Another Plenary, More Uncertainty

I write this letter 5 days after the 2017 ASH annual meeting. The ASH meeting is always a highlight of the year for hematologists. It is tremendously exhilarating to see the international efforts being made to reduce the suffering caused by hematologic malignancies and benign hematologic disorders. It is also a joy to see friends who have traveled to this meeting from all over the world. The meeting was held in Atlanta, usually a city with easy access, but access was made difficult on this occasion by a Friday snowstorm that closed the Atlanta airport and created a travel nightmare for many. I am not sure that ASH should again choose Atlanta to host the meeting anytime soon. The meeting seems too big for that convention center, with all its bottlenecks. Getting from point A to point B was quite a challenge at times. Attending the president's reception was a thrill, though. It was held in the Mercedes-Benz Stadium, an amazing, brand-new football stadium with a retractable roof.

For the second year in a row, the ASH Plenary Scientific Session left me wondering what to do with the information I had just acquired. Last year, we heard the results from the GALLIUM study, which compared obinutuzumab plus chemotherapy vs rituximab plus chemotherapy in the frontline treatment of follicular lymphoma. A small but statistically significant improvement in PFS was observed in the obinutuzumab arm. Whether obinutuzumab is truly a better anti-CD20 monoclonal antibody in follicular lymphoma remains unclear, however, because the patients in the trial received a significantly higher dose of obinutuzumab than of rituximab. I remain unconvinced that these results represent a true therapeutic advance. Obinutuzumab did receive a frontline indication in follicular lymphoma from the FDA on November 16, and it will be interesting to see what sort of adoption it receives in the United States. I am also curious to see how the national health systems in the United Kingdom and Canada will deal with this issue.

This year, we heard the results of the ECHELON-1 study, a frontline trial for advanced-stage Hodgkin lymphoma. In this international trial, patients were randomly assigned to receive standard ABVD chemotherapy or an experimental regimen that eliminated bleomycin and substituted brentuximab vedotin; the new regimen was termed A-AVD. The logic behind the trial was sound. Bleomycin is the most problematic agent in the ABVD regimen, and its elimination is a worthy goal. Brentuximab vedotin has unprecedented single-agent activity in relapsed/refractory Hodgkin lymphoma, and its incorporation into frontline therapy is also a worthy goal. The trial showed a statistically significant improvement in the modified PFS at 2 years for A-AVD vs ABVD—82% vs 77%. There was no difference in overall survival.

Because the goal of frontline treatment in Hodgkin lymphoma is cure, and because PFS usually correlates well with the cure rate in Hodgkin lymphoma, you may be wondering what the issue is. Give A-AVD, and cure more patients! There are 3 issues making interpretation of the results of this trial less straightforward, however. Issue No. 1: modified PFS counted inability to achieve a CR on PET, plus the initiation of additional treatment, as an event. I wish they had simply chosen a primary endpoint of EFS, which is more traditional, then analyzed the trial by both EFS and conventional PFS. The PFS difference would have been significantly smaller. Issue No. 2: A-AVD adds toxicity. It is more likely to cause neutropenia, requiring growth factor support (which is rarely needed with ABVD), and more likely to cause peripheral neuropathy. In my opinion, grade 2 peripheral neuropathy is a big deal. Issue No. 3: the elimination of bleomycin is already accomplished for approximately 80% of the patient population if one follows the treatment paradigm established in the RATHL study (Johnson and colleagues, *NEJM* 2016). For patients with negative PET results after 2 cycles of ABVD, bleomycin can be eliminated from the subsequent 4 cycles, with a negligible effect on outcomes. Patients with positive PET results in the interim can be triaged to the escalated BEACOPP regimen. The overall population in the RATHL trial had a 3-year PFS of approximately 82%, similar to that of the A-AVD population in ECHELON-1.

So, should one adopt A-AVD as the new standard, or follow the RATHL strategy? I am planning to follow the RATHL strategy for the time being. It will be interesting to see how other practitioners react to these data. Clinical trials do not always provide answers that are crystal clear. That's okay. It's our job to interpret the findings and integrate them into practice.

Until next month …

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