Belinostat for Peripheral T-Cell Lymphoma

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Abstract

The majority of patients with peripheral T-cell lymphoma (PTCL) will either be refractory or relapse to the currently available frontline therapies with a subsequent median overall survival <6 months. Histone deacetylase (HDAC) inhibitors have demonstrated significant activity in T-cell neoplasms, and recently the BELIEF trial of belinostat (Beleodaq), a pan-HDAC inhibitor with high affinity for class I and II HDACs, was completed in relapsed/refractory PTCL. This study demonstrated a complete response rate of 11%, with an overall response rate of 26%. These results have been confirmed in a smaller trial that also included patients with cutaneous T-cell lymphomas. Given the similar response rates achieved by pralatrexate (Folotyn) and romidepsin (Istodax), belinostat has become the third agent approved by the US Food and Drug Administration for use in relapsed/refractory PTCL, thus providing another option for patients with these aggressive malignancies.

The peripheral T-cell lymphomas (PTCLs) are a diverse group of mature T-cell neoplasms that typically display aggressive clinical features with inferior response rates and survival outcomes to conventional chemotherapy when compared with their B-cell counterparts.[1,2] In the largest population registry to date in which 84% of patients receiving chemotherapy received either CHOP or CHOEP as initial therapy, 25% of patients were primary refractory, with a median overall survival (OS) of 2.5 months.[3] Of those who managed a response to induction chemotherapy, 53% relapsed with a median OS of 6 months.[3] Given the dismal prognosis of relapsed/refractory PTCL, the major challenges that are faced today include improving frontline therapies to induce more durable remissions, and also identifying effective salvage regimens. In July 2014, belinostat (Beleodaq) became the third agent behind the antifolate pralatrexate (Folotyn) and fellow histone deacetylase (HDAC) inhibitor romidepsin (Istodax) to be approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed/refractory PTCL.

Histone deacetylases are a group of enzymes along with histone acetyltransferases (HATs) that regulate the acetylation of histone and nonhistone proteins.[4] The acetylation status of these proteins greatly influences the degree of binding between histones and DNA within the nucleus, and the subsequent accessibility of DNA for transcription, thereby affecting protein expression in a manner that could promote malignant behavior. Although lymphomagenesis is complex, dysregulation of HDACs has been well established as a significant step in this process, and this provides the rationale towards utilizing HDAC inhibitors in these neoplasms.[5] Eighteen different HDACs are described, belonging to four different classes that can be further differentiated by their zinc dependency. Zinc-dependent HDACs encompass class I (HDACs 1, 2, 3, and 8), IIa (HDACs 4, 5, 7, and 9), IIb (HDACs 6 and 10), and IV (HDAC 11), while class III HDACs, otherwise known as sirtuins (SIRT1-7), are dependent on nicotinamide adenine dinucleotide (NAD).[4,6]

HDAC inhibitors have demonstrated efficacy in PTCLs and cutaneous T-cell lymphomas (CTCLs),as well as other hematological and solid-organ malignancies.[7-10] Through epigenetic modification, HDAC inhibitors primarily exert their effects by lowering the apoptotic threshold of malignant cells by the downregulation of antiapoptotic proteins, upregulation of proapoptotic proteins, inhibition of DNA repair, and induction of DNA damage.[10] HDAC inhibitors are pleiotropic agents, and beyond the histone-DNA complex they affect the acetylation status of many nonhistone proteins such as chaperones, oncogenes, signaling molecules and transcription factors, contributing to their effectiveness as antineoplastic agents.[5]

Belinostat is a hydroxamic acid-derived, pan-HDAC inhibitor that demonstrates high affinity for the class I and II HDACs.[11-12] In comparison, romidepsin is a cyclic tetrapeptide-derived pan-HDAC inhibitor that primarily functions through class I HDACs, with only weak effects on the class IIb HDAC6.[12,13]

Phase II Trials in Belinostat

The BELIEF study is the largest phase II trial conducted with belinostat in PTCL.[14] Eligible patients were adults with relapsed/refractory PTCL following at least one prior systemic treatment. Belinostat 1000 mg/m^2 administered intravenously over 30 minutes daily on days 1-5 of a 21-day regimen was given to 129 patients across 62 sites in North America, Europe, and Africa. The number of cycles administered was not limited, with patients treated until the development of progressive disease, unacceptable toxicity, stem cell transplantation, withdrawal of consent, or death. The median age of 64 years (age range, 29-81 years) reflects the epidemiological characteristics of this disease, and 96% of patients had previously progressed on or after CHOP or CHOP-like therapy, reflecting current treatment practices. The median number of lines of previous therapy for this cohort was 2 (range, 1-8), with 19% having undergone a prior autologous stem cell transplant and 2% an allogeneic stem cell transplant. Significantly, of the 120 evaluable patients, 13 achieved a complete response (CR; 11%), with a further 18 demonstrating par-

Practical Application

This review examines the published studies to date of belinostat in peripheral T-cell lymphoma, concentrating on BELIEF, the largest phase II trial. Other topics highlighted in this review include:

- Prognosis of relapsed/refractory peripheral T-cell lymphoma
- Physiologic role of histone deacetylases
- Impact of histone deacetylase inhibitors and other agents in peripheral T-cell lymphoma
- Comparison between the three FDA-approved agents in relapsed/refractory peripheral T-cell lymphoma: belinostat, pralatrexate, and romidepsin

tial response (PR; 15%), for an overall response rate (ORR) of 26%. In responding patients, the median time to response was 5.6 weeks, with the earliest after 4.3 weeks and the latest at 50.4 weeks. The median duration of response (DOR), defined as the date of first response to the date of disease progression or death, was 8.4 months (95% confidence interval [CI], 4.5-29.4). Importantly, 9 patients (7.5%) were able to proceed to a stem cell transplant.

With regard to toxicity, belinostat was well tolerated, with dose reductions of 25% to 50% occurring in 13% of patients and only 7% of all discontinuations due to adverse events. Progressive disease was the most common reason for discontinuation (64%), followed by death (11%), and patient request (8%). Significant myelosuppression was not a factor in this study, with <10% grade 3 or 4 thrombocytopenia or neutropenia. One aspect unique to BELIEF was that patients were eligible with a platelet count >50,000/μL, unlike studies with pralatrexate (>100,000/μL) and romidepsin (>100,000/μL unless documented bone marrow involvement, upon which 75,000-100,000/μL was permitted).[7,15]

A second smaller study of belinostat in PTCL that also included patients with relapsed/refractory CTCLs has been conducted.[16] Fifty-three patients were enrolled; 20 had relapsed/refractory PTCL. Similar results to BELIEF were encountered, with a CR of 10% and a PR of 15%, for an ORR of 25% in PTCLs. With respect to CTCLs, 14% of patients responded with a CR of 7%. Grade 3 or 4 hematologic toxicity was seen in <10% of patients.

Given the safety prolife of belinostat, a phase I clinical trial combining it with CHOP has been initiated in newly diagnosed PTCL (NCT01839097), with a view to conducting a phase III randomized study in the future comparing it with standard CHOP therapy in these patients.

Although all three FDA-approved agents for relapsed/refractory PTCL have never been compared directly in randomized studies, each individual agent produces similar response rates but with differing toxicity profiles. It must be noted that when comparing across the three studies, the patients treated with pralatrexate in the PROPEL trial were the most heavily pretreated and demonstrated the greatest diversity of PTCL subtypes.[15] PROPEL (115 patients) demonstrated an ORR of 29%, with the main grade 3/4 toxicities being thrombocytopenia (32%), mucositis (22%), and neutropenia (22%).[15] Meanwhile, an international phase II study of romidepsin (131 patients) demonstrated an ORR of 25%, with the main grade 3/4 toxicities being thrombocytopenia (24%), neutropenia (20%), and infection (19%).[7] Brentuximab vedotin, a chimeric anti-CD30 monoclonal antibody conjugated to the antimitotic agent monomethyl auristatin E, is another option, although its current FDA approval is limited to relapsed/refractory systemic anaplastic large-cell lymphoma (ALCL). In a phase II trial in relapsed/refractory ALCL, brentuximab demonstrated a remarkable 57% CR rate with an ORR of 86%.[17]

Until studies comparing these agents directly are completed, firm recommendations as to the optimal therapy in relapsed/refractory PTCL cannot be made at this time, though good options are now emerging. Therapeutic decisions should be based on individual patient circumstances, histology, and the risk-benefit profiles of each agent. For example, a patient with significant cardiac abnormalities would be at risk of QT prolongation with HDAC inhibitors, and therefore pralatrexate may represent a more logical option, whereas a patient who currently has or is unable to tolerate severe mucositis should be considered for HDAC inhibitors in preference to antifolate therapy.

The majority of patients with PTCL will either be refractory or relapse to current frontline therapies. The prognosis of these patients is dismal, with median OS <6 months. Belinostat has recently been approved for use in these malignancies based on the results of the BELIEF trial, which demonstrated an ORR of 25%, with a median DOR of 8.4 months. Though this is not the breakthrough we are looking for, it is a step in the right direction as it adds another option for patients where few exist.

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