When Will We Beat R-CHOP?

I was joking around with one of my AML colleagues a while back, teasing him about giving 7 + 3 chemotherapy. That recipe has been around for 30-plus years. For lymphoma docs like me, it makes attending on the leukemia service pretty easy. I know 7 + 3. I can explain it to patients. I know what to expect each week of induction therapy. I know when the counts should start to recover. I know when things are going to go bad. It's sad for patients, of course, that the AML field has struggled to move beyond 7 + 3 after all of these years. It's not for lack of effort. There are outstanding people working in this area, and they have tried. AML is a tough nut to crack.

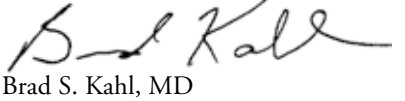
I suppose that by making my dig, I was acting as if the lymphoma docs had somehow cracked the code in diffuse large B-cell lymphoma. My leukemia colleague called me on this, asking, "if not for rituximab, where would you be in DLBCL?" We had been stuck with CHOP for 25 years, curing about 45% of patients, when the field took a quantum leap forward with the addition of rituximab. The "cure rate" jumped by about 15 percentage points overnight. We now expect to cure about 60% of unselected patients with DLBCL. It was a huge advance. The problem is that there has been no additional progress for the past 15 years. We are more than halfway to another 25-year lull. This past ASH meeting was another sobering experience, with 2 high-profile negative studies.

CALGB/Alliance 50303 was a randomized clinical trial, conducted by the US Intergroup, that compared R-CHOP vs dose-adjusted EPOCH-R for previously untreated DLBCL. The rationale for DA-EPOCH-R was solid, with infusional chemotherapy designed to overcome drug resistance and pharmacodynamically guided dose adjustments with each cycle designed to maximize the cell kill. The phase 2 data were strong, suggesting a cure rate close to 80% in a multicenter trial. In the phase 3 trial reported at ASH, 524 patients were randomized over an 8-year period. DA-EPOCH-R demonstrated more myelosuppression, febrile neutropenia, neuropathy, and early discontinuations than R-CHOP. There was no difference between the 2 regimens in efficacy. The event-free survival was approximately 80% in both arms at 3 years. So what happened? The problem was not with the experimental arm, which performed essentially as expected. The problem was with the control arm, which exceeded the study expectations. In retrospective data sets, R-CHOP appears to cure about 60% of patients with unselected DLBCL. In most clinical trials, where the eligibility criteria result in the enrollment of younger, healthier individuals, the cure rate usually comes in at around 70%. The 80% rate observed in CALGB/Alliance 50303 is likely the result of "extreme vetting" of patients by requiring a fresh tumor biopsy before study enrollment. This requirement precluded the sickest patients from enrollment. The statistical projection was for a 55% cure rate with R-CHOP. The correct assumptions would have required a trial twice as large and twice as long, so this was a substantial design flaw.

The other negative DLBCL trial presented at ASH was GOYA. This was a Roche-sponsored, multicenter, international trial comparing R-CHOP vs G-CHOP in previously untreated DLBCL. In this instance, G stands for Gazyva, which is the trade name for obinutuzumab, the novel anti-CD20 agent tested in the GALLIUM trial I discussed last month. In this trial, 1400 patients were enrolled in less than 4 years. Contrast that with the 8 years it took to enroll 500 patients in CALGB/Alliance 50303—a testament to what adequate funding of a trial can do. G-CHOP demonstrated slightly more myelosuppression and infections than R-CHOP, but the difference in toxicity generally was not clinically significant. The 3-year PFS was 70% in both arms. R-CHOP beat back another challenger.

In addition to the 2 trials mentioned above, other recent nonwinning strategies have included upfront stem cell transplant and dose-dense R-CHOP. So where to go from here? Obviously, significant hope rests upon our ability to capitalize on a better understanding of DLBCL biology. We can reliably distinguish among different subtypes of DLBCL by cell-of-origin testing. Ibrutinib and lenalidomide both appear to have preferential activity in the ABC subtype, and RCTs testing these agents with an R-CHOP backbone are underway. In addition, DLBCL with high expression of MYC and BCL-2 (double expressors) and with MYC and BCL-2 rearrangements (formerly known as double-hit DLBCL) will soon be tested with the selective BCL-2 inhibitor venetoclax. There is a saying that persistence pays off. For the sake of our DLBCL patients (and our AML patients), we must persevere.

Until next month . . .



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