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REVIEW

Targeted therapies for CLL: Practical issues with the changing treatment paradigm

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ABSTRACT

Chemoimmunotherapy (CIT) such as FCR (fludarabine, cyclophosphamide, rituximab) has been the standard first-line therapy for younger patients with CLL. In the last few years, several novel targeted therapies have been developed for patients with CLL. These include B-cell receptor (BCR) inhibitors such as Bruton tyrosine kinase (BTK) inhibitors, PI3 kinase inhibitors, and Syk inhibitors, novel anti-CD20 monoclonal antibodies such as ofatumumab and obinutuzumab, and Bcl-2 antagonists such as venetoclax (ABT-199). Strategies targeting the immune system such as lenalidomide, chimeric antigen receptor (CAR) T cells, and more recently, checkpoint inhibitors, are in clinical development. Ibrutinib and idelalisib are already approved for patients with relapsed and refractory CLL. Ibrutinib is also approved for first-line treatment of CLL patients with del(17p). Several ongoing phase III clinical trials with novel therapies will further define the role of targeted agents in CLL.

1. Introduction

Chemoimmunotherapy (CIT) regimens such as fludarabine, cyclophosphamide, and rituximab (FCR) have been the standard treatment for patients with chronic lymphocytic leukemia (CLL) [1]. However, given that the median age of diagnosis of a patient with CLL is 72 years, a large number of patients are not eligible for CIT due to age and comorbidities. Patients with high-risk genomic features such as del(17p) or unmutated immunoglobulin heavy chain variable (*IGHV*) gene respond poorly to CIT. Additionally, relapses are common after CIT. Management of patients with relapsed or refractory (R/R) CLL is challenging, and is generally complicated by cytopenias from prior therapies, worsening immune function, and frequent infections. Fortunately, in the last several years' major strides have been made in understanding the disease biology of CLL, and several of these discoveries are making their way into the clinics. These include B-cell receptor (BCR) inhibitors such as Bruton tyrosine kinase (BTK) inhibitors, PI3 kinase inhibitors, and Syk inhibitors. Several novel anti-CD20 monoclonal antibodies are in clinical development. Targeting Bcl-2, an anti-apoptotic protein that is over-expressed in CLL cells, with a small molecule, venetoclax (ABT-199), represents another important novel strategy. Several studies have reported clinical activity with the immunomodulatory drug lenalidomide in patients with CLL. Immunotherapy with genetically modified T cells [chimeric antigen receptor (CAR) T cells] represents another novel approach to target the CLL cells. Preclinical data supports the use of checkpoint inhibitors in patients with CLL, and clinical trials with agents targeting the PD-1/PD-L1 axis are in clinical trials. In this review, first we summarize the available clinical data with these novel agents in CLL, and then we discuss the incorporation of these agents into the current therapeutic armamentarium.

2. Targeted therapies for CLL

2.1. B-cell receptor (BCR) inhibitors

BCR activation plays a crucial role in the pathogenesis of CLL and several preclinical studies provided strong rationale for targeting BCR as a therapeutic target [2,3].

2.1.1. BTK inhibition

BTK is a non-receptor tyrosine kinase of the Tec kinase family and plays a crucial role in BCR signaling [4].

2.1.1.1. Ibrutinib. Ibrutinib is an oral, selective and irreversible inhibitor of BTK. It forms a bond with the cysteine-481 of BTK [5]. Ibrutinib also inhibits several other kinases such as ITK (interleukin-2-inducible T-cell kinase), TEC, BMX, and EGFR. Byrd et al. reported outcomes of 101 patients with R/R CLL who received ibrutinib [6,7]. The median age was 64 years (range, 37–82). Thirty-four percent of the patients had del(17p), and 78% had unmutated *IGHV*. The median number of prior therapies was 4. The overall response rate (ORR) was 90% with a 7% complete remission (CR) and 65% partial remission (PR). The estimated progression-free survival (PFS) at 30 months was 69%. For patients with

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del(17p) and del11(q), the median PFS was 28 months and 38.7 months, respectively, and was notably inferior to that of patients without del(17p) or del(11q) [7]. Thus, patients with high-risk cytogenetics continue to have a higher risk of disease progression after ibrutinib treatment; of note, these results are significantly better than that achieved with CIT in patients with R/R high-risk CLL. The most common toxicity with ibrutinib was diarrhea, occurring in 55% of patients; however, the majority of events were grade 1–2. Notable grade ≥ 3 adverse events (AEs) were hypertension (20%), pneumonia (25%), neutropenia (18%), thrombocytopenia (10%), bleeding (8%), and atrial fibrillation (6%). Bleeding is likely secondary to inhibition of collagen and von Willebrand factor-dependent platelet functions by ibrutinib [8,9]. BTK and TEC are critical mediators of platelet glycoprotein VI signaling following collagen binding, and both enzymes are irreversibly inhibited by ibrutinib at clinically relevant concentrations [9]. The phase 1–2 trials led to the pivotal phase III trial (RESONATE trial) where patients with R/R CLL were randomized to receive ibrutinib (n = 195) or ofatumumab (n = 196). The ibrutinib arm had much higher ORR and superior PFS and overall survival (OS) compared to the ofatumumab arm [10]. Based on this trial, ibrutinib (420 mg orally once daily) was approved by the Food and Drug Administration (FDA) for patients with R/R CLL. There are limited data with ibrutinib in the first-line setting. O'Brien et al. reported on the outcomes of 31 patients with treatment-naïve CLL who received ibrutinib monotherapy [11]. The median age was 71 years (range, 65–84). After a median follow-up of 35 months, an ORR of 84% was noted with 23% achieving a CR [7]. The 30-month PFS and OS were impressive at 96% and 97%, respectively. The RESONATE-2 trial randomized treatment-naïve patients 65 years or older to ibrutinib vs. chlorambucil and has completed enrollment (NCT01722487), and ibrutinib resulted in an improvement in both PFS and OS (press release, June 4, 2015). These data will likely result in the approval of ibrutinib in treatment-naïve CLL. Several additional ongoing phase III trials in the treatment-naïve population [NCT02264574, ibrutinib + obinutuzumab vs. chlorambucil + obinutuzumab; NCT02048813, ibrutinib + rituximab (IR) vs. FCR; NCT01886872, ibrutinib vs. IR vs. bendamustine + rituximab (BR)] will further help establish the frontline role of ibrutinib in patients with CLL.

It is important to note that most patients will develop lymphocytosis after initiating ibrutinib. This is thought to be due to trafficking of CLL cells from the lymph nodes and other tumor sites into the peripheral blood, likely due to inhibition of several molecular pathways involved in adhesion, including CXCR4/5 [12–15]. This is an expected finding with ibrutinib and other BCR inhibitors and it generally resolves over the course of 6–9 months with continued treatment [16]. Approximately 20% of patients have prolonged lymphocytosis (>12 months) with ibrutinib treatment [16]. Lymphocytosis is more pronounced in patients with mutated *IGHV* and in those with del(13q) [13]. In the absence of other objective evidence of progressive disease, lymphocytosis alone should not be considered an indicator of disease progression. Development of lymphocytosis does not appear to be detrimental to long-term clinical outcomes [13,16,17]. To account for this reactive lymphocytosis, a new response category has been created called PR with lymphocytosis (PR-L) [18]. Leukostasis symptoms are rare in patients with CLL who experience lymphocytosis.

The mechanism of resistance to ibrutinib remains an area of active research. Several of the patients who progress on ibrutinib have been found to have an acquired mutation of *BTK* at cysteine-481 (C481S), and gain of function mutations in *PLCγ2*, a signaling molecule downstream of BTK [19,20]. BTK C481S mutation reduces the binding affinity of ibrutinib to BTK, and only allows for reversible BTK inhibition leading to transient BTK inhibition [21].

Ibrutinib is also being evaluated in combination therapies. Burger et al. reported data from a phase II study with ibrutinib in combination with rituximab (IR) in 40 patients with CLL [36 R/R, 4 treatment-naïve with del(17p)] [22]. The ORR was 95% (8% CR, 87% PR). The 18-month PFS was 78%. Not surprisingly, lymphocytosis was less pronounced compared to that seen with ibrutinib monotherapy. Jaglowski et al. reported on a phase 1b/2 study of the combination of ibrutinib and ofatumumab [23]. A total of 71 patients were treated; most had high-risk disease including del(17p) (44%) or del(11q) (31%). Three different dosing schema were studied; ibrutinib lead-in followed by ofatumumab (group 1); concurrent treatment start (group 2), or ofatumumab lead-in (group 3). The ORR was 100%, 79%, and 71% in groups 1, 2, and 3, respectively. Unexpectedly, peripheral sensory neuropathy was noted in 44% patients (mostly grade 1–2, 2 patients with grade ≥ 3). Again, lymphocytosis was less pronounced. Preliminary results using ibrutinib and ublituximab were recently reported [24]. Forty-four patients with R/R CLL were enrolled. Forty-eight percent of patients were high-risk [del(17p) or del (11q)]. Grade 3–4 infusion reactions occurred in 7% of the patients. The ORR was 88% with a 10% CR rate, and 3 patients achieved minimal residual disease (MRD)-negative remission. A phase III randomized trial of ibrutinib ± ublituximab in patients with R/R CLL with high-risk features [del(17p), *TP53* mutation, del(11q)] is currently enrolling patients (NCT02301156). Though some preclinical studies have reported antagonism between ibrutinib and rituximab due to inhibition of ADCC by ibrutinib [25–28], the data from the phase II clinical trials of ibrutinib and anti-CD20 monoclonal antibody (mAb) looks promising. An ongoing randomized phase II trial of Ibrutinib ± rituximab in patients with CLL will further help clarify this issue (NCT02007044). In addition, the phase III trial ibrutinib ± ublituximab trial (NCT02301156) will further address the issue of addition of CD20 mAb to ibrutinib.

Ibrutinib has also been combined with chemotherapy in patients with CLL. A phase 1b study of ibrutinib in combination with BR in patients with R/R CLL showed an ORR of 93.3% and a PFS rate of 70.3% at 36 months [29]. The preliminary results from HELIOS trial (BR ± ibrutinib in R/R CLL, NCT01611090) showed improvement in PFS (hazard ratio, HR 0.203, $p < 0.0001$) and ORR (83% vs. 68%, $p < 0.0001$) with the addition of ibrutinib [30]. The safety profile of BR + ibrutinib was similar to the known individual safety profile of the drugs. From a clinical standpoint, ibrutinib is approved in patients with CLL, and whether the combination of BR + ibrutinib is superior to ibrutinib monotherapy remains unknown (there was no ibrutinib monotherapy arm in the HELIOS trial).

2.1.1.2. ACP-196. ACP-196 is a novel, irreversible second generation BTK inhibitor which is more selective for BTK than ibrutinib [31]. Unlike ibrutinib, ACP-196 does not inhibit EGFR and ITK. ACP-196 inhibits proliferation of CLL cells in xenograft models [32]. A phase I trial of ACP-196 is currently ongoing (NCT02029443). A phase III study of ACP-196 vs. ibrutinib in patients with R/R CLL with high-risk features [del(17p), del(11q)] is ongoing (NCT02477696). Additionally, a phase III study of ACP-196 (obinutuzumab + ACP-196 vs. obinutuzumab + chlorambucil vs. ACP-196) in treatment-naïve patients with CLL is currently enrolling patients (NCT02475681).

2.1.1.3. ONO-4059. ONO-4059 is a highly potent and selective oral BTK inhibitor. In a phase I study in patients with CLL, 25 patients were administered ONO-4059 as monotherapy, given once daily [33]. A total of 8 dose-cohorts with dose range from 20 to 600 mg were studied. The treatment was well-tolerated with mostly grade 1–2 adverse events. Six patients had grade 3–4 neutropenia. The ORR was 84% with a similar response rate in patients with del(17p).

2.1.1.4. CC-292 (AVL-292, spebrutinib). CC-292 (AVL-292, spebrutinib) is a specific irreversible inhibitor of BTK, and unlike ibrutinib, it does not inhibit SRC family kinases or ITK. In a phase I study, 83 patients with R/R CLL were enrolled [34]. The most frequent grade 3/4 adverse events included neutropenia (21%), thrombocytopenia (15%), pneumonia (10%), and anemia (8%). The recommended phase II dose was identified as 500 mg twice daily. At this dose, the ORR was 63% (all PR/PR-L).