Going retro on lymphoma

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In this issue of Blood, Cerchietti and colleagues describe the development of a highly active peptide inhibitor for the BCL6 oncoprotein that shows great promise for the clinical treatment of BCL6-dependent diffuse large cell lymphoma.

Diffuse large B-cell lymphoma (DLBCL) is a common and aggressive subtype of non-Hodgkin lymphoma that is frequently associated with deregulation of the BCL6 gene. Chromosomal translocations and mutations alter the BCL6 promoter without affecting the BCL6 coding region. Deregulated BCL6 transcription due to genetic alteration of the promoter appears to keep B cells in a rapidly proliferating germinal center–like state and promote the process of B-cell transformation. In mouse model systems, constitutive expression of BCL6 can immortalize primary B cells and promote the development of lymphomas, showing that BCL6 can act as an oncogene.

The high levels of BCL6 expression in DLBCL coupled with the low expression of BCL6 in the vast majority of normal cells have made BCL6 an attractive candidate for anticancer drug development. However, BCL6 is a transcriptional repressor protein, and functional interference with BCL6 protein in the nucleus of tumor cells using pharmaceutical agents presents a challenge. In 2004, the Melnick group described the initial development of a peptide inhibitor for BCL6. This early version of BCL6 inhibitory peptide (BPI) was a relatively large 120 amino acid peptide that worked by interfering with the ability of BCL6 to bind its critical corepressor proteins, N-CoR and SMRT. BPI was able to enter cells via the addition of an HIV-TAT sequence to the peptide, facilitating the crossing of the cell membrane after macropinocytosis.

While growth inhibition by BPI was highly specific and effective at low-peptide concentrations, the major drawback of BPI was its instability—cells required a fresh dose every few hours for a sustained inhibitory effect. At this point, the Melnick group decided to retain the idea of a peptide inhibitor that interrupted the interaction of BCL6 with its corepressor proteins and focus their efforts on refining the inhibitory peptide to make it more stable. The result of that work is the current study from Cerchietti et al., which represents a technical tour-de-force in inhibitory peptide design and testing. The authors went through multiple iterations of peptide refinement by adding an additional fusogenic motif besides the TAT sequence, shortening the inhibitory sequence to 9 amino acids, modifying peptide configuration by mutating a proline residue, and lastly, making the peptide in retro-inverso (D isomer) configuration. The eventual result was the “S6.2 RI-BPI” peptide, which was highly stable in cells, required only 1 dose every 48 hours, and was also inhibitory at micromolar concentration. The S6.2 RI-BPI peptide worked to inhibit lymphoma growth in vivo, was remarkably specific for lymphoma subtypes dependent upon BCL6, and showed no overt signs of toxicity when injected into mice over a 1-year period. Normal germinal center B cells are dependent upon BCL6 function, and treatment of mice with the S6.2 RI-BPI peptide inhibited germinal center formation. This again showed that S6.2 RI-BPI peptide could inhibit BCL6 function in vivo. Importantly, the S6.2 RI-BPI peptide did not induce inflammatory disease in mice, which was a concern as Bcl6-deficient mice develop lethal inflammatory disease at a high frequency. Clearly more careful studies on toxicity of the S6.2 RI-BPI peptide in vivo are required, but these initial results are very encouraging.

Overall, this work by Cerchietti et al represents an excellent case study of rational drug design for cancer therapy. More importantly, this new study from the Melnick lab shows...
that therapeutic use of BCL6 peptide inhibitors to treat lymphoma should be a reality in the very near future.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

 Commentary on Ludwig et al, page 3435

Thalidomide/dexamethasone in myeloma: a double-edged sword

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In this issue of Blood, Ludwig and colleagues show that TD may result in treatment-related mortality in elderly patients with multiple myeloma.

Thalidomide was introduced for multiple myeloma (MM) in 1998. Its mode of action makes it a suitable candidate to combine with corticosteroids. Hence, it has been combined with dexamethasone or melphalan/prednisolone (MP) as upfront treatment for patients who are not eligible for high-dose therapy.1 Peripheral poly-neuropathy (PNP) and deep venous thrombosis (DVT) are serious clinical side effects. Dexamethasone has long been used as an oral schedule of repeating 4-days blocks. In the study by Ludwig et al,2 the clinical effects of thalidomide plus dexamethasone (TD), in a slightly modified schedule derived from the Eastern Cooperative Oncology Group (ECOG), is compared with classical MP in patients with MM who were not transplant candidates.3,4 The outcome of the trial demonstrates that TD results in a higher response rate, but survival is worse than with MP because of treatment-related mortality with TD in patients over 75 years.

The toxicity of TD is 2-sided and strongly depends on age: thalidomide-associated DVT and dose-related PNP directly affect the quality of life, and these effects may have an even stronger impact in the elderly MM patient. Dexamethasone has many unwanted side effects, such as mineralocorticoid disturbances, psychiatric disease, hormonal imbalance, and an increased risk of infections. These and other clinical symptoms have long been accepted because of the rapid disease reduction affected by this potent corticosteroid. The lesson from the Ludwig trial is that TD can result in excess early mortality in patients over 75 years of age with poor performance status, in particular from infections that are presumed linked to dexamethasone.

While there are good reasons to consider dexamethasone for myeloma treatment, the standard-dose regimen has too long been taken for granted. Recently, an ongoing trial by the ECOG (E4A03), which compared lenalidomide with standard-dose versus low-dose dexamethasone, reported that standard-dose dexamethasone is associated with higher early mortality in the first year as compared with low-dose. These data indicate that standard-dose dexamethasone in older patients is a poor choice during early treatment when disease control has not yet been established.5 Along the same line, an initial high dose of thalidomide should be avoided because of a risk of early mortality in older patients as observed by the Nordic Myeloma Study Group.6 Thalidomide, bortezomib, and lenalidomide have changed the spectrum of MM treatment. They induce a fast improvement of disease-related symptoms and a high response rate, especially when combined with other agents. In an elderly patient with MM, they can be used effectively, provided that excessive toxicity is avoided. The trial reported here indicates prudence is called for in treatment of the older patient, and that adjustment of the dose and schedule of both thalidomide and dexamethasone is desirable. Alternatively, in order to avoid the hazards of dexamethasone and to use the effect of an alkylating agent, thalidomide can be combined at an appropriate dose with MP (MP-T), resulting in good efficacy and less mortality.7

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