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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Dimopoulos et al, page 3276

Proteasome inhibitors in Waldenström macroglobulinemia

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In this issue of *Blood*, Dimopoulos and colleagues report on a prospective multicenter clinical trial conducted by the European Myeloma Network (EMN) that evaluated the activity of bortezomib, dexamethasone, and rituximab (BDR) in patients with untreated, symptomatic Waldenström macroglobulinemia (WM).¹

Using a novel schedule of administration, patients were transitioned from twice weekly to weekly administration of bortezomib after cycle 1. An overall response rate (ORR) of 85% was attained, including very good partial response (VGPR) or better responses in 10% of patients. The median progression-free survival (PFS) in this study was 43 months, and patients with VGPR or better had longer PFS. No maintenance therapy was used. Treatment-related peripheral neuropathy (PN) occurred in 46% of patients, with grade 3 events representing 7%; 8% of patients discontinued proteasome inhibitor therapy for PN. Rituximab was also omitted during cycle 1 to prevent immunoglobulin M (IgM) flaring, a common and potentially life-threatening complication in WM patients with high serum IgM levels. Following cycle 1 of administration of bortezomib alone, rituximab and dexamethasone were added, and subsequent IgM flaring was observed in 11% of patients without need for preemptive plasmapheresis.

The study by the EMN group addresses some important hurdles that impact delivery of safe and effective therapy for WM patients. Bortezomib is a highly active and stem cell-sparing therapy, particularly in combination with rituximab and/or steroids in WM. An ORR of 95%, including VGPR or better in 35% of untreated, symptomatic patients was observed with BDR on a twice-weekly bortezomib schedule by the Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG).² Maintenance

therapy with BDR every 3 months for 1 year was used in this study. The ORR and VGPR or better response rate represents one of the highest for WM, with an estimated time to progression of >4 years. Patients with VGPR or better similar to the EMN study demonstrated longer PFS. Unfortunately, 69% of patients experienced PN, including 30% at the grade ≥ 3 level in the WMCTG study. Similar findings have been reported by others with twice-weekly dosed bortezomib in WM.^{3,4} Treatment-related PN led to discontinuation of bortezomib in 20% to 30% of WM patients on twice-weekly dosing.

The development of treatment-related PN is concerning because it can persist long after discontinuance of proteasome inhibitor therapy, and often requires chronic gabapentin, pregabalin, and/or narcotics use. The seemingly higher incidence of bortezomib-related PN in WM may reflect underlying nerve damage due to paraprotein-mediated demyelination or amyloid deposition that commonly occurs in WM (Table 1). The use of weekly bortezomib represented one of the first attempts to modulate PN risk in WM. Overall response rates of 80% to 90% were recognized in these studies, with grade 3 PN observed in 5% to 20% of cases.^{5,6} Treatment discontinuation is less than twice-weekly dosed bortezomib but still occurs in 10% to 20% of WM patients receiving weekly bortezomib. Lower rates of VGPR or better may have accompanied weekly bortezomib use, a finding that

potentially could impact long-term disease control.^{1,2} The use of subcutaneous bortezomib, while commonly used in WM patients, has not been formally examined in this patient population. Carfilzomib, a second-generation proteasome inhibitor that is associated with a lower incidence of PN, was recently evaluated in combination with rituximab and dexamethasone (CaRD) in mainly untreated, symptomatic patients with WM.⁷ Differences in off-target (nonproteasome) effects between bortezomib and carfilzomib have been proposed to account for the lower neuropathic potential of carfilzomib.⁸ An overall response rate of 81% was observed with CaRD, with VGPR or better attained in 21% of WM patients in this study. Importantly, no grade 3 PN events were observed. Twenty percent of patients on this study experienced IgM flaring. Duration of disease control remains to be determined with this regimen. Other proteasome inhibitors including orally administered ixazomib and oprozomib are in clinical trials, and their activity and safety remain to be clarified in WM.

The study by the EMN group also has important implications for timing of rituximab inclusion with proteasome inhibitor-based therapy. IgM flaring, defined as a $\geq 25\%$ increase in serum IgM, occurs in half of WM patients following rituximab monotherapy.⁹ The use of concurrent proteasome inhibitors can decrease the risk of IgM flaring, with occurrence estimates of 10% and 20% with twice-weekly and once-weekly dosed bortezomib, respectively.^{2,5} Preemptive plasmapheresis is recommended in the National Comprehensive Cancer Care Network guidelines for WM patients with IgM levels ≥ 4000 mg/dL prior to rituximab administration to decrease risk of symptomatic hyperviscosity associated with IgM flaring.¹⁰ The availability of plasmapheresis facilities, associated costs, occasional procedure-related complications, as well as delays in starting therapy while awaiting plasmapheresis are important reasons for seeking alternative approaches. The use of bortezomib alone for the first cycle offers a practical approach for decreasing the serum IgM burden and risk of IgM flaring, though close monitoring of serial serum IgM levels, assessment for hyperviscosity complaints, and possible preemptive plasmapheresis should be considered in those patients who continue to exhibit high serum levels (≥ 4000 mg/dL) prior to rituximab addition.

Table 1. Bortezomib-related PN and treatment discontinuation in patients with WM

	Grade 1, 2, %	Grade ≥ 3 , %	Treatment discontinuation, %
Twice weekly	40-70	20-30	20-30
Weekly	15-40	5-20	10-20

In summary, the study by the EMN provides a practical approach for dealing with the perils associated with proteasome inhibitor and rituximab-based therapy in WM patients. PN, however, continues to remain a significant problem with bortezomib use despite schedule modifications in WM patients. More work is still needed to optimize proteasome inhibitor-based therapy in WM patients.

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● ● ● LYMPHOID NEOPLASIA

Comment on Barta et al, page 3251

AIDS-lymphoma (ARL): one more step along the way

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In this issue of *Blood*, some of the controversies surrounding optimal therapy for patients with AIDS-related lymphoma (ARL) are now clarified by the analyses of Barta et al.¹

The profound immunodeficiency characteristic of HIV infection serves as an etiologic factor in the pathogenesis of ARL while also limiting the efficacy of standard multiagent chemotherapy due to development of intercurrent life-threatening infections, as well as depletion in bone marrow reserves. Prior to the availability of combination antiretroviral therapy (cART), use of standard multiagent chemotherapy was extremely difficult due to these factors, and low-dose chemotherapy was advocated.² The introduction of cART provided a stunning reversal in prognosis, with an increase in overall survival (OS) among those with full-blown AIDS and a decrease in development of AIDS-defining conditions among those with HIV infection alone.³ Although concomitant use of cART and multiagent chemotherapy was shown to be safe in terms of pharmacokinetics,⁴ concerns remained about additive depletion of bone marrow reserve, potential overlapping toxicities, and limitations of chemotherapy dosing. At the same time, initiation of cART at the conclusion of systemic chemotherapy was shown to be an effective paradigm, as demonstrated by the initial infusional etoposide, prednisone, infusional vincristine, infusional doxorubicin, and cyclophosphamide (EPOCH) trials from the National Cancer Institute.⁵ Despite an increase in HIV viral load and a decrease in CD4 cells during the course of EPOCH, these parameters returned to baseline within 6 to 12 months following (re-)institution of cART. Although this study demonstrated that control of HIV viral load was not required for attainment of complete response (CR), still, development of opportunistic infection occurred in 8% of the initial EPOCH-treated patients within the

first 3 months of completion of chemotherapy, and patients with CD4 cells <100/mm³ fared significantly worse than those with more intact immunity. Would these patients have done better if cART had been given earlier, concurrently with chemotherapy? A recent study from the AIDS Malignancy Consortium (AMC), in which patients received concomitant cART and chemotherapy, found that approximately half of complete responders had CD4 cells <100/mm³ at study entry, with a viral load >50 000 copies/mL, indicating that control of HIV infection is not mandatory for attainment of CR.⁶ The paper by Barta et al¹ brings further clarity to this question by demonstrating that concurrent use of cART and chemotherapy was associated with statistically improved CR rates, with a trend toward improved OS among 1546 patients with ARL, studied as part of 19 prospective trials. Thus, although it is clearly possible to attain CR in the absence of concurrent cART, results are likely to be improved when cART is added. This is an important finding from the analyses of Barta et al.

Whether to use rituximab with chemotherapy has been another controversy in terms of ARL patients. Although clearly associated with improved outcome in patients without HIV infection,⁷ early studies from the AMC indicated that rituximab was associated with a statistically significant increase in infectious death,⁸ leading to the conundrum: to use or not to use? Careful evaluation of the AMC data, however, demonstrated that the infectious deaths occurred primarily among patients with CD4 counts <100/mm³. Further, subsequent studies from the AMC and elsewhere failed to confirm the initial conclusions, demonstrating that rituximab could be used safely with chemotherapy,