

Investigational Agents for Lymphoma

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The incidence of non-Hodgkin lymphoma (NHL) continues to increase, with more than 65,000 cases per year.

The prevalence of this malignancy is even greater with the improvement in therapy resulting in even more survivors. The novel agents being explored in these cancers range from chronic oral dosing of small-molecule biologics to the immunoconjugates, monoclonal antibodies linked to potent cytotoxics.

An example of these promising investigational therapies comes from the family of PI3 kinases, intracellular signaling proteins that are essential components of migration, proliferation, survival, and differentiation pathways in many cell types. The PI3K delta isoform shows an expression pattern largely restricted to cells of hematopoietic origin.

form of PI3K. Its selectivity minimizes the potential for hyperglycemia seen with pan-PI3K inhibitors. In a phase 1 study evaluating once-a-day and twice-a-day dosing of CAL-101 in patients with indolent NHL (iNHL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), doses up to 350 mg orally twice a day were reasonably well tolerated. In 28 patients with relapsed or refractory iNHL, 17 partial responses (61% overall response rate [ORR]) were noted. Substantial activity was also seen in patients with CLL and MCL.

Development of the promising agent is moving forward in phase 2 and in combination trials. A particularly inter-

CAL-101 (Calistoga/Gilead) is a potent, oral, small-molecule inhibitor of the p110 delta iso-

esting study presented by Flinn and colleagues dosed CAL-101 along with either rituximab or bendamustine in patients with iNHL or CLL. Despite prior therapy that included these approved agents among others, the vast majority of patients responded to the combinations. In those with iNHL, bendamustine/CAL-101 therapy resulted in 13 of 15 responders (87%, two complete responses [CRs]), and rituximab/CAL-101 yielded 11 of 12 responders (92%). No safety concerns were noted.^{1,2}

Another group of drugs from this pathway being explored in lymphomas are the mTOR/TORC inhibitors. The rapalogues or allosteric inhibitors of mTOR include everolimus (Afinitor, Novartis) or temsirolimus (Torisel, Pfizer). Initially approved for the treatment of renal cell cancer, these agents have shown activity against NHLs, specifically the often-difficult-to-treat MCL.



The rapalogues inhibit only TORC1, while the serine/threonine protein kinase inhibitors block both cellular signaling complexes TORC1 and TORC2. An agent in this class being evaluated in NHL includes INK 128 (Intellikine), although compounds from Celgene, Genentech, Sanofi, and others are in various stages of exploration. The potent activity down the PI3K/AKT/TORC pathway appears to be an attractive strategy for a number of hematologic malignancies.

A novel mechanism of action, the inhibition of Bruton's tyrosine kinase, is being exploited by PCI-32765 (Pharmacocyclics). The potent, orally bioavailable small molecule has completed phase 1 studies, and the results are impressive across a broad spectrum of lymphomas.

In a phase 1 dose-finding study of 40 heavily pretreated NHL patients, responses were seen in almost 50%. Confirmed partial responses were noted in patients with CLL/SLL (small lymphocytic lymphoma), MCL, diffuse large B-cell, follicular, and marginal zone lymphomas. Interestingly, 13 of 17 responders had tumor decreases of at least 75%.³

A number of clinical trials continue to be explored with lenalidomide

(Revlimid, Celgene) in NHL. The use of immunomodulatory drugs has become standard of care in multiple myeloma, and the activity has carried over to a number of B-cell malignancies. Single-agent responses have been seen in MCL, and larger trials are under way in combination with rituximab. Strategies exploring lenalidomide with conventional regimens such as CHOP (the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone) and as maintenance therapy are in progress.

As mentioned, the excitement around the immunoconjugates continues to expand. These novel therapies explore the combination of a monoclonal antibody with an established target and a potent cytotoxic, usually a maytansinoid or an auristatin analogue. The key to success of late is the superior linker technology, enabling the use of these powerful chemotherapeutics without the systemic toxicities. After binding, the immunoconjugate is internalized by the cell and the moiety is degraded, releasing the effector molecule.

Recently approved by the U.S. Food and Drug Administration, brentuximab vedotin (Seattle Genetics) is an antibody-drug conjugate of an anti-CD30 monoclonal antibody and

the cytotoxic auristatin E. The activity demonstrated an ORR of 73% (32% CR) in 102 patients with Hodgkin lymphoma that relapsed after stem cell transplant (or two prior regimens in nontransplant candidates). A second approval was given in anaplastic large-cell lymphoma based on 58 relapsed patients experiencing an 86% ORR (57% CR). Serious adverse events were seen in 31% of patients, including neutropenia and neuropathy, although the side effects were described as manageable.

Lastly, the alkylating agent bendamustine (Treanda, Cephalon) continues to generate enthusiasm for its activity and ability to be combined with other agents. After an initial approval in CLL from a positive study vs. chlorambucil, the rituximab/bendamustine combination is being studied as a replacement of the standard fludarabine/cyclophosphamide/rituximab (FCR) regimen as frontline therapy. Similarly, the 74% ORR (17% CR) against relapsed postrituximab iNHL for single-agent bendamustine has made the therapy an attractive option for physicians.

In summary, the treatment of lymphomas continues to improve dramatically with greater options against most of the very particular subsets. The identification of specific targets has made the development of small-molecule biologics and immunoconjugates both practical and effective. Well-designed clinical trials will help move these treatments into frontline, and potentially curative, settings.

References

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