a synergistic effect [10].

a. A phase 1 dose escalation trial of combination of INCB040093, a PI3K δ inhibitor and INCB039110, a selective JAK1 inhibitor, in R/R cHL patients showed an acceptable safety profile. The ORR was 50% [10].

b. A phase 2 trial investigates the efficacy of pembrolizumab (PD-1 inhibitor) after ASCT in R/R cHL (NCT02362997) [10]. Eligible patients in this study were those who failed BV treatment [12].

c. Clinical trials combining PD-1 inhibitors to Bruton tyrosine kinase inhibitors (NCT02362035), bispecific NK-cell engager antibodies (NCT02665650), BV (NCT01896999 and NCT02572167), other immune checkpoint inhibitors (NCT01896999, NCT02304458, and NCT01592370) or standard cytotoxic chemotherapy (NCT02181738) are under active development in an attempt to increase efficacy [10].

Conclusion

There have been a large number of novel agents approved and currently being investigated for treatment of HL. Many of these agents have shown durable responses with improved safety profiles. This may modify the treatment paradigm in the future.

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