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First-line therapy for young patients with CLL

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A 61-year-old man with a history of chronic lymphocytic leukemia (CLL) presents with complaints of worsening fatigue and night sweats. He was diagnosed with CLL 3 years ago on routine blood count testing. He has no major medical comorbidities. On examination, he has several 2- to 3-cm lymph nodes in the cervical and axillary area. Spleen is palpable 5 cm below the costal margin. Blood counts show lymphocytosis with thrombocytopenia and anemia. Prognostic markers include deletion 13q by fluorescence in situ hybridization analysis and mutated *IGHV*. You are asked by the hematology fellow you are supervising about the best treatment of this patient.

Learning Objectives

- To understand the role of chemoimmunotherapy in the management of young patients with CLL
- To understand the role of novel targeted therapies in this patient population
- To recognize the emerging role of *IGHV* mutation status in treatment selection for these patients

Therapy options for patients with chronic lymphocytic leukemia (CLL) have undergone a remarkable evolution in the last several years.[1] Though chemoimmunotherapy (CIT) has been the standard first-line option for young fit patients with CLL, the overall role of CIT in the management of patients with CLL is diminishing with an increasing role for targeted therapies. Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, has shown remarkable clinical activity in patients with CLL, and is currently approved for patients with CLL, both for previously untreated, and for patients with relapsed disease. Idelalisib, a phosphatidylinositol 3-kinase (P13K) kinase inhibitor, is approved in combination with rituximab for patients with relapsed CLL. Venetoclax, a BCL-2 inhibitor, was recently approved for patients with relapsed CLL with deletion 17p. Several other agents are in clinical development and will likely further enhance the therapeutic armamentarium. Early trials with these targeted therapies were conducted in relapsed/refractory patients; these drugs are now being explored in the first-line setting in several trials, including in "young fit" patients (the patient in the scenario in the Abstract).

The definition of "young fit" (ie, those eligible for intensive CIT) varies.[2] In the United States, age is most commonly used to identify patients eligible for intensive CIT, with patients younger than 65 years of age typically offered CIT as first-line therapy. The German CLL Study Group (GCLLSG) has used comorbidity index (Cumulative Illness Rating Scale [CIRS]) and renal function to identify CIT-eligible patients (CIRS $\leq$6 and creatinine clearance $\geq$70 mL per minute).[3] CIT has been the standard therapy for this group of patients; however, ibrutinib is currently approved for all patients with CLL, including young fit patients with CLL who would otherwise be eligible for CIT. This poses a question about the appropriate therapy for this group of patients.

Chemoimmunotherapy

CIT, such as with fludarabine, cyclophosphamide (FC), rituximab (FCR), has been the standard therapy for CLL (Table 1). In a single-center report from the MD Anderson Cancer Center (MDACC), a complete response (CR) rate of 72% was noted with a median progression-free survival (PFS) of 77 months.[4-6] Subsequently, the GCLLSG conducted a randomized study of FC vs FCR (CLL8 trial), showing superiority of FCR over FC, establishing FCR as the standard of care in young fit patients with CLL.[7] In the FCR arm of this trial, the CR rate was noted to be 44% with a median PFS of 52 months.

Bendamustine in combination with rituximab (BR) has also been studied in the first-line setting[8]; however, in the GCLLSG CLL 10 trial, a randomized study of FCR vs BR in the first-line setting, the FCR arm produced a superior median PFS (55.2 months vs 41.7 months for the BR arm, $P = .0003$).[9] Based on these data, FCR remains the preferred CIT option for patients with CLL. Besides FCR and BR, several other CIT combinations have been explored; however, none of these regimens have been compared directly to the standard FCR regimen, and do not appear to be superior based on the reported phase 2 data.[2]

It is important to note that the outcomes of patients with deletion 17p or *TP53* mutation remain dismal with CIT, with a median PFS of $<$12 months[5]; therefore, targeted therapies (described in the next section) are the standard first-line choice for this group of patients.

Targeted therapies

The last few years have seen a tremendous growth in the development of novel therapies for patients with CLL.[1] The major therapeutic agents include BTK inhibitors (such as ibrutinib, acalabrutinib), PI3K inhibitors (such as idelalisib, duvelisib, TGR1202), and BCL2 inhibitors (venetoclax). Obinutuzumab, a type II CD20 monoclonal antibody, has been shown to be superior to rituximab,

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Table 1. First-line treatment trials/series in "young fit" CLL

Regimen	Trial	No. of patients	Median age, y	CR %	ORR %	Median PFS, mo	PFS in mutated *IGHV*	PFS in unmutated *IGHV*
FCR	MDACC[4-6]	300	57	72	95	77	80% at 5 y 55% at 10 y	45% at 5 y 10% at 10 y
	GCLLSG CLL8[7,18]	408	61	44	90	52	67% at 5 y	33% at 5 y
	GCLLSG CLL10[9]	282	61	40	95	55	75% at 4 y	45% at 4 y
	Italian retrospective series[19]	404	—	—	—	55	60% at 5 y	35% at 5 y
BR	GCLLSG CLL10[9]	279	62	31	96	42	65% at 4 y	25% at 4 y

—, not reported; ORR, overall response rate.

when combined with chlorambucil (CLL11 trial), as first-line therapy in older adults.[10] Of the newer targeted therapies, at present, only ibrutinib is approved for first-line treatment of patients with CLL.

Ibrutinib is an oral, selective, and irreversible inhibitor of BTK. It forms a bond with the cysteine-481 of BTK.[11] Ibrutinib has shown activity in both the relapsed and front-line settings. Byrd et al reported data from the phase 3 trial in patients with relapsed CLL wherein patients were randomized to receive ibrutinib vs ofatumumab (RESONATE trial).[12] The ibrutinib arm resulted in a significantly higher response rate, as well as longer PFS and overall survival (OS) as compared with that seen in the ofatumumab arm. Burger et al reported results from a phase 3 trial of ibrutinib in older adults (≥65 years) with previously untreated CLL (RESONATE 2 trial).[13] A total of 269 patients were randomized to receive ibrutinib or chlorambucil. The median age of the patients was 73 years. After a median follow-up of 1.5 years, ibrutinib, as compared with chlorambucil, resulted in a significantly higher overall response rate (86% vs 35%; $P < .001$), longer PFS (median, not reached vs 18.9 months; $P < .001$), and superior OS (2-year OS, 98% vs 85%; $P = .001$). The benefit of ibrutinib was seen irrespective of high-risk prognostic markers such as unmutated *IGHV* status, deletion 11q, and high β2 microglobulin. This trial led to the approval of ibrutinib in the first-line setting for all patients with CLL. Though the trial only included patients who were 65 years of age and older, the US Food and Drug Administration (FDA) approval did not specify any age limit.

Idelalisib, a PI3K δ inhibitor, is currently approved for relapsed CLL. Idelalisib has been pursued in the first-line setting as well; however, due to increased risk of death in the phase 3 trials, due to infectious complications, the first-line trials have been suspended.

Venetoclax, a BCL2 inhibitor, is currently approved for relapsed CLL with deletion 17p.[14,15] Several phase 2 trials are under way in the first-line setting in combination with other drugs such as obinutuzumab and with BR. A phase 3 trial is under way for patients with high CIRS score comparing venetoclax plus obinutuzumab vs chlorambucil plus obinutuzumab (NCT02242942). This trial is directed toward older patients with CLL who are not eligible for intensive CIT.

Duvelisib, a P13K γ/δ inhibitor, has clinical activity in relapsed CLL, and phase 3 trials are under way in relapsed CLL (NCT02004522).

Acalabrutinib is a more selective BTK inhibitor than ibrutinib,[16] and is currently being pursued in a randomized phase 3 study for previously untreated patients with CLL and high CIRS score (acalabrutinib vs acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab; NCT02475681). This trial is directed toward older patients with CLL who are not eligible for intensive CIT.

Targeted therapies offer a less toxic treatment strategy compared with CIT; however, long-term results are not available. Additionally, targeted therapies have not typically led to minimal residual disease (MRD) negative remissions, especially when used as single agents. With the use of CIT, achievement of MRD negative remission has been shown to be the most important factor leading to favorable long-term outcomes.[17]

Though ibrutinib is currently approved for young fit patients with CLL, there is lack of randomized data in this patient population for CIT vs targeted therapies. There is an intergroup phase 3 trial of ibrutinib plus rituximab vs FCR for young fit patients with CLL (NCT02048813) that recently reached accrual. The primary end point of the trial is PFS. This trial will help establish the role of CIT vs targeted therapy in young fit patients with CLL.

Mutated *IGHV*, non-del(17p) subgroup

Studies reporting long-term outcomes with FCR have identified a group of patients who benefit the most from the CIT approach.[6,18,19] In a report from the MDACC of the first 300 patients treated on the FCR trial, at a median follow-up of 12.8 years, the PFS was 30.9% with a median PFS of 6.4 years.[6] On multivariable analysis, unmutated *IGHV* and del(17p) by conventional karyotyping (fluorescence in situ hybridization data not available) were significantly associated with inferior PFS. For the patients with a mutated *IGHV*, the PFS at 12.8 years was 53.9% compared with only 8.7% for those in the unmutated *IGHV* group ($P < .0001$). Notably, for patients with mutated *IGHV* who achieved bone marrow MRD negativity, the PFS was 80% at 12.8 years. The GCLLSG also recently reported long-term outcomes of the CLL8 trial.[18] With a median follow-up of 5.9 years, median PFS was 4.7 years for the FCR arm (n = 408). At 5 years, the PFS was 66.6% for patients with a mutated *IGHV* compared with 33.1% for those with an unmutated *IGHV* ($P < .001$). Rossi and colleagues recently reported an observational retrospective study of first-line treatment with FCR (n = 404).[19] At 5 years, the PFS was 58.6% for patients with a mutated *IGHV* compared with 36.3% for those with an unmutated *IGHV* group ($P = .0005$). The observation of favorable long-term PFS in patients with a mutated *IGHV* (without del17p) after FCR treatment in these studies is important for several reasons: (1) it favors the argument that CIT should remain standard of care for this group of patients, given unknown long-term outcomes with targeted therapies; (2) future clinical trials with CIT or targeted therapies should be designed specifically for this subgroup of patients, keeping in mind long-term favorable outcomes with CIT alone. Such approaches have already started to be evaluated in clinical trials (NCT02629809). On the other hand, for patients with unmutated *IGHV*, given the poorer long-term PFS with FCR, alternative treatment options (such as enrollment in clinical trials with targeted therapies) should be strongly considered.

Conclusions

The patient in the opening scenario was noted to have deletion 13q by fluorescence in situ hybridization and mutated *IGHV*. He was offered treatment on a phase 2 clinical trial specifically designed for this group of patients (NCT02629809). Outside of a clinical trial, CIT regimens such as FCR would be the appropriate first-line therapy for this patient. Ongoing and planned phase 3 trials will help establish the role of CIT vs targeted therapies in first-line treatment of young fit with CLL.

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