Arbitrary vs Rational Treatment

As I write my first post-ASH Letter From the Editor and think back to the amazing advancements seen in the world of hematology, I am struck by two notions. First, the ways in which our treatment regimens are designed have become arbitrary. Second, and very much related to the first point, the focus on combining multiple agents—which may increase the risk for toxicities—often lacks a clear rationale or identified benefit. These two statements certainly do not apply to all regimens and diseases. Many malignancies remain incredibly difficult to treat, and the use of additional agents may afford the only way to improve responses. But in CLL, where we have achieved many successes, we have started to become sloppy.

When ibrutinib and idelalisib were first being investigated, the treatment course was straightforward. Treatment would be continued until disease progression or unacceptable toxicity. This strategy was driven in part by the continuous improvement in response over time. As long as the therapy was well tolerated and controlling the patient's lethal disease, we would need good justification for stopping therapy. All physicians know the adage, "above all else, do no harm." But a second, and perhaps equally important one, is "don't deny patients effective therapies."

Next came venetoclax, which was able to drive deep responses very quickly. With venetoclax, MRD negativity was achievable with less than two years of therapy—an endpoint that was potentially useful as a therapeutic goal.

These developments, which have been paradigm-changing for CLL therapy, have given rise to a new CLL therapeutic landscape. The HELIOS and Gilead 115 studies demonstrated that the addition of ibrutinib and idelalisib, respectively, to standard treatment with BR improved outcomes over treatment with BR alone. Every novel agent was also combined with every anti-CD20 monoclonal antibody, creating an array of new regimens. Venetoclax was combined with rituximab in the MURANO trial and with obinutuzumab in the CLL14 trial, and ibrutinib was combined with rituximab in the FLAIR trial and with obinutuzumab in the iLLUMINATE trial.

What all these trials are missing is an arm to determine whether the drug added to the novel agent provides any greater benefit than that obtained with the novel agent by itself. HELIOS would have been more interesting if it had compared ibrutinib alone vs BR + ibrutinib vs BR alone. Such a study design would have enabled physicians to know whether BR added benefit to ibrutinib. Similarly, if MURANO had tested venetoclax alone vs venetoclax + rituximab vs BR, we would have been able to determine whether rituximab added benefit to venetoclax. For now, we are stuck holding up curves from different trials and trying to determine whether they look similar and overlap. Dr Peter Hillmen did this nicely in a poster he presented at the 2015 ASH annual meeting (Abstract 642). However, it is important to remember that every treatment has potential toxicities, and we really should know whether a benefit is to be gained before we take additional risks.

We are now testing treatment regimens that are of a fixed duration, including rituximab + venetoclax (MURANO), obinutuzumab + venetoclax (CLL14), and ibrutinib + venetoclax (CAPTIVATE). In the early days of chemoimmunotherapy for CLL, our only option was a fixed duration of treatment because of the toxicities that would accumulate with repeated cycles of treatment. We never demonstrated, however, that six cycles of FCR was superior to four cycles. In other diseases, investigators have looked to lessen the amount of chemoimmunotherapy by evaluating PET scans or genetic markers. Now that we are dealing with agents like venetoclax, which has demonstrated excellent tolerability with continued dosing, open-ended treatment is an option. The MURANO and CLL14 trials led to the approval of fixed-duration regimens because they demonstrated outcomes better than those obtained with previously approved regimens, in keeping with FDA practices. But we never determined the best means for using these treatments. Are we harming our patients by discontinuing therapy before the full benefits are obtained? Might our patients' progression-free survival—and most importantly, their overall survival—be better if they remained on therapy?

It becomes extremely important as we investigate new treatment regimens that we go beyond answering the question of whether they are effective, and also answer the question of whether they are the best treatment for our patients. Are we exposing our patients to additional harm without additional benefit by adding more agents? Are we denying our patients benefit by shortening their therapy? The current process for drug approval does not lend itself to determining the optimal treatment. How many of us prescribed chlorambucil to be taken with obinutuzumab when it was first approved on the basis of CLL11? How many of us add obinutuzumab when we prescribe venetoclax to patients with treatment-naive CLL? May we find the answers to these and other important questions in the coming years.

Sincerely,

Richard R. Furman, MD