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Does FCR Have the Potential to Cure a Subgroup of Patients With Chronic Lymphocytic Leukemia?

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H&O When is first-line treatment initiated in patients with CLL?

WW In chronic lymphocytic leukemia (CLL), patients should meet a standard criteria to initiate treatment. For the most part, patients with CLL are diagnosed when their disease is not active; they have no symptoms and have not developed anemia or thrombocytopenia. The diagnosis typically follows an incidental finding of an elevated white blood cell count on a routine blood test. We usually monitor these patients until they demonstrate some evidence of active disease. Trials from many years ago showed no benefit with early treatment vs watch and wait until active disease develops.

Treatment is indicated when the disease is active, with clinically significant and progressive disease-related symptoms. The major symptoms are fatigue and night sweats. Others include unintentional weight loss and fever without evidence of infection. For me, symptoms must impact the patient's quality of life to be an indication to start treatment. Other indications include progressive anemia, with a hemoglobin level of 10 g/dL or 11 g/dL, and progressive thrombocytopenia, with a platelet count of 100,000/μL. There are some exceptions, but in general, these are the criteria for initiation of first-line treatment.

H&O Why is the appropriate selection of first-line treatment important?

WW The selection of the best first-line treatment for patients is important for several reasons. The first treatment provides the best opportunity to manage the disease. Treatment-naive patients are typically sensitive to whatever agent they receive. First-line is the best opportunity to use the most effective treatment to achieve a deep remission and then discontinue therapy with the expectation of a long treatment-free interval. This principle applies to chemoimmunotherapy (CIT)-based treatment, such as fludarabine, cyclophosphamide, and rituximab (FCR). With small-molecule inhibitor therapies, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen), the goal is not a deep remission, but rather durable long-term disease control. First-line use of ibrutinib leads to longer disease control and remission duration compared with the use of ibrutinib in the relapsed setting, but requires continuous and indefinite treatment.

H&O What patient characteristics impact the selection of first-line treatment in CLL?

WW In CLL, there are patient factors and characteristics that drive selection of treatment. Before initiating therapy, it is important to determine whether a patient has a 17p deletion (del[17p]), which refers to loss of the short arm of chromosome 17, or a mutation in *TP53*, the gene that is located on the short arm of chromosome 17. In patients with any of these characteristics, chemotherapy does not lead to durable responses and is therefore not used. Fortunately, these features are uncommon in treatment-naive patients who have not received any prior treatment. They are more common in treated patients who develop recurrent disease. It is therefore important to check for these

features not only before first-line therapy, but also before initiation of therapy for relapsed disease. For patients who have del(17p) or mutated *TP53*, first-line therapy is with a Bruton tyrosine kinase (BTK) inhibitor; CIT is contraindicated for these patients.

Other important characteristics include the patient's age, comorbidities, and fitness level. Patients who are older than 65 years and those with comorbidities do not tolerate the most effective chemotherapy regimen, FCR. For these patients, a BTK inhibitor would be the indicated first-line treatment, regardless of other characteristics. Recent phase 3 trials of these patients demonstrated improved progression-free survival (PFS) with ibrutinib-based treatment compared with CIT, including less intensive regimens than FCR.

In younger patients, it is important to evaluate the immunoglobulin heavy-chain variable region (*IGHV*) gene sequence and mutation status. Patients with a mutated *IGHV* gene who can tolerate treatment with FCR have the best and most durable response to this therapy. Long-term follow-up data from MD Anderson, the German CLL study group, and an Italian multi-institutional analysis showed that treatment with FCR among patients who are young and fit and who have mutated *IGHV* leads to a PFS exceeding 10 years in approximately 55%. This group of patients might be considered cured. Therefore, I recommend first-line FCR for patients who are fit, have no comorbidities, do not have del(17p) or mutated *TP53*, and have a mutated *IGHV* gene.

Among the CIT regimens, only FCR has been associated with these long-term benefits. A plateau on the PFS curve was not seen with the combination of bendamustine (Bendeka, Teva) plus rituximab (Rituxan, Genentech/Biogen). I do not recommend bendamustine/rituximab (BR) for this population when the intent is to achieve long-term PFS.

In younger, fit patients who have an unmutated *IGHV* gene, FCR or BR may lead to a remission, but patients will eventually relapse. My first-line preference for these patients is BTK inhibitor–based therapy, particularly ibrutinib. Data from the E-1912 trial, presented in 2018 at the American Society of Hematology (ASH) meeting, showed that ibrutinib improved PFS in these patients.

To summarize, for the most part, I use ibrutinib-based therapy in the first-line setting for all patients, except those who are young, fit, have a mutated *IGHV* gene, do not have del(17p) or mutated *TP53*, and can tolerate CIT. For these patients, I use FCR. Recent randomized trials have also shown that younger patients have improvement in PFS with ibrutinib-based therapy; FCR, BR, and chlorambucil/obinutuzumab are options, although the disease will come back and need to be retreated.

H&O How do treatment goals impact the selection of first-line therapy for patients with CLL?

WW It is important to discuss treatment goals with the patient. These goals can differ across providers. If the short-term goal is to obtain a remission and discontinue treatment for some period, with the expectation that retreatment will be needed after relapse, then a CIT-based strategy is reasonable. Some CIT regimens, such as BR and chlorambucil/obinutuzumab, are better tolerated by older patients. Patients with unmutated *IGHV* are expected to relapse following CIT. At the 2018 ASH meeting, 3 presentations compared CIT regimens vs ibrutinib-based therapy. All of the trials showed improvement in PFS with ibrutinib-based therapy over CIT. The challenge is that ibrutinib-based therapy is continuous and indefinite treatment. Toxicities are an additional consideration.

H&O What are the typical response rates with FCR?

WW With FCR, the rates of complete remission across several different trials were 50% to 70%. It is thought that patients need to achieve a complete remission to achieve long-term disease control. Among the subgroup of patients with a mutated *IGHV* gene, our data have shown that approximately 55% are progression-free longer than 10 years. Many in the field think that these patients may potentially be cured by FCR.

H&O What options are available for patients who require treatment after FCR?

WW There are 2 main options: ibrutinib and venetoclax (Venclexta, AbbVie/Genentech). For a small group of patients, FCR might be used again. This group includes patients who achieved a long first remission—between 7 to 10 years—and are now hoping to achieve a deep remission with time off treatment. When considering retreatment with FCR, it is necessary to check whether the patient has developed del(17p) or mutated *TP53*.

In most patients treated with FCR, the disease will relapse within 5 to 7 years. These patients have 2 treatment options, both supported by randomized data. The use of ibrutinib in this setting is based on the phase 3 RESONATE trial (A Phase 3 Study of Ibrutinib [PCI-32765] Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia), which compared ibrutinib vs ofatumumab in the relapsed setting. The trial showed durable long-term disease control with ibrutinib. The median PFS was not reached. However, phase 1b studies have shown a median PFS of approximately 51 months with ibrutinib monotherapy in the relapsed

setting. Ibrutinib is effective in patients who have del(17p) or mutated *TP53*. In the relapsed setting, these patients have a shorter PFS of approximately 28 months.

The other treatment option is venetoclax-based therapy, particularly venetoclax plus rituximab. Venetoclax is an oral BCL-2 small-molecule inhibitor. It is a potent inducer of apoptosis in CLL cells. The randomized MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL]) compared venetoclax vs bendamustine, both with rituximab. There was improvement in PFS among patients treated with venetoclax/rituximab; the median PFS was not reached for this group. In contrast to ibrutinib, the treatment duration of venetoclax is limited to 2 years, given with 6 monthly doses of rituximab. Venetoclax also works in patients with the del(17p) and mutated *TP53*. A trial of venetoclax monotherapy showed an estimated median PFS of 28 months, which is similar to that seen with ibrutinib in patients with similar characteristics. This PFS in relapsed patients with the del(17p) is better than that seen with the CIT regimens used before the advent of the small-molecule inhibitor targeted therapies.

H&O Can FCR be combined with newer therapies?

WW A trial from MD Anderson Cancer Center, reported at the 2018 ASH meeting, evaluated a modification of the FCR regimen as first-line treatment for fit patients with mutated *IGHV*. The research and therapeutic goals are to improve outcomes for patients. Patients who do best with FCR-based treatment are those who are young, fit, and have a mutated *IGHV* gene. The standard FCR regimen is given for 6 cycles. This trial evaluated 3 cycles of FC. We wanted to reduce the amount of chemotherapy because of the associated risk of myelodysplastic syndrome and acute myeloid leukemia. We combined this regimen with 1 year of continuous ibrutinib. We replaced the rituximab with obinutuzumab and gave 6 to 12 cycles, depending on the patient's minimal residual disease status after the first 3 cycles. The results were encouraging, and the regimen was safe. Follow-up is continuing.

Other clinical trials have added small-molecule inhibitors to FCR-based therapy. For example, a study from the Dana-Farber Cancer Institute combined standard-dose FCR with ibrutinib in the first-line setting. The response rates were encouraging. The trial did not select patients according to *IGHV* mutation status, and ibrutinib was given continuously and indefinitely. The strategy at MD Anderson Cancer Center was targeted toward the patients who benefit the most from FCR-based therapy. We are using combinations of small-molecule inhibitors in our trials of patients who have the unmutated *IGHV* gene and in others for whom FCR is not the best option.

H&O Do you think that the use of FCR in CLL will evolve?

WW The current clinical trials of FCR-based regimens combined with small-molecule inhibitors will show whether similar results can be achieved with targeted therapy combinations vs CIT-based combinations. What happens with FCR in the long-term will depend on the quality of remissions achieved with the small-molecule inhibitor combinations (without chemotherapy), and whether they match or improve the quality of remissions seen with FCR-based therapy. Because there is a group of patients who benefit from FCR-based therapy—with the potential for a cure—we have been reluctant to abandon this strategy. It is not yet known whether the new small-molecule inhibitor combinations will offer the same long-term benefit for that group of patients as is seen with FCR-based therapy. We will continue to work with FCR-based regimens with the intent of minimizing exposure to chemotherapy while improving responses among appropriate patients.

Disclosure

Dr Wierda has no conflicts of interest to report.

Suggested Readings

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