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Cure for CLL?

Farrukh T. Awan THE OHIO STATE UNIVERSITY

In this issue of *Blood*, Thompson et al present their exciting long-term results with the use of fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukemia (CLL).[1]

Combination chemoimmunotherapy has been an established and effective therapeutic modality for patients with CLL. In an effort to enhance efficacy while limiting toxicity, multiple iterations of chemoimmunotherapy have been developed for CLL with varying success over the last decade. FCR is considered the standard-of-care regimen for younger patients with good performance status and limited comorbid conditions. Earlier results from the same study (FCR300) were critical in establishing FCR as the leading CLL therapeutic option when it reported an overall response rate of 95% with 72% complete responses and a median progression-free survival (PFS) of 6 years.[2] The FCR300 and subsequent larger phase 3 studies confirmed the efficacy and further established the role of FCR. However, concerns remained about patient tolerability, toxicities, and secondary malignancies with the use of FCR. Multiple studies and analyses were performed both in patients with previously untreated or treated disease that identified specific groups of patients for whom FCR may not be an ideal option.[3] These included patients older than 65 years of age, patients with compromised renal function and multiple comorbid conditions, and patients with high-risk del17p disease. These factors have limited the extensive use of FCR because almost 70% of the patients diagnosed in the United States are older than 65 years of age and frequently present with coexistent medical issues.

In the current study, Thompson et al detail long-term results with the use of FCR. They confirm earlier findings that unmutated *IGHV* status and del17p predict for inferior PFS, along with the presence of bone marrow minimal residual disease (MRD) at the completion of therapy and a β2-microglobulin ≥4 for patients with the mutated immunoglobulin heavy chain variable (*IGHV*) region. Most importantly, FCR results in prolonged and sustained remissions in patients with mutated *IGHV*. No relapses were observed in this group of patients beyond 7 years, if they had not relapsed prior to that time, and were MRD-negative at the completion of therapy, and beyond 10 years if they were MRD-positive. MRD status was also predictive of overall survival in patients with mutated *IGHV* but not in patients with unmutated *IGHV* who had inferior outcomes, along with patients ≥65 years of age and those with β2-microglobulin ≥4 and del17p disease. These long-term disease-free states raise the tantalizing possibility of cures for around 80% of patients with mutated *IGHV* who achieve MRD-negative status in the bone marrow after FCR, and around 40% of patients who fail to achieve MRD negativity.

This represents the first time in the history of CLL that a nontransplant therapeutic option has resulted in sustained disease-free intervals and raises the possibility of a cure for a subset of patients with generally good-risk disease and excellent response to therapy. FCR use does come at a price though, with poor overall tolerability and outcomes in patients ≥65 years of age and with >30% of the patients experiencing grade 2-4 neutropenia that is sustained for >9 months in >10%. This results in a significant increase in infectious complications in these patients. FCR is also associated with an almost 6% to 10% incidence of secondary hematologic malignancies especially myelodysplastic syndromes and acute myeloid leukemia.[3] Moreover, in this cohort of previously untreated patients, ~8% of the patients developed Richter transformation. Considering all of these issues, a very strong argument can be made that despite all of the issues associated with FCR, a percentage of patients who can be treated with it experience prolonged remissions, and may even be cured of their CLL. Although this is an extremely attractive option for some patients, the advent of kinase inhibitors and early data reported with their use in patients with previously untreated disease are exceptionally promising.[4,5] Though kinase inhibitors may not be able to effect a cure, they have the potential to effectively transform the management of patients with CLL, commensurate with the management of patients with chronic myeloid leukemia or other chronic illnesses. Various combination strategies have demonstrated improvement in the depth of responses, and survival outcomes are already being compared in ongoing large randomized multicenter trials; however, these have to be balanced with regards to patient preference, therapeutic burden, quality of life, cost, and their presumptive integration into a normative CLL social matrix.

These are the best of times and these are the worst of times. The advent of novel therapeutic options and the excitement surrounding them is well justified, but wisdom decrees deliberate and thoughtful evaluation of the existing and evolving evidence and advocating patient prosperity in this spring of hope for CLL.

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