CancerNetwork speaks with Hagop Kantarjian, MD, M.D. Anderson Cancer Center, who shares his impressions of some of the highlights of this year’s ASCO meeting with regard to hematologic malignancies.

—Interviewed by Michael Kaufman

Dr. Kantarjian, thank you for being with us.

Dr. Kantarjian: Thank you for inviting me.

CancerNetwork: What are the areas that generated the most excitement among attendees at this year's meeting?

Dr. Kantarjian: In leukemia there were three major areas at ASCO that were of critical importance. The first one is the development of the monoclonal antibodies in acute lymphocytic leukemia (ALL), and these are showing very impressive results in patients with refractory/relapsed ALL. The second area is the updated results with the BCR-ABL tyrosine kinase inhibitors (TKIs), in particular the third-generation TKI ponatinib, which is effective against the T315I mutation, which has been resistant to the previous TKIs. The third area involves the very exciting results with the new B-cell receptor inhibitors in chronic lymphocytic leukemia (CLL).

I am going to start first with the monoclonal antibodies in ALL, and at the ASCO meeting there were updates of two of these monoclonal antibodies. The first is blinatumomab, a two-armed monoclonal antibody, where one arm attaches to the leukemic cell, attaching to the CD19 receptor, and the other arm attaches to the CD3 receptor, which is on the T cells, and this brings the two cells together and the T cells kill the ALL cells. So it is a very appropriate from of immunotherapy. Blinatumomab has already undergone several studies in lymphoma and in this update investigators looked at an optimized schedule of a continuous infusion of blinatumomab starting at a low dose of 5 µg/m² by continuous infusion daily for a week and then the dose is upgraded to 15 µg/m² for the rest of the treatment, given as a continuous infusion over 4 weeks every 6 weeks. The authors report the update in a total of 36 patients who have failed standard of care and who are considered to have a poor prognosis. And what they show is that they can achieve a complete remission in about 45% of the patients and marrow complete remissions in about 72% of the patients. So these are very impressive results. The responses are also quite durable. The duration of remission is about 9 months and the median survival is also about 9 months.

The drug does have side effects, including the cytokine release syndrome, which is essentially fever, discomfort, and flu-like symptoms, which usually happen at the beginning of the treatment. The second pattern of side effects is neurologic problems, including seizures in 3 of the 36 patients and mental changes or encephalopathy in 3 patients. So, very positive results which are now leading to development of a global phase II study of the same drug in the same setting, hoping that this will be encouraging enough to seek a potential FDA approval.

The second drug in ALL is inotuzumab, a monoclonal antibody directed against CD22, and the monoclonal is attached to a toxin called calecheamicin. This study looked at a different schedule of inotuzumab given weekly during the induction, and the authors reported among 27 patients treated an overall response rate of 52% and a complete response rate of 11%. Again, those responses were durable; response duration of 7 months and median survival of 7 months. The importance of this drug is its convenience. It's given as a short infusion once a week and the only significant side effect is some liver dysfunction which is usually mild to moderate and reversible.

These two monoclonal antibodies open the way for a new form of investigation in ALL of using these monoclonal antibodies either alone or in cocktails, or in combination with chemotherapy. So ... very exciting results in ALL.

The second area is chronic myeloid leukemia (CML). There were updates of the two front-line...
randomized studies looking at the second generation TKIs, nilotinib and dasatinib vs the standard of care, which is imatinib. And in both of these updates the investigators report that the second-generation TKIs continue to show an advantage in terms of the early surrogate endpoints—incidence of major molecular response, complete molecular response, and reduction in incidence of transformation to accelerated and blastic phase. So nothing much new in these two updates of the ENESTnd trial for nilotinib vs imatinib, or the DECISION trial for dasatinib vs imatinib, but it is reassuring that the updates continue to show a benefit for the second-generation TKIs.

I think the more important study is the one with ponatinib, which is also a BCR-ABL tyrosine kinase inhibitor, but in contrast to the other two drugs it is also active against the T315I mutation, which other drugs have not been effective against. In this ASCO there was an update of a large study, 449 patients, surprisingly accrued over a period of one year. Patients were divided into chronic phase, accelerated phase, or blastic phase and Philadelphia-positive ALL. And they were divided into whether they were refractory or previously intolerant to other TKIs or had a T315I mutation.

In summary, the results with ponatinib are very, very impressive. What was seen in the chronic phase, for example, is a complete cytogenetic response rate of 44%, a major cytogenetic response rate of 54%, and a major molecular response rate of 30%. And those responses were durable. With a follow-up of about 10 months 93% of the major cytogenetic responses were continuing to be there.

Dr. Kantarjian: How do those results compare with the current standard of care?

The standard of care in refractory or relapsed patients to multiple TKIs doesn’t exist. What we have usually is some data on either dasatinib or nilotinib in patients who have failed imatinib and one of the other TKIs. This drug is effective even when those three drugs have failed. So it establishes a new standard of care of highly effective therapy. If you ask if we can anticipate how this drug will compare to the other TKIs in the same setting, I think this drug will be more effective than the second-generation TKIs in the setting of salvage therapy, but that remains to be seen. But this drug is also highly effective against the T315I mutation.

There were 64 patients with the T315I mutation in chronic phase and among them the complete cytogenetic response rate was 66%, the major cytogenetic response rate was 70%, and the major molecular response rate was 50%, which is very exciting data. We believe that this information may evolve into FDA approval of this drug for patients with refractory disease to at least two TKIs, as well as in patients with the T315I mutation. And the question is whether we can move the drug into the setting of salvage and in the front-line setting, and these are the studies that are being proposed now.

The last area of research is the B-cell receptor kinase inhibitors in CLL. There are two kinds of these B-cell receptor inhibitors, ones that are active against Bruton tyrosine kinase, which we call BTK inhibitors, and the other kind are the PI3 kinase inhibitors. The excitement is because these drugs are given orally on a daily basis, they have minimal side effects, and they are producing very high response rates which are durable. So people are starting to make analogies of these B-cell receptor inhibitors to the early trials with the TKIs, namely imatinib in chronic CML. We think that this is a new era in CLL, which is going to be very exciting.

At this ASCO meeting there was an update of one of the BTK inhibitors, ibrutinib (formerly PCI-32765). The update was for both newly diagnosed older patients with CLL and for patients with relapsed or refractory disease. In the front-line study in older patients, Dr. Byrd updated results in 31 patients and what he shows in these patients is minimal side effects, essentially no severe side effect. He showed also that as was seen in the salvage setting, there was initially a transient increase in the lymphocyte count while there is a general decrease in the disease overall in the lymph nodes and the bone marrow. Among those 31 patients he has shown that overall the response rate is 74%. The complete response rate is low, only 10% but as the patients continue to be treated, many of the patients convert from a partial response to a complete response.

Interestingly, they saw responses in the worst categories, such as patients with deletion in chromosome 17, and they also updated the results among patients who received the BTK inhibitor in the salvage setting, showing again that those responses are occurring at a high rate and they are durable. So for example, in the 31 newly diagnosed older patients treated with ibrutinib, after a median follow-up of about 15 months, 90% of the patients continued to respond. In summary, they report that in the newly diagnosed older patients with CLL the overall cumulative response rate is about 80%, the estimated 15-month progression-free survival is 96%, and the drug is very well tolerated on an oral daily basis.

So that forms the basis of the excitement and the belief that these B-cell receptor inhibitors, including BTK inhibitors and PI3 kinase inhibitors may open a new era of research and treatment and establish new standards of care in patients with chronic lymphocytic leukemia.
Thank you, Dr. Kantarjian.

Dr. Kantarjian: My pleasure.

Hagop Kantarjian, MD

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