The Fast-Changing World of CLL

Do you remember when CLL was managed largely with chlorambucil? The big decision was whether to give the agent daily or in pulses every two weeks. It's a different ball game now. Before making therapeutic decisions, one needs to determine cytogenetics with a CLL FISH panel and determine the heavy-chain gene mutational status (mutated vs unmutated *IGHV*). Frontline therapeutic options now include fludarabine/cyclophosphamide/rituximab (FCR), bendamustine/rituximab (BR), obinutuzumab/chlorambucil, and the Bruton tyrosine kinase inhibitor ibrutinib. So how does one decide?

As much as everyone tells us not to factor a patient's age into decision making, I feel that age is a good starting point for choosing regimens. There are exceptions, of course, but age provides a reasonable first approximation of fitness, and many patients with CLL are simply not candidates for FCR therapy. For patients older than 65, FCR is simply too hard on the bone marrow and the immune system.

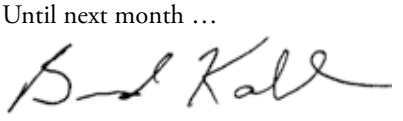
FCR is an option, however, for patients younger than 65 who are fit and healthy. This is where FISH testing and *IGHV* mutation testing are helpful. Several data sets reveal excellent long-term outcomes with FCR therapy as long as patients have mutated *IGHV* and do not have adverse cytogenetics (that is, no deletions in 11q or 17p). Outcomes with FCR are not nearly as good if the patients have unmutated *IGHV*, and ibrutinib can be considered for frontline therapy in these patients. Available data suggest that ibrutinib is equally effective in mutated and unmutated CLL. Ibrutinib, of course, requires a commitment to indefinite therapy, and it is incredibly expensive. Counseling a young, fit patient with CLL about the pros and cons of FCR vs ibrutinib involves a long and complicated discussion. For patients between the ages of 65 and 80, I follow the same logic and algorithm but substitute the BR regimen for FCR. FCR was slightly better than BR for progression-free survival in the German CLL10 trial, but BR performed as well as FCR in patients older than 65 and was less toxic.

For patients older than 80, I typically consider obinutuzumab/chlorambucil. This combination was the winning regimen in the German CLL11 trial and is reasonably well tolerated by older and frail patients. One can certainly consider ibrutinib for patients with CLL who are older or frail, rather than obinutuzumab/chlorambucil. Again, a commitment to indefinite therapy is required. Some of the chronic low-grade toxicities of ibrutinib therapy—such as arthralgias, myalgias, easy bruising and bleeding, and hypertension—can be problematic in the elderly. So again, when the clinician is considering obinutuzumab/chlorambucil vs ibrutinib for an elderly patient, it's a complicated discussion of pros and cons, with no clear-cut "right" answer. However, if a patient has very high-risk disease with a known 17p deletion, decision making is pretty easy. Ibrutinib appears to perform substantially better than any immunochemotherapy option.

In the management of the group of patients with relapsed or refractory CLL, even more considerations come into play. It is certainly worthwhile to repeat FISH testing, given that patients can acquire a 17p clone over time. If a patient with relapsed or refractory disease did not receive ibrutinib in the frontline setting, this is typically the best option. If a patient cannot receive ibrutinib because of a risk for bleeding or some other form of intolerance, idelalisib/rituximab can be considered. Finally, venetoclax, the oral small-molecule BCL2 inhibitor, is FDA-approved for patients with 17p-deleted CLL. Venetoclax has not been compared head-to-head with ibrutinib, but it certainly appears to be just as effective or nearly so. You may have seen the article in the March 22 *New England Journal of Medicine* by John Seymour and colleagues, which compared venetoclax/rituximab with BR in relapsed or refractory CLL. Venetoclax/rituximab beat BR handily, and this will likely lead to a broader label for venetoclax, allowing us to use it in any patient with relapse rather than just patients with 17p-deleted CLL. After the period of risk for tumor lysis syndrome has ended, venetoclax is actually a very well-tolerated drug.

The decision making in CLL has certainly become more complicated, but this is a nice problem to have.

Until next month …



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