

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Advances in the Management of B-cell Lymphomas

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H&O What research led to the introduction of monoclonal antibodies as therapy for B-cell lymphomas?

GW B-cell lymphomas are highly diverse. Some, such as follicular lymphomas, may not require therapy for many years, whereas others, such as Burkitt lymphoma, are among the fastest growing of all malignancies. Over the past several years we have made excellent progress in understanding the molecular changes responsible for this varied behavior. More recent advances have focused on how interactions with the host also can affect the behavior of B-cell lymphomas. Historically, lymphomas were treated with chemotherapy. In fact, the lymphoid malignancies were among the first cancers to be treated effectively with chemotherapy. This advance was based on the discovery that soldiers exposed to nitrogen mustard gas in World War I lost most of their lymphoid tissues. Over time, additional drugs were found to have antilymphoma activity, but until they were combined we were not able to cure some patients. The well-known regimen of cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) became the standard of care for large cell lymphoma and remained so for a number of decades. Many attempts were made to add drugs to the CHOP regimen to improve the overall response rates. The most important example was the large four-arm intergroup study comparing CHOP to more intensive chemotherapy regimens as a treatment for intermediate- and high-grade B-cell malignancies. Although subgroup analysis sug-

gested that more intensive treatment might be superior for the most aggressive histologies of B-cell malignancies, overall, CHOP was as good therapeutically, and less toxic, than the more complex regimens.

At approximately the same time, there was interest in using monoclonal antibodies to treat cancer. The work of Dr. Ronald Levy and colleagues from Stanford University provided proof of principle for this approach. Dr. Levy produced tailor-made anti-idiotypic monoclonal antibodies for a series of patients with follicular lymphoma and found a significant percentage of them responded to this therapy. The process of making individualized antibodies for each patient was highly labor intensive and was not practical in general, but it did demonstrate that monoclonal antibody treatment of human B-cell lymphoma could result in significant clinical responses. Trials in other cancers were less promising, and a number of leaders in oncology believed that antibody therapy of cancer was a failed hypothesis. Nevertheless, the promise presented by Dr. Levy's results provided the impetus for a number of investigators, including me, to enter the field of antibody therapy.

H&O Could you discuss the response rates seen with antibody-containing regimens in the setting of B-cell lymphomas?

GW As with most cancer therapies, quoted response rates vary from study to study based on the specific antibody in question, the patient population, and other factors. If we focus on single-agent rituximab (Rituxan, Genentech/Biogen Idec) in the treatment of relapsed indolent B-cell lymphoma, the population that led to approval of the drug by the US Food and Drug Administration, approximately half of treated patients achieve a partial or complete remission using standard criteria. A significantly higher frac-

tion benefit clinically from therapy, and a higher fraction still respond to upfront rituximab therapy or rituximab therapy combined with chemotherapy. The addition of rituximab has clearly changed the paradigm of treatment for B-cell lymphoma, yet there are still many unknowns related to when and how it should be integrated into treatment regimens. All one needs to do is look at ongoing clinical trials or attend a meeting of lymphoma experts to learn that there is no doubt that rituximab is an important addition, but there is no consensus on how it should be used. Several additional antibodies, including other anti-CD20 antibodies and antibodies targeting other B-cell antigens, such as CD22, CD80, and class II MHC, have entered clinical trials. With the notable exception of the radiolabeled anti-CD20 antibodies, none of these has yet been shown to be an advance over rituximab.

H&O How do the response rates to antibody-containing regimens differ with different types of B-cell lymphomas?

GW There are differences in response and cure rates among different B-cell malignancies. In follicular lymphoma, rituximab plus chemotherapy clearly results in a greater response rate than does chemotherapy alone, and emerging data suggest the combination also results in an improvement in survival. The addition of rituximab to standard chemotherapy for diffuse large B-cell lymphoma (DLBCL) also improves the overall response rate and cure rate. Mantle cell lymphoma remains the nemesis of the lymphoma specialist, and though the addition of rituximab to chemotherapy appears to enhance the response rate, the ultimate effect of such therapy on survival is still unclear. We are now moving into an era of classifying B-cell malignancies based on gene expression, and learning that the host immune makeup and response can affect the efficacy of therapy. This new approach could well change our understanding of who is likely to benefit most from antibody therapy.

H&O Could you discuss the role of subtyping in predicting response to therapy?

GW Traditionally, clinicians used histology and standard clinical criteria to predict how a patient would respond to a particular therapy. As with other cancers, we have learned that lymphomas that appear the same histologically can be very different genetically, and that the differences can affect response rates and prognosis. Gene expression signatures of large cell lymphomas have allowed identification of a number of different subsets. For example, diffuse large cell lymphomas can be classified as being of the activated B-cell (ABC) type or the germinal center B-cell (GCB) type. The prognosis of patients with the

ABC type is generally poorer than for patients with the GCB type. There is also growing evidence that the host response affects response to therapy. Patients with a polymorphism for CD16 that has a higher affinity for CD16 respond better to rituximab than do patients with lower-affinity CD16. Ongoing research is exploring the effect of other polymorphisms on prognosis in lymphoma and is likely to identify other genes of interest in the next few years. Additionally, the number and type of infiltrating benign cells within a lymphoma correlate with clinical response to therapy. We do not yet understand whether these differences are related to the malignancy itself, the host response to the malignancy, or a combination thereof. As we learn more, it is clear many of these factors will affect our ability to predict response to therapy.

H&O What is the current role of dose-dense chemotherapy in the setting of B-cell lymphomas?

GW Dose-intense therapy and autologous transplantation remains the best option, indeed the only option with curative potential, for some lymphoma patients. However, knowing a given patient with lymphoma is not likely to do well with additional standard-dose therapy does not necessarily mean dose-intense therapy is going to be better. There is still much we do not know about how to identify the subset of patients that will benefit most from the dose-dense approach. In addition, we are only now beginning to apply information related to lymphoma genetics and host response to our understanding of who is likely to benefit most from dose-intense therapy.

H&O What is the role of radioimmunotherapy in the treatment of B-cell lymphomas?

GW Radioimmunotherapy is clearly an effective approach to therapy of B-cell malignancies. The fact that it has not been more widely adopted is due to practice patterns and market forces, not to a lack of efficacy or undue toxicity. Multiple studies have shown that radioimmunotherapy, appropriately administered, has limited toxicity and is highly effective. ¹³¹I-tositumomab (Bexxar, GlaxoSmithKline) and ⁹⁰Y-ibritumomab (Zevalin, Biogen Idec) both are associated with response rates greater than those seen with rituximab, and uncontrolled data suggest upfront therapy may result in improved survival. Nevertheless, the adoption of radioimmunotherapy in the oncology community has been limited due to the difficulty and logistics of administering it. Among these difficulties is the need to train and involve additional specialties (nuclear medicine physicians), and reimbursement patterns that discourage use, which is a shame, because these are highly effective agents.

H&O What other new agents are being studied in the setting of B-cell lymphoma?

GW Much of the work in the area of antibody therapy has focused on identifying antibodies that recognize different antigens. We are only now beginning to focus on the other end of the antibody—ie, the constant region that interacts with the immune system. We know how to change antibody structure, dial up or dial down the ability of the antibody to interact with IgG receptors or complement. Some antibodies with effector function are now in clinical trials, and I believe this is a promising approach.

Another approach is to combine antibodies with treatments that activate immune effector mechanisms. We have been interested in exploring the combination of antibodies and toll-like receptor 9 (TLR9) agonists such as oligodeoxynucleotides containing unmethylated CpG motifs. Other investigators have looked at combining antibodies with immunostimulatory agents including recombinant cytokines and natural products. Rituximab is now most commonly used in combination with chemotherapy, and rituximab maintenance therapy has been shown to be helpful. This rapid evolution of standard practice in rituximab use has created challenges related to the design of a drug development programs intended to evaluate whether immunostimulatory agents add to the efficacy of rituximab therapy. It has yet to be determined whether immunostimulatory agents can enhance the efficacy of antibody therapy.

Despite my own interest in the area of immunotherapy of lymphoma, I would be remiss if I did not mention development of drugs that target signal transduction in lymphoma and show considerable promise. These include agents that inhibit farnesyltransferase, Raf kinase, PI3 kinase, mammalian target of rapamycin (mTOR), and other pathways. There is much to learn about how well these agents work in different lymphomas, and how best to combine them with each other and with standard chemotherapy. A project in the current Iowa University/Mayo Clinic lymphoma SPORE, led by Dr. Thomas Witzig, is designed to begin to address some of these questions.

H&O What new directions do you envision for the future of treating B-cell lymphoma?

GW A future direction that intersects with each of the various treatment approaches outlined above is the individualization of therapy. It is becoming clearer that both tumor factors and host factors can affect the efficacy of therapy, and that taking these factors into account will allow us to design the most effective, least toxic therapy for each patient. The transition from our current approach of using rituximab plus CHOP for most B-cell lymphoma patients, to development of individualized treatment based on not only histology and clinical characteristics, but also tumor gene expression and genomic polymorphisms, will be challenging. Nevertheless, this adjustment will be necessary if we are to take advantage of current advances in our understanding of lymphoma therapy.

Suggested Readings

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