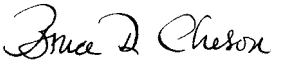
LETTER FROM THE EDITOR

The world is finally changing! For decades, it has been CHOP, m-BACOD, M-BACOD, MACOP-B, VACOP-B, F-MACHOP, EPOCH, CHOEP, ProMACE-MOPP, ProMACE-CytaBOM (alternating, syncopating), and a series of anthracyclines and related agents. Finally, along came rituximab, which changed our world and gave us hope that the boring era of anagrams might be at an end. But, then we suffered through R-CHOP-21 vs R-CHOP-14, and R-CHOP vs R-EPOCH. If there was any take-home message from ASH 2012, it was that the ennui may finally be coming to an end. For years, we and others have been working towards a chemo-free world for patients with hematologic malignancies, and we now have ample evidence that this dream is an impending reality. Look around! There are virtually no chemotherapy agents (save 50-year-old bendamustine) in development for this collection of diseases. Data were presented for patients with acute promyelocytic leukemia suggesting that all-trans-retinoic acid (ATRA) and arsenic might be sufficient for cure, without the dreaded anthracycline or cytarabine. The exquisitely active antibody-drug conjugate (ADC) brentuximab vedotin is not only effective against relapsed and refractory Hodgkin lymphoma and anaplastic large cell lymphoma, but was shown to achieve impressive response rates in other CD30-positive malignancies as well. Current studies are moving this agent into the frontline where it may do its most good, and where it may replace at least part of multi-agent chemotherapy regimens. But, this approach is not limited to these histologic entities. Interesting data were presented for two other ADCs targeting CD22 (DCDT2980s) and CD79b (DCDS4501A), using the same linker and toxin as with brentuximab. Responses were observed not only in indolent lymphoma, but also relapsed and refractory diffuse large B-cell lymphoma. Great excitement was also focused on the internal workings of the malignant cells. The B-cell receptor (BCR), when stimulated, activates a number of downstream pathways that are responsible for lymphoma longevity and resistance to therapy. In both CLL and NHL, indolent, mantle cell, and aggressive, ibrutinib, a Bruton tyrosine kinase inhibitor, was shown to be highly effective, with response rates in the range of what would be expected with chemotherapy. Yet, it is oral with a favorable toxicity profile. The PI3-kinase pathway has been successfully interrupted with the delta-isoform–specific idelalisib (formerly CAL-101 and then GS-1101) in CLL, indolent, and mantle cell lymphomas. And then along comes IPI-145, which inhibits both the delta and gamma isoforms, with preliminary data suggesting promise.

Bill Dameshek, one of the founders of Hematology, once reflected that CLL was not a lymphoproliferative disorder, but was, instead, a lymphoaccumulative disorder. This original concept that the cells were relatively immortal is now understood as a defect in apoptosis, programmed cell death. Subsequent studies identified a number of responsible proteins, notably Bcl-2. At ASH, data on the next-generation proapoptotic ABT-199, which specifically targets Bcl-2, in CLL were the stuff dreams are made of. Finally, we saw the "final" analysis of one study of the lenalidomide/rituximab (R^2) regimen, in which almost all of the previously untreated patients with follicular lymphoma responded. The subsequent study, known as RELEVANCE, is comparing chemo-rituximab head-to-head with R^2, winner take all! In Alliance, we are trying to be prescient and taking the next step with R^2 + ibrutinib as the initial treatment of follicular lymphoma, and R^2 + idelalisib in relapsed follicular and mantle cell lymphomas. A unifying theme here is that all of these drugs are targeted, specific, oral, relatively well tolerated, and, yes, highly effective. Even in mantle cell lymphoma, once one of the more frustrating disorders which remained incurable with intensive anti-leukemia–like strategies and transplant, there are now numerous active drugs. We are well on our way to personalized therapy. The challenge will be to figure out how best to combine these agents in a rational fashion, and, that minor point, getting the various companies to agree to such combinations in the best interest of science and our patients.

I returned from ASH exhilarated, predicting that the meeting had signaled the death knell for cytotoxic treatments. I used to show a slide (in the Kodachrome days) that said, "More isn't better . . . different is better," and things certainly look different.

Until next month . . .



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