mTOR, modulated the balance between active and inactive TIF-90 complexes.

What are the implications for AML and other hematologic malignancies? Often there is a concern that targeting central processes such as ribosomal biogenesis or translation will cause overt toxicity. However, this does not seem to be the case, most likely because cancer cells are more sensitive to inhibition of these processes than normal cells due to oncogene addiction. Indeed, targeting of the translation factor eIF4E in refractory and relapsed AML led to clinical responses including remissions with minimal therapy-associated toxicities.7 RNA synthesis itself may be targetable. For example, Pol I inhibitors are under development such as CX-5461.2 Indeed, many standard chemotherapies such as doxorubicin are known to inadvertently affect Pol I activity.2 The studies by Nguyen et al suggest that Akt inhibitors could be important tools for targeting elevated rRNA synthesis in AML. Clearly, Akt inhibitors would have pleiotropic effects, but perhaps it is the combination of these effects that will prove to be more efficacious than targeting any single event.

Many exciting questions remain to be answered. For instance, are the outcomes for AML patients with higher levels of TIF-90 worse than others? Similarly, for those patients with uncleaved vs cleaved FLNA? What are the mechanisms underpinning the alternative splicing leading to TIF-90 generation? How are these mechanisms dysregulated in AML? Can these be modified to reduce levels of TIF-90? Future studies will undoubtedly lead the way to understanding these aspects of rRNA synthesis and better reveal the intricate control of this critical cellular process.

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W M is a B-cell malignancy characterized by bone marrow infiltration of clonal lymphoplasmacytic cells, which produce a monoclonal immunoglobulin M (IgM). This condition corresponds to the lymphoplasmacytic lymphoma as defined by the World Health Organization classification.

Treatment of WM must be reserved for symptomatic patients, and the therapeutic strategy should be based on individual patient characteristics. Symptoms that indicate a need for treatment include cytopenias, systemic symptoms, hyperviscosity, peripheral neuropathy, symptomatic lymphadenopathy or organomegaly, cryoglobulinemia, amyloidosis, and cold agglutinin disease. Before starting treatment, the patient risk profile needs to be defined (WM-International Prognostic Scoring System, comorbidities, performance status, fitness status), as well as eligibility for stem cell transplant. Immunotherapy represents the standard for medically fit patients. In studies with a long follow-up, rituximab combinations with cyclophosphamide and dexamethasone, with bendamustine, or with bortezomib and dexamethasone (BDR) have shown good efficacy with durable responses.

The proteasome inhibitor bortezomib proved to be active in WM as a single agent (60-70% responses), both in untreated and relapsed/refractory patients, with a response duration of 8 to 16 months.2,3 In the frontline setting, responses were rapid (within 2-3 months) and of good quality. Treon et al treated 23 patients with BDR as primary therapy using bortezomib at the standard dose of 1.3 mg/m² with the twice weekly schedule. An overall response rate (ORR) of 96% was observed, with very good partial responses (VGPR) or better in 53% of cases. The median progression-free survival (PFS) exceeded 4 years. However, 70% of patients developed grade ≥ 2 peripheral neuropathy (PN). This led to premature discontinuation of bortezomib in 60% of patients for neurotoxicity.4 Neurotoxicity is in fact the major concern of bortezomib-based therapy in WM patients, a population characterized by advanced age and frequent underlying neuropathy, either IgM-related or secondary to other comorbidities. To reduce bortezomib-related neurotoxicity, the use of weekly bortezomib has been adopted. In the multicenter study by the European Myeloma Network, 59 previously untreated WM patients received BDR: an induction cycle of bortezomib (1.3 mg/m² intravenously on days 1, 4, 8, and 11) was followed by weekly bortezomib (1.6 mg/m² intravenously on days 1, 8, 15, and 22) every 35 days for 4 additional cycles, with rituximab

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Carfilzomib: a new opportunity for WM patients

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In this issue of Blood, Treon et al report the results of carfilzomib combined with rituximab and dexamethasone as a new effective and neuropathy-sparing treatment for patients with Waldenström macroglobulinemia (WM) requiring proteasome inhibitor-based therapy.1
and dexamethasone on days 1, 8, 15, and 22 of cycles 2 and 5. With this regimen of weekly bortezomib, the ORR was 85%, with a median PFS of 42 months. Grade ≥ 2 PN was observed in 24% of patients, leading to discontinuation of bortezomib in 8%. Only 10% of patients, however, reached VGPR/complete response (CR). A low rate of deep responses may possibly impact the long-term control of the disease.6

This proteasome inhibitor induces a rapid decrease in the IgM paraprotein, with a good quality of responses. Therefore, this agent appears appropriate for symptomatic WM patients with high IgM levels, risk of hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutininemia, amyloidosis, and renal failure due to paraprotein-related complications. Younger WM patients may also be candidates for bortezomib-based treatment because this agent is not stem cell toxic and does not show a risk of secondary malignancies. Neurotoxicity, however, remains the main limit of bortezomib-based treatments. In fact, PN is common, which is often severe and long lasting, leading to discontinuation of otherwise effective programs.

Carfilzomib, a second-generation selective proteasome inhibitor, showed a favorable toxicity profile in the myeloma setting. Notably, in a large report on the safety of single-agent carfilzomib in relapsed/refractory myeloma patients, the incidence of PN was low (13.9%), including patients with baseline neuropathy.7 Treon et al evaluated the efficacy and safety of the combination of carfilzomib, rituximab, and dexamethasone (CaRD) in 31 patients with symptomatic WM, naive to bortezomib and rituximab.1 Induction therapy consisted of intravenous carfilzomib 20 mg/m² infused over 20 minutes in cycle 1, and then 36 mg/m² in cycles 2 to 6, with intravenous dexamethasone 20 mg given on days 1, 2, 8, and 9 and rituximab 375 mg/m² on days 2 and 9 every 21 days for 6 cycles. In patients with stable disease or better, a maintenance was started 8 weeks later consisting of intravenous carfilzomib 36 mg/m² and intravenous dexamethasone 20 mg on days 1 and 2 along with rituximab 375 mg/m² on day 2 every 8 weeks for a total of 8 cycles. After therapy, median serum IgM levels decreased from 3375 to 749 mg/dL (P < .0001); bone marrow disease decreased from 60% to 5% (P < .0001); and the hematocrit increased from 32.3% to 41.3% (P < .0001). ORR was 87.1%, and 36% of patients achieved VGPR/CR. One patient attained a molecular CR (the first observation of molecular CR in WM). Responses were not impacted by the International Scoring System for WM. Treon et al also showed that the response to CaRD is independent of the presence of the CXCR4\(^{\text{WHIM}}\) mutation (35.3% of patients in the study). This is of particular interest, given the negative impact on response carried by this mutation.8 At a median follow-up of 15.4 months, 20 patients (64.5%) remain progression free. Protocol therapy was interrupted for nonresponse or progression in 10 patients, for progressive IgA/IgG hypogammaglobulinemia with infections in 2 patients, and for cardiomyopathy in 1 patient with multiple risk factors. Grade ≥ 2 carfilzomib-related toxicities included reversible asymptomatic hyperlipasemia (41.9%). Concerning treatment-related PN, it should be underlined that only 1 patient suffered grade 2 PN, and no patient needed discontinuation of the CaRD program because of neuropathy. This is of great clinical relevance, given the high incidence of neurologic toxicity usually observed with the proteasome inhibitor bortezomib. IgG and IgA hypogammaglobulinemia, which is a common finding in advanced WM patients, may have been aggravated by rituximab both during induction and during maintenance.

The results reported by Treon et al indicate that the carfilzomib-based CaRD combination represents an advancement in the treatment of WM patients requiring a proteasome inhibitor-based therapy. In fact, the efficacy of the combination, associated with a very low incidence of peripheral nerve toxicity, offers a neuropathy-sparing alternative to bortezomib-based protocols. The intensity and duration of rituximab therapy, both in induction and maintenance, probably need to be reconsidered in new studies to prevent the risk of infection.

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