Frontline Therapy for Chronic Lymphocytic Leukemia: The Dilemma Continues

To the Editor: I would like to congratulate Bosch and colleagues on a well-conducted clinical investigation confirming the activity of the FCM (fludarabine, cyclophosphamide, and mitoxantrone) program in previously untreated chronic lymphocytic leukemia (1). Bosch and colleagues reported that FCM provides an overall response rate of 90% with a complete response of 64%. In addition, using a highly sensitive four-color flow cytometry assay, minimal residual disease—negative remissions were attained in 26% of patients. Median duration of response was 37 months and 70% of patients remained alive at 4 years.

Where does this report leave us? Does FCM substitute chemoimmunotherapy, the approach that has been widely adapted and accepted by U.S. investigators as the standard approach? I believe that it is timely that we look carefully and critically into our frontline chronic lymphocytic leukemia therapies to move forward.

It is essential to make our treatment decisions and recommendations based on the best evidence-based medicine. In that regard, the FCM is simply another phase II trial that is yet to be put to the test of rigorous prospective phase III randomized studies. Many other phase II studies have been investigated in chronic lymphocytic leukemia, but chemoimmunotherapy regimens became more popularized. The FCR (fludarabine, cyclophosphamide, and rituximab) and the PCR (pentostatin, cyclophosphamide, and rituximab) programs are phase II studies that have produced impressive results as single-institution trials (2, 3). Both programs showed over 90% overall response rate with FCR showing a more robust complete response compared with PCR. Chemoimmunotherapy regimens, however, have not been compared with chemotherapy alone. The suggestion that chemoimmunotherapy might be superior to chemotherapy alone was proposed by Byrd et al. (4) when a retrospective analysis of two separate Cancer and Leukemia Group B studies suggested that the addition of rituximab might improve the outcome of chronic lymphocytic leukemia patients when added to fludarabine. Such combination, however, was never compared with fludarabine alone in a prospective manner. The claim that one regimen is superior to another by its ability to eradicate minimal residual disease is refuted by the fact that minimal residual disease detection methods were not standardized among these studies. At the end, changing our patterns of practice and care should never be based on single-institution phase II studies.

The only combination program that has shown superiority to fludarabine alone was the FC regimen, which combines fludarabine and cyclophosphamide. The better efficacy of FC over fludarabine alone was reproduced by three separate groups across the Atlantic (5–7). Nonetheless, investigators across the board continue to advocate chemoimmunotherapy as an approach ignoring the lack of phase III data and forgetting that cost-effective analysis is important as it would avoid the use of unnecessary expensive compounds.

Adding more phase II studies would not help advancing this field forward, and until a regimen shows a true superiority over the FC program, FC should remain the standard arm against which experimental arms are compared. Chemoimmunotherapy use remains investigational despite its popularity.

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References


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