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Novel Therapeutic Agents in Waldenström's Macroglobulinemia

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Abstract

Within the past few years, major advances in the preclinical and clinical testing of novel therapeutic agents have occurred in Waldenström's macroglobulinemia (WM). These include agents that target the PI3K/Akt/mTOR pathway, PKC pathways, NF-κB signaling pathway, as well as tyrosine kinases and histone deacetylase inhibitors. In this review, we summarize the current understanding of the clinical development of these agents in WM.

Keywords

Akt; Bortezomib; Everolimus; Perifosine; Waldenstrom

Introduction

Waldenstrom's macroglobulinemia (WM) is a distinct low-grade B-cell lymphoma characterized by the presence of lymphoplasmacytic cells in bone marrow and a serum monoclonal immunoglobulin (Ig) M protein.^{1–3} There is no standard of therapy for the treatment of WM.⁴ In addition, to date, there are no FDA-approved therapeutic agents for the specific treatment of WM. Most treatment options were originally derived from other lymphoproliferative diseases, including multiple myeloma and chronic lymphocytic leukemia.⁵ Therefore, there is a need for the development of novel therapeutic agents that are based on the activity of these agents in WM preclinically and clinically.

To date, we have tested multiple agents in the preclinical setting, including small targeted molecules such as the Akt inhibitor perifosine (KRX-0401; Keryx Biopharmaceuticals); mammalian target of rapamycin (mTOR) inhibitor everolimus (RAD001; Novartis Pharmaceuticals Inc); PKC inhibitor enzastaurin (Eli Lilly and Company)⁶; proteasome inhibitors, including bortezomib (Millennium Inc), salinosporamide A (NPI-0052; Nereus Inc),⁷ and carfilzomib (PR-171; Proteolix Inc); histone deacetylase inhibitor LBH589 (Novartis Pharmaceuticals Inc); pan tyrosine kinase inhibitor TKI258 (Novartis Pharmaceuticals Inc); pan-PKC inhibitor midostaurin (PKC412; Novartis Pharmaceuticals Inc); PI3K/mTOR inhibitor BEZ235 (Novartis Pharmaceuticals Inc), Src inhibitor AZD0530 (AstraZeneca Inc); and CXCR4 inhibitor plerixafor (AMD3100; Genzyme Inc).

In clinical trials, we have recently completed a phase II clinical trial of single-agent perifosine in relapsed or relapsed/refractory WM, a phase II clinical trial of single-agent everolimus in relapsed or relapsed/refractory WM, and a phase II clinical trial of the combination of bortezomib and rituximab in relapsed or relapsed/refractory WM. Ongoing

studies include first-line therapy with weekly bortezomib and rituximab as well as the phase II trial of enzastaurin in relapsed/refractory WM. Upcoming studies include the use of everolimus in combination with rituximab or in combination with bortezomib and rituximab as well as the single-agent study of LBH589 in relapsed/refractory WM.

Perifosine

Perifosine is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkylphospholipids.⁸ It has shown activity in phase II trials in MM. Our previous studies have shown that the activity of the survival protein Akt is upregulated in patients with WM compared with normal B cells, and that downregulation of Akt leads to significant inhibition of proliferation and induction of apoptosis in WM cells in vitro.⁹ In vivo studies of perifosine have shown significant cytotoxicity and inhibition of tumor growth in a xenograft mouse model.¹⁰ Subsequently, perifosine was shown to induce synergistic cytotoxicity with rituximab and bortezomib as well as with other conventional agents, including fludarabine and cyclophosphamide.¹¹

Based on this preclinical activity, we initiated a phase II trial of single-agent perifosine in patients with relapsed or relapsed/refractory disease using 150-mg oral daily dosing. Patients who had ≥ 1 previous therapy for WM and who had relapsed/refractory disease were eligible. National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used for toxicity assessment. Response was assessed by criteria established at the second consensus panel for WM, and included minimal response (MR), partial response (PR), and complete response (CR). All patients received perifosine 150 mg daily for 28 days per cycle until progression or excessive toxicity. The trial accrued from October 2006 to November 2007, with 37 patients (27 men and 10 women; median age; 65 years; range, 44–82 years) treated. Of these patients, 65% were relapsed, and 35% were relapsed and refractory to previous therapy. The median number of lines of previous treatment was 3 (range, 1–5 lines), with 35% of the patients having > 3 lines of previous therapy. Previous therapy included rituximab, nucleoside analogues (fludarabine and 2-CDA), combination chemotherapy (eg, CHOP, CVP), chlorambucil, and bortezomib. A total of 36 patients are evaluable for response after ≥ 2 cycles of therapy. The overall response rate (PR + MR) was 36%. Partial response occurred in 2 patients (6%), with a median duration of response of 9+ and 18+ months; MR occurred in 11 patients (30%), with a median duration of response of 7 months (range, 2–21+ months). Stable disease occurred in 21 patients (58%) and progressive disease in 2 patients (6%) at 2 and 4 months. The most common adverse events were gastrointestinal toxicities (nausea, vomiting, and diarrhea) with grade 1/2 in 36% of the patients. Grade 3/4 events included anemia (9%) and leukopenia (9%). Grade 3 arthritis occurred in 9% of the patients, was considered likely related to therapy (especially in rapidly responding patients), and reversed with symptomatic treatment as well as dose reduction. Dose reductions to 100 mg occurred in a total of 36% of the patients and were otherwise due to gastrointestinal toxicity or cytopenias. Responses were maintained despite dose reductions in 16 patients. As of August 2008, the progression-free survival (PFS) and time to progression (TTP) are similar at a median of 10.7 months (7.2-not reached). Therefore, perifosine alone induces a prolonged TTP in relapsed/refractory WM, with a promising response rate of 36%, stabilization of disease in 58% of patients, and manageable toxicity, as well as the convenience of oral administration.

Everolimus

Based on the preclinical data showing increased activity of the PI3K/mTOR pathway in WM, rapamycin (mTOR inhibitor) has been studied in vitro in WM and showed significant cytotoxicity in WM cells lines, specifically when combined with bortezomib (unpublished

data). A phase II trial of single-agent everolimus was initiated patients with WM with relapsed or relapsed/refractory disease. All patients received daily everolimus 10 mg. A cycle was considered 28 days. Patients were allowed to stay on therapy until progression of disease or excessive toxicity. This study was conducted in a collaborative effort between Dana-Farber Cancer Institute (DFCI) and Mayo Clinic College of Medicine. Here, we report the data on the patients accrued at DFCI.

A total of 19 patients (15 men and 4 women) have been treated to date. All patients had symptomatic disease and required therapy. The median number of lines of previous treatment was 3 (range, 1–5 lines), including rituximab, nucleoside analogues (fludarabine or 2-CDA), combination chemotherapy (eg, CHOP, CVP), chlorambucil, and bortezomib. The median IgM at baseline was 3330 mg/dL (range, 1010–7410 mg/dL). The median follow on everolimus was 8 months (range, 3–22 months). A total of 18 patients are currently evaluable for response. Best responses to everolimus after 2 cycles using IgM monoclonal protein were as follows: PR in 8 (44%), MR in 5 (28%). Progressive disease occurred in 4 (22%), and stable disease occurred in 1 (6%). The overall response rate (PR + MR) was 72%. The median duration of response has not been reached (range, 3–22+ months). Patients tolerated therapy well without significant toxicities. Grade 3/4 toxicities included grade 4 thrombocytopenia in 1 patient, grade 3 pneumonia in 1 patient, grade 3 hyperglycemia in 1 patient, and grade 3 mucositis in 1 patient. Other adverse events of grade ≤ 2 included nail cracking, mucositis, diarrhea, and fatigue. Attributable toxicities otherwise proved manageable with appropriate supportive care, and everolimus was generally well tolerated. One patient enrolled on the study withdrew consent and changed to hospice care within 3 weeks of therapy and passed away because of disease progression. Therefore, the use of the oral single-agent everolimus in patients with relapsed or refractory WM was well tolerated and demonstrated significant activity, achieving an overall response rate of 72%. Future studies of combination of this agent with rituximab and bortezomib are currently being planned.

Bortezomib

Previous studies have demonstrated the clinical activity of bortezomib as a single agent in patients with WM. We performed preclinical studies that demonstrated synergistic activity of bortezomib with the anti-CD20 antibody rituximab in WM cell lines and patient samples. This phase II study aimed to determine safety and activity of weekly bortezomib in combination with rituximab in patients with relapsed/refractory WM. All patients received bortezomib intravenously weekly at 1.6 mg/m² on days 1, 8, and 15 every 28 days $\times$ 6 cycles, and rituximab 375 mg/m² on days 1, 8, 15, and 22 on cycles 1 and 4. A total of 37 patients (26 men and 11 women; median age, 62 years; range, 42–73 years) have been treated to date. All of them had symptomatic disease and required therapy. The median number of lines of previous treatment was 3 (range, 1–5 lines), including previous bortezomib and previous rituximab in some of those patients. The median IgM at baseline was 3540 mg/dL (range, 700–10,800 mg/dL). The median follow up is 10 months (range, 1–24 months). A total of 35 patients are currently evaluable for response. Complete remission and near-complete remission occurred in 2 (6%), PR in 17 (48%), and MR in 10 (29%). Progressive disease occurred in 1 (3%), and stable disease occurred in 5 (14%). Most patients experienced response rapidly within 3 months of therapy (2–7 months). Rituximab flare occurred only in 6 patients (20%). The median duration of response has not been reached (range, 5–26+ months). After 2 years of follow-up, 14 patients have shown progression/death (40%), 10 of which had intermediate/high-risk disease and 4 low-risk disease. Patients who had a CR or PR had a longer TTP compared to those who had an MR. Patients tolerated therapy well, without significant toxicities: grade 3 peripheral neuropathy occurred in only 2 patients at cycle 6 and completely resolved in 1 of these patients within 1

month after stopping therapy. Overall, 12 patients (32%) developed peripheral neuropathy (grade 1–4), of which 5 were grade 1 and 5 grade 2. Other grade 3/4 toxicities included neutropenia in 3 patients, and anemia and hyponatremia in 1 patient, and thrombocytopenia in 1 patient. Grade 5 pneumonia and viral infection occurred in 1 patient who was within the first cycle of therapy, and the family changed his status to comfort care, and the patient passed away within 1 week. Attributable toxicities otherwise proved manageable with appropriate supportive care, and the combination was generally well tolerated. The combination of weekly bortezomib and rituximab has been well tolerated and demonstrates encouraging activity, with CR+ PR + MR in 83% of evaluable patients with relapsed WM. No significant peripheral neuropathy has been observed to date with this regimen. Studies using this combination in newly diagnosed patients are ongoing.

Conclusion

In summary, multiple targeted agents are currently being tested in WM in the preclinical and clinical setting. Future combinations of these novel agents might lead to high overall responses with minimal long-term toxicities compared with traditional chemotherapeutic agents, leading to an improvement in the quality of life and survival of patients with this disease.

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