Brentuximab vedotin ushers in a new era in treating lymphomas

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Hodgkin lymphoma represents one of the major successes of modern oncology. Several decades ago, it was fatal in most patients. With the development of the combination therapy mechlorethamine, vincristine, prednisone, and procarbazine (MOPP), many patients were cured of this disease. However, the regimen was associated with an unacceptable risk of acute toxicities, infertility, and secondary malignancies.[1] Several subsequent studies established adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) as the standard treatment because of its greater efficacy and less toxicity compared with MOPP.[2] As a result, about 90% of patients with limited-stage disease are now cured, as are 60% of those with advanced disease. Newer regimens such as bleomycin, etoposide, adriamycin, cyclophosphamide, prednisone, and procarbazine (BEACOPP) seem to prolong time to treatment failure, but with considerably greater toxicity,[3] and with no clear improvement in overall survival. A minority of patients who are either refractory to initial treatment or who subsequently relapse can be cured with such modalities as stem-cell transplantation. However, few effective options are available for the remainder of patients.

The situation is even more challenging for T-cell non-Hodgkin lymphomas (T-NHLs), which are about 15% of all NHLs. The most common subtypes of T-NHL are peripheral T-cell lymphoma, not otherwise specified; angioimmunoblastic T-NHL; and anaplastic large-cell lymphoma (ALCL), which accounts for 10%-15% of T-NHL. Front-line chemotherapy regimens, such as the standard cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP), achieve pronged progression-free survival in a minority of patients. Adding other conventional agents has not clearly improved outcome.[4] Stem-cell transplant is rarely an option because of the rapidly progressive nature of these diseases. Two new agents, pralatrexate, an antifol, and romidepsin, a histone deacetylase inhibitor, induce responses in 25%-30% of patients,[5,6] with a median progression-free survival of 3-4 months for each. Combinations of these drugs with each other and with other agents are currently in development. If one of these were to show promise, it should be compared with CHOP as initial treatment and hopefully replace CHOP as the standard approach.

Brentuximab vedotin represents a new class of agents, the antibody-drug conjugate.[7] The first of these to gain approval by the Food and Drug Administration was gemtuzumab ozogamycin (Mylotarg), which has been recently withdrawn from the market because of limited activity and substantial toxicity. However, the toxin calicheamycin and linker are quite different from those in brentuximab vedotin, which uses monomethyl auristatin E (MMAE). The response rates to brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell NHL as reviewed on page 5 are very exciting and provide a true proof-of-principle.[8] As a result, other drug antibody conjugates are currently in clinical trial for non-Hodgkin lymphoma.

The question will be how best to position these drugs to the benefit of patients. The efficacy of brentuximab vedotin in patients with both ALK-positive and ALK-negative ALCL clearly establishes this drug as the standard agent for patients with relapsed and refractory anaplastic disease. A clinical trial to determine whether it can become a part of the initial treatment of patients with ALK-negative ALCL who have poorer prognosis would be worthwhile.

Studies are underway looking at other CD30-positive T-NHL histologies to determine their responsiveness to brentuximab vedotin, as well as the population of diffuse large B-cell NHL that expresses this antigen. Other clinical trials are attempting to move the agent earlier in the course of these diseases, even as part of initial therapy. However, although brentuximab vedotin is a biological

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therapy, combinations with it and chemotherapy should be approached with caution. In a study conducted by the research cooperative CALGB (Cancer and Leukemia Group B) in which the backbone antibody of brentuximab, SGN-30 (anti-CD30 monoclonal antibody), was combined with gemcitabine, vinorelbine, and liposomal doxorubicin,[9] the study was terminated early because of life-threatening and fatal pulmonary toxicity.[10] Thus, this drug should not be combined with drugs such as bleomycin, a standard drug for this disease which, fortunately, is probably not essential for therapeutic efficacy of regimens such as ABVD, or gemcitabine. How it will react with other agents remains to be evaluated. In an abstract presented at the American Society of Hematology meeting in December, investigators reported that combining brentuximab vedotin with AVD resulted in PET-confirmed complete remissions in more than 90% of the study patients. A trial comparing ABVD and AVD plus brentuximab as the initial treatment in patients with advanced-stage disease is ongoing.[11]

Of concern are three cases of fatal, progressive multifocal leukopencephalopathy recently reported out of about 2 000 treated patients. The specific characteristics of these patients need to be evaluated to determine if there were predisposing factors, and diligent reporting of future instances.

We are clearly in a new era in the treatment of patients with many types of lymphomas. With the availability of new, targeted therapies, the role for nonspecific and toxic chemotherapy will become increasingly limited. To achieve further progress toward prolongation of survival and increased rates of cure while decreasing the adverse effects of therapy will require accrual of patients to high quality clinical research studies.

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