Recent Advances in the Treatment of Chronic Lymphocytic Leukemia, Diffuse Large B-cell Lymphoma, and Follicular Lymphoma

An Expert Interview with Ian W Flinn

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Chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and follicular lymphoma are the three most common lymphoproliferative malignancies.[1] All are B-cell malignancies and, although diverse in their underlying pathologies and clinical presentation, until recently have been treated the same way. The standard first-line therapy is rituximab and combination chemotherapy, usually the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen.[1] However, many patients relapse early or eventually become resistant to treatment.[2–4] The prognosis for these patients is poor; salvage chemotherapy followed by autologous stem cell transplantation is the standard second-line treatment for relapsed and refractory disease. However, many patients are not eligible for transplantation, and others will relapse after autologous stem cell transplantation.[2] In recent years, a number of new approaches, including monoclonal antibodies, small molecule targeted therapies, and immunomodulatory agents, have emerged. These new therapies are transforming the treatment landscapes for these diseases, and at the same time, raise new questions.

In an expert interview, conducted at the American Society of Clinical Oncology (ASCO) Annual Meeting, which was held in Chicago, Illinois, from June 1–5, 2018, Dr Ian W Flinn discusses some of the most exciting emerging therapies in the treatment of these B-cell malignancies and the future challenges clinicians face in the treatment of relapsed and refractory patients.

Q. What are the most important unmet needs in the treatment of relapsed/refractory chronic lymphocytic leukemia?

In the last few years we have seen developments for the treatment of patients in the first-line setting, particularly small molecule targeted therapies such as Bruton's tyrosine kinase inhibitors and BCL-2 inhibitors. As these therapies move forward in the treatment paradigm to first-line therapy, treatment of patients following relapse is becoming a serious challenge. We don't know whether we can go back

to using chemotherapy in patients who become resistant to ibrutinib or venetoclax and this is becoming an important unmet need.

Q. What do you consider the most promising treatments in clinical development for relapsed/refractory chronic lymphocytic leukemia?

The most promising therapies have been combination therapies such as the combination of rituximab with venetoclax. This is showing impressive results, including deep remissions in people on time-limited therapies.[5] How we treat patients after they progress on venetoclax or ibruntinb is an unknown area. Many new small molecules and immunotherapies are in clinical development but at the moment there is no leading candidate.

Q. Can we predict in advance who is at high risk to relapse and then modify therapy for these high-risk patients?

We can predict risk of relapse based on pre-treatment characteristics, such as fluorescence *in situ* hybridization for 17p deletions and 11q deletions, and mutational status of the variable region of the immunoglobulin heavy chain. Many centers are using next-generation sequencing to detect mutations in some genes such as *TP53* and *ATM*, so we have a good idea of who is at high risk of relapse. What we don't know is whether we should be modifying first-line therapy based on these findings. It is clear that using chemotherapy in patients with 17p deletions is not the right thing to do. In these patients, we need to consider ibrutinib or venetoclax combinations, and perhaps other kinase inhibitors that are in development. But whether we should be modifying treatment beyond that is unknown at this time.

Q. What have been the most exciting recent developments in the treatment of diffuse large B-cell lymphoma?

By far the most exciting development in diffuse large B-cell lymphoma is chimeric antigen receptor-T (CAR-T) cell therapy. Two different products, axicabtagene ciloleucel (Yescarta®; Kite Pharma, Los Angeles, CA, US) and tisagenlecleucel (Kymriah®; Novartis, Basel, Switzerland), are now approved in the US, and a third, lisocabtagene maraleucel, has generated promising preliminary data.[8] These CAR-T cell therapies have incredible efficacy in patients that are not responding to anything after stem cell transplantation or are refractory to chemotherapy.[8] This is a very exciting area. The next question we must answer is whether we can move CAR-T cells earlier in the treatment paradigm. Randomized trials are now going on looking at replacing stem cell transplant with CAR-T cell therapy. If the findings from these studies are positive, this could result in a major shift in how we treat patients with large cell lymphoma.

Q. What are the most exciting developments in the first-line treatment of follicular lymphoma?

The most exciting development has been the use of lenalidomide and rituximab. The results of a large study called the RELEVANCE trial is being presented at ASCO,[9] and shows that this non-chemotherapy regimen has equivalent efficacy to giving patients combination chemotherapy. The primary endpoint of superiority was not met but the fact that it this regimen provided equivalent efficacy without the side effects of chemotherapy is exciting. It is likely that many patients will choose treatment this over conventional chemotherapy. ❑

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