

ADVANCES IN LLM

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The Evolving Role of Chemoimmunotherapy in Chronic Lymphocytic Leukemia



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H&O What has been the traditional role of chemoimmunotherapy in patients with CLL?

NL Traditionally, chemoimmunotherapy was the standard approach in both the frontline and relapsed settings of chronic lymphocytic leukemia (CLL). Common examples of chemoimmunotherapy regimens include fludarabine/cyclophosphamide/rituximab (Rituxan, Genentech/Biogen; FCR) and bendamustine (Treanda, Teva)/rituximab. The immunotherapy component usually consists of rituximab or another monoclonal antibody. After completing a course of therapy, patients undergo monitoring for the development of recurrent cytopenias or bulky adenopathy. Retreatment can consist of the original regimen if the first response duration lasted a long time, from 5 to 10 years. If the remission lasted just a few months to a few years, then a different chemoimmunotherapy program is typically chosen.

Part of the challenge of treatment with chemoimmunotherapy is the need to consider the patient's age and comorbidities. There are scoring systems to help predict whether a patient can tolerate a more aggressive chemoimmunotherapy approach, but treatment choice is typically an intuitive decision based on the patient's comorbidities. As patients with CLL age, they develop more comorbidities, such as renal dysfunction, which can complicate treatment with chemoimmunotherapy. Older patients, particularly those who are frail or have poor renal function, are unlikely to tolerate FCR. We are

therefore always searching for alternative choices in this patient population, and good options include bendamustine/rituximab, chlorambucil-based antibody combinations, or dose-reduced chemoimmunotherapy programs.

H&O What are some recent drug approvals in CLL?

NL The recent approval of several new agents has led to a shift away from chemoimmunotherapy. Ibrutinib (Imbruvica, Pharmacyclics/Janssen) and idelalisib (Zydelig, Gilead) target specific kinases in the B-cell receptor pathway. Venetoclax (Venclexta, AbbVie/Genentech) is a BCL-2 inhibitor that was recently approved for previously treated patients with the 17p deletion. These novel agents are frequently being used in patients who relapse after an initial course of some form of chemoimmunotherapy. Ibrutinib, however, is also approved in the frontline setting.

H&O What considerations inform the selection of chemoimmunotherapy vs targeted therapy in the frontline setting?

NL There is still an appropriate role for chemoimmunotherapy, although it is diminishing. For example, patients who are more physically fit might be candidates for FCR. The German CLL Study Group CLL8 trial (Fludarabine and Cyclophosphamide With or Without Rituximab in

Patients With Previously Untreated Chronic B-Cell Lymphocytic Leukemia) evaluated fludarabine/cyclophosphamide, with or without rituximab, as frontline treatment in physically fit patients. At a median follow-up of 5.9 years, the median progression-free survival (PFS) was 56.8 months for FCR vs 32.9 months for fludarabine/cyclophosphamide ($P < .001$). Median overall survival was not reached for the FCR arm vs 86.0 months for the fludarabine/cyclophosphamide arm. This improvement was maintained in all cytogenetic subgroups, with the exception of patients with the 17p deletion.

Thompson and colleagues from MD Anderson Cancer Center recently published data showing long-term remission in a subset of patients treated in an earlier trial of FCR. Among patients with the immunoglobulin heavy chain variable (*IGHV*) mutation, there was a plateau in PFS. The percentage of patients who maintained PFS at 12.8 years was 53.9% in the *IGHV*-mutated group vs 8.9% in the *IGHV*-unmutated group. Therefore, when I see patients with this particular favorable prognostic profile who are otherwise candidates for FCR, these data are discussed. I inform these patients that the biology of their disease is so favorable that FCR should work well. One could argue, however, that their biology is so good that an oral agent, such as ibrutinib, might yield similar long-term results. (We do not yet know for certain because long-term data [>10 years] for these novel agents are lacking.) A decision about therapy with FCR or an alternative, such as bendamustine/rituximab, vs a novel agent, such as ibrutinib, is then made based on patient preference and other factors. Considerations include the use of short-term therapy (FCR for 6 months) vs long-term or chronic oral therapy (ie, treatment with novel agents). In addition, the potential economic implications of chronic oral therapy may be a barrier for some patients.

H&O What is the significance of the 17p deletion?

NL We have learned that patients with poor prognostic markers, such as 17p (p53) deletion, have a very brief duration of response with chemoimmunotherapy. Patients with the 17p deletion respond well, however, to ibrutinib, idelalisib, and other novel oral agents. These patients achieve a much longer duration of response, as well as improved PFS, when treated with these novel agents as compared with traditional chemoimmunotherapy. Data showing that these therapies improved outcome among patients with the 17p deletion led to the initial approval of ibrutinib in this setting, as well as to the more recent approval of venetoclax. Therefore, patients with 17p deletion who have not yet been treated should receive a novel agent, such as ibrutinib, over chemoimmunotherapy. If they have received treatment already with chemoim-

munotherapy and then relapse, they can receive a novel regimen, such as ibrutinib, idelalisib and rituximab, or venetoclax.

H&O What is known about how to treat patients with relapsed disease?

NL In the relapsed setting, the choice of treatment will be based on the patient's initial course of therapy, the types of side effects he or she experienced, tolerability, and response duration. Most patients in relapse have been treated with multiple chemoimmunotherapy regimens up front because it has been the standard of care for so long. These patients are multiply relapsed. For them, it is a natural fit to utilize a novel agent.

A smaller group of patients have received upfront treatment with one of the novel therapies, and were intolerant to it or developed relapsed disease. If a patient is treated with a novel agent up front and then relapses, the choices include chemoimmunotherapy or another novel agent. If the second novel agent targets the same pathway as the first, the patient can still achieve a response, albeit a shorter one, as suggested by emerging data from Mato and colleagues. It may be preferable to use a second novel therapy with a different target. Data are still lacking regarding the utility of salvage chemoimmunotherapy after a patient has relapsed on a novel agent up front.

Clinical trials evaluating novel agents in the upfront setting should provide some insight into the best way to sequence treatment in the near future. Can first-line treatment with a new oral inhibitor be followed by chemoimmunotherapy? We have experience with the reverse: initial treatment with chemoimmunotherapy followed by the oral inhibitors, which seems to work well. But now that patients are receiving some of these novel agents up front, what happens when they require salvage therapy? Is there a proper way to sequence the new drugs and the chemoimmunotherapy regimens? It will be challenging to find an answer, as it will require a clinical study in which all patients are treated in sequence with the same regimens. Currently, the population has a varied treatment history.

As the newer therapies move to frontline treatment, there may be a larger role for chemoimmunotherapy in relapsed disease. An exception may be patients who enroll in a clinical trial with a novel targeted therapy still in development. In the community, however, if a patient is treated with novel agents up front and is intolerant to these agents or relapses and develops progressive disease, then many physicians will likely prescribe a chemoimmunotherapy regimen such as bendamustine/rituximab or a monoclonal antibody if the patient is older and frail with multiple comorbidities.

H&O What are some new areas of research?

NL Several trials are combining novel agents (such as ibrutinib and venetoclax) with each other or with other chemoimmunotherapies or monoclonal antibodies. Researchers are trying to determine via clinical trials whether it is possible to safely combine novel agents with chemoimmunotherapy and how best to sequence these therapies. Several trials will also be evaluating the role of minimal residual disease (MRD) and whether patients who achieve MRD negativity can truncate treatment on oral therapy (vs the current approach, in which these oral agents are continued indefinitely). In addition, the role of chimeric antigen receptor (CAR) T-cell therapy will continue to be explored. There are also several second-generation formulations of the already approved novel therapies, which aim to improve upon the side effect profiles. Finally, there are always new therapies that are in development since none of the existing treatments are curative as of yet.

Disclosure

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Suggested Readings

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