

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Chemoimmunotherapy in Chronic Lymphocytic Leukemia

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H&O What characteristics predict outcome in chronic lymphocytic leukemia (CLL)?

SS CLL is usually a disease of the elderly, but approximately a quarter of patients are younger than 60 years. The disease follows a variable clinical course; some patients have stable disease, but in others, the disease progresses rapidly and the prognosis is highly variable. In recent years, several clinical and biologic prognostic markers have been identified that can be used to assess risk in CLL patients. Among the most important clinical characteristics are age, physical fitness, and disease stage. Biologic factors include serum markers such as beta-2 microglobulin and thymidine kinase, and genetic markers of the leukemia cells, such as the mutational status of the variable immunoglobulin genes (IGHV) and genomic abnormalities.

H&O How effective are the current treatment approaches for CLL?

SS Treatment approaches for CLL have been largely based on chemotherapy. Recently, chemotherapy has been combined with biologic agents, mostly monoclonal antibodies. Chemotherapy alone cannot cure CLL, but it can palliate symptoms. Chemotherapy agents include chlorambucil, fludarabine, and fludarabine-based combinations, such as fludarabine plus cyclophosphamide (FC). Another option is bendamustine (Treanda, Cephalon), which was approved by the US Food and Drug Administration (FDA) in 2008 for use in CLL. Treatment of CLL has dramatically improved with the addition of monoclonal antibodies to chemotherapeutic

regimens—in particular, use of the monoclonal antibody rituximab (Rituxan, Genentech/Roche) against the CD20 antigen. Other antibodies include alemtuzumab (Campath, Genzyme), which is directed against CD52. Other novel CD20 antibodies include ofatumumab (Arzerra, GlaxoSmithKline), which is approved for patients refractory to fludarabine and alemtuzumab, and GA-101 (obinutuzumab; Roche/GlycArt/Genentech), which is not yet FDA-approved.

H&O What have phase II studies suggested about the addition of the monoclonal antibody rituximab to first-line chemotherapy with FC in CLL?

SS In the first-line setting, the chemoimmunotherapy regimen of FC plus rituximab (FCR) markedly improved response rates up to 95%, with a complete response rate of up to 70%. These responses, as well as the response duration, have been better than those achieved in previous studies in CLL. In a historical comparison from M.D. Anderson Cancer Center, data suggested that the overall survival of CLL patients may be improved by treatment with FCR.

H&O What were the study design and results of the phase III CLL8 trial?

SS The CLL8 study of the German CLL study group compared FC against FCR in the first-line treatment of CLL patients. This trial accrued physically fit CLL patients. The other eligibility criteria included patients with active disease according to the guidelines. The trial was a randomized comparison, 1 to 1, of FC against FCR at the usual dosing regimen used in phase II trials. The trial accrued 817 patients overall.

Most importantly, the study showed that the FCR regimen improved not only overall response rate (ORR), complete response, and progression-free survival (PFS),

but also overall survival (OS). This trial is the first randomized comparison in CLL to show that a specific first-line treatment led to significantly improved OS. This trial is expected to lead to a practice change in the treatment of physically fit patients with CLL.

H&O Were adverse reactions a concern?

SS The adverse reactions in the CLL8 trial were mostly the expected ones; hematologic toxicities were the most common. These reactions were somewhat increased in the FCR treatment arm. Grade 3/4 neutropenia, for example, was observed in about one third of patients. Of more importance, however, was that the rate of grade 3/4 infections was not significantly increased in the FCR arm. The rate of grade 3/4 infections was 25% in the FCR arm, which is similar to rates seen with chemotherapy alone. No unexpected adverse reactions or atypical infections were observed. Importantly, infusion reactions with rituximab occurred at a very low rate and were manageable with the usual premedication. Overall, FCR was a well-tolerated treatment that had no unexpected or dramatically increased side effects as compared with chemotherapy alone.

H&O How did response to treatment vary across subgroups?

SS Improvement was most notable in patients with Binet stage A or B disease, and there was also improvement in stage C patients. The prognosis of patients with unmutated IGHV genes was improved. Patients with 11q deletion experienced improved prognosis, with a tripled complete response rate, as well as improvement in PFS and OS.

There was an improvement seen across all genetic subgroups except the most problematic one—patients with 17p deletion or TP53 deletion. These patients are characterized by a very poor prognosis, which was only

modestly changed with the FCR regimen. These patients had a very poor response rate; only 1 of 21 achieved a complete response. PFS and overall survival were short and not much improved in the FCR patients compared to the FC patients. This trial confirms other studies showing that patients with the 17p deletion are very problematic. Alternative treatment approaches should be investigated in clinical trials. Elevated serum markers, such as beta-2 microglobulin and thymidine kinase, were associated with an inferior outcome, but this result was not very different across specific subgroups.

H&O What is the clinical significance of this trial?

SS The CLL8 trial is the first to show marked and very significant improvement not only in response and PFS but also in OS. The trial indicates that the choice of a particular type of first-line treatment can change the natural course of the disease. Rituximab combined with chemotherapy should be the therapy of choice for physically fit patients with CLL.

Problematic subgroups of patients remain, namely patients with 17p deletions or T53 deletion/mutation. These patients are candidates for alternative treatment approaches. They should be considered for allogeneic stem cell transplantation when a remission is achieved.

Suggested Readings

Hallek M, Fischer K, Fingerle-Rowson G, et al; for the German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376:1164-1174.

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Parikh SA, Wierda WG, Badoux X, et al. Comparison of fludarabine (F) plus cyclophosphamide (C) versus FC plus rituximab (R) in previously untreated Rai stage III/IV chronic lymphocytic leukemia (CLL). *J Clin Oncol* (ASCO Annual Proceedings). 2010;28(15S). Abstract 6519.