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Optimal management of the young patient CLL patient

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ABSTRACT

The emergence of targeted therapy for patients with chronic lymphocytic leukemia (CLL) has permanently altered the therapeutic landscape. In both upfront and relapsed settings, safe and effective oral kinase inhibitors are available which rival the responses and durability seen with standard chemo immunotherapy regimens. In 2016, ibrutinib was granted Federal Drug Administration approval for first-line therapy in patients with CLL. While its role as initial therapy for older, unfit or deleted 17p CLL patients is less controversial, its role as first-line treatment for younger fit patients is less clear, begging the question, what is the optimal treatment for these patients, novel agents or standard CIT strategies? In this review, we aim to provide guidance for what we believe is the optimal management of young fit patients with CLL.

1. Introduction

First in class agents such as ibrutinib, venetoclax, and idelalisib have resulted in improved responses and survival for patients with CLL and have expanded the therapeutic repertoire. Since 2013, 4 drugs have been approved in addition to expanded indications for many of them. Both obinutuzumab or ofatumumab in combination with chlorambucil (Chl), as well as single agent ibrutinib achieved approval for upfront therapy for patients with CLL. While these drugs gained approval for frontline treatment, the registration studies demonstrating their effectiveness were executed in older patient populations generally considered unfit for aggressive chemo-immunotherapy (CIT). While novel therapeutics offer distinct advantages over CIT regimens, questions remain how drugs like ibrutinib and other novel non-chemotherapy based combinations compare with more aggressive standard fludarabine based strategies in younger fit patients, which now, has promising long-term safety and outcome data.

In this review we seek to highlight these controversies and provide guidance regarding what we believe to be optimal management of a young fit patient with CLL. We will review the epidemiology and biology of the disease and also look to the horizon to identify opportunities and challenges in the treatment of young fit CLL patients.

2. Epidemiology

While the median age at diagnosis is 71, 33% of 20,000 annually diagnosed patients are less than 65 years at diagnosis [1]. Genome-wide association studies have identified common variants at 34 reported loci which contribute to the heritable risk of developing CLL, which commonly presents at younger ages [2–7]. Several of these studies have demonstrated increased

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odds of CLL development with increasing numbers of inherited susceptibility polymorphisms, with odds ratios approaching 12, when 8 or more at risk polymorphisms are inherited [2,3]. Involved genes and genetic loci have roles in apoptosis, telomere regulation, and transcription factor binding among others, many of which require further elucidation. In patients with a familial history of CLL, affected probands tend to present at younger ages than those with sporadic CLL and that familial cases display the phenomenon of anticipation, which is defined as the onset of inherited disease at earlier ages in subsequent generations [8–11], while other studies find limited evidence for this anticipation effect in CLL [11,12].

A few groups have investigated the biological differences of early onset CLL highlighting several differences. Initial retrospective studies with small numbers of patients identified similar overall survival in patients diagnosed <55 years of age, compared to those >55 years of age, but with differing causes of death with younger patients most commonly dying due to direct causes of the underlying leukemia [13,14]. More recently, the Mayo clinic evaluated a large cohort identifying 844 newly diagnosed CLL patients ≤55 and compared those patients to 2324 newly diagnosed CLL patients ≥55 years of age [15]. This study identified that the youngest patients, <45 years of age, were more likely to present with intermediate or high risk Rai stage categories and present with an unmutated IGHV compared to their counterparts aged 45–55 years. No differences were noted in gender, CD38 status or fluorescence in situ hybridization (FISH) abnormalities between the <55 or >55 groups. At a median follow-up of 5.5 years, patients ≤55 years of age had a shorter median time to first treatment (TTFT) (4.0 years versus 5.2 years) but demonstrated superior overall survival (OS) (12.5 vs. 9.5 years). They also had superior OS when compared to the next youngest cohort patients 55–65 years of age (12.5 vs 11.0 years). When restricted to Rai stage 0 patients who were classified as IGHV mutated, 13q deleted or with normal FISH cytogenetics, survival was comparable to matched controls identifying a young patient that will likely have excellent long-term outcomes.

3. Current options for upfront therapy without deletion 17p

3.1. CIT

Pivotal randomized trials have informed treating physicians about the best upfront CIT regimens for young and fit patients with CLL. In the early 2000s, fludarabine based therapy, either as fludarabine (F) alone versus Chl, or as in the CLL4 study, fludarabine in combination with cyclophosphamide (FC) versus F, was found to improve response rates and progression free survival (PFS) [16–18]. The CLL 8 study, subsequently randomized over 800 patients to receive FC plus rituximab (FCR) or FC alone. First reported in 2010, this study now has updated long term follow-up with median observation of 5.9 years [19]. The updated analyses confirmed the superiority of FCR versus FC with a median PFS of 56.8 months versus 32.9 months respectively. Overall survival was also superior with FCR with median OS not reached versus 86 months for FC. Treatment with FCR was especially beneficial in patients ≤65 years with a median OS not reached versus 80.8 months for patients ≥65 years. While effective, the regimen was associated with a high rates of Grade 3/4 toxicities with 25% of patients developing grade 3/4 infections and 13.1% of patients developing secondary malignancies including Richter's transformation, after 5.9 years of median follow-up.

To identify a regimen that was equally effective with less toxicity, the German CLL study group initiated the CLL 10 study, a non-inferiority trial investigating initial treatment with bendamustine plus rituximab (BR) versus FCR [20]. The results showed a significantly shorter PFS, lower rates of CR and lower minimal residual disease negativity (MRD) in the BR group compared to the FCR arm. Despite the benefit of FCR on PFS, there was no significant differences in OS. When the analysis was restricted to patients greater than 65 years of age no significant difference in PFS was noted. These results established BR as an effective frontline therapy for older patients with comorbidities and solidified FCR as the standard CIT regimen for younger patients requiring treatment initiation.

Other randomized trials have evaluated whether additional chemotherapy or immunotherapy could improve upon the efficacy seen with FCR and resulted in no significant improvements in response rates, MRD negativity, or survival in the upfront setting [21] and are summarized in Table 1. Combinations of FCR plus or minus alemtuzumab were met with significant toxicities and increased death in the alemtuzumab arms limiting its adoption and use [22]. Thus for a CIT approach in a younger patient, FCR would be considered the standard of care.

3.2. Novel targeted therapies

The unprecedented response rates and durability of disease control with novel agents such as ibrutinib, venetoclax, and idelalisib in relapsed and refractory settings has garnered great enthusiasm and widespread adoption of these agents in the management of relapsed disease. There remains little data however, on long-term safety and efficacy outcomes when used as upfront therapy for younger patient cohorts. Only ibrutinib has achieved FDA approval for upfront treatment of CLL based on the results of the RESONATE-2 study which compared ibrutinib to chlorambucil in treatment naïve patients 65 years or older. This study demonstrated response rates and survival outcomes that rivaled the historical outcomes seen with FCR in the frontline setting [23]. After a median follow-up of 29 months, the ibrutinib monotherapy arm of the RESONATE-2 study demonstrated an ORR of 92%, with a CR rate of 18%, PFS of 89% with 2 year OS of 95% [24]. No significant differences were noted in overall survival between ibrutinib treated patients and IGHV mutational status which has been previously demonstrated in patients treated with FCR. This data provided rationale for upfront use of ibrutinib which received an expanded indication and an upfront label without any restriction for patients with CLL in March 2016.

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