LETTER FROM THE EDITOR

Last year I returned from the American Society of Hematology (ASH) meeting feeling that the world had changed for lymphoid malignancies. However, that same electrifying sensation was not as palpable this year. Perhaps the reason was the timing of the intervening American Society of Clinical Oncology and International Conference on Malignant Lymphoma meetings, in addition to some advisory boards where I saw repeated updates of the data on the novel new agents that have created a tsunami of enthusiasm. Nonetheless, I came home with more questions than answers.

I had eagerly awaited the CLL-10 trial comparing fludarabine-cyclophosphamide-rituximab (FCR) with bendamustine-rituximab (BR) in untreated, fit patients with chronic lymphocytic leukemia (CLL). As might have been predicted, the results were ambiguous, and the interpretation was left to the clinician. It seems as if FCR produces a higher complete response rate and a longer progression-free survival than BR. There is no survival benefit with FCR at this time, however, and toxicity is considerably higher than with BR, especially in older patients. Lengthy discussions with patients about the options will continue.

The combination of obinutuzumab (O) and chlorambucil was superior to that of rituximab (R) and chlorambucil in complete remission rates and progression-free survival. Was this a dose effect, however, or simply the lipstick on the pig phenomenon: that anything can make chlorambucil look better? Indeed, the fludarabine-cyclophosphamide-O data were surprisingly disappointing. So, let us see what happens in a bendamustine-R vs bendamustine-O comparison and then, perhaps, data will emerge that will change my practice.

Despite the success with single-agent ibrutinib, there were little more than updates at ASH, notably the combinations with rituximab and bendamustine. The updated data in patients with Waldenström macroglobulinemia will surely result in a paradigm shift. I did see new and interesting data regarding the PI3K inhibitor idelalisib, notably the late-breaking abstract reporting on the double-blind, placebo-controlled trial in relapsed or refractory CLL where patients were randomized to rituximab and either placebo or idelalisib, with a built-in crossover. Of note were a superior progression-free survival and overall survival in the investigational arm. But then, I had déjà vu all over again. I remembered a time when a series of anthracyclines entered clinical trials in lymphoma, with no good reason why one should be better than any other. Various abstracts regarding new PI3K inhibitors were presented at the lymphoma session, with no good answer to the question of why they should be better than idelalisib, already far more advanced in its clinical development.

In the lymphoma sessions, I was impressed by some of the new data with noncytotoxic chemotherapeutic approaches, including those with rituximab and lenalidomide for follicular lymphoma from the Alliance for Clinical Trials in Oncology. Mantle cell lymphoma has remained a therapeutic challenge since it was first distinguished from other lymphomas in the early 1980s. Physicians have tended to treat younger patients aggressively, with regimens such as rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate and cytarabine (R-hyperCVAD), often followed by autologous stem cell transplantation. The Cornell-led multicenter trial, however, produced impressive results simply with rituximab and lenalidomide as initial treatment. The question of the role of maintenance therapy for follicular lymphoma remains controversial, although studies were presented that provided further support for those of us who do not subscribe to that approach. The Swiss Group for Clinical Cancer Research (SAKK) study comparing 2 vs 5 years of maintenance failed to meet its primary endpoint. An update of the PRIMA (Rituximab Plus Chemotherapy Followed by Maintenance or Observation) trial continued to show an advantage in progression-free survival, still without any survival benefit for maintenance.

Despite our enthusiasm for these novel targeted agents, caution must be exercised, as we are still unaware of the potential long-term complications. The more a drug is used, the more likely an untoward effect will occur. Such was the case with brentuximab vedotin, the remarkable antibody-drug conjugate that is so effective in Hodgkin lymphoma and anaplastic large cell lymphoma; data from ASH showed its activity in other CD30-positive lymphoid malignancies. However, we saw reports at ASH of life-threatening and fatal pancreatitis in patients treated with this agent.

There is still much to be learned about these new agents: their optimal use, mechanisms of resistance, and how best to combine them with other drugs. A large number of studies are ongoing that address these and other issues. I anticipate seeing more exciting data next year in San Francisco at ASH 2014.

Until next month . . .

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