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**Supplement Article**

# VIII. Treatment of chronic lymphocytic leukaemia, where are we heading?

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## Introduction

The past year has seen enormous changes in the treatment of chronic lymphocytic leukaemia (CLL), partly based on the approval of several new molecules. In fact, the American Society of Clinical Oncology (ASCO) named CLL therapies the 'the Cancer advance of the year' in its annual report of January 2015. This was the first time that ASCO singled out a particular advance in cancer treatment in its annual report. There were four new therapies approved for the treatment of CLL in 2014 (Figure 1). The four new therapies include two immunotherapies, ofatumumab and obinutuzumab, as well as two targeted agents, idelalisib and ibrutinib. Both immunotherapies are anti-CD20 monoclonal antibodies, and both have been approved in combination with chlorambucil for previously untreated patients with advanced CLL requiring therapy. The other drugs are oral agents and are both B-cell receptor inhibitors. Idelalisib is a PI3K delta inhibitor approved in combination with rituximab for patients with relapsed/refractory CLL. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor approved for relapsed patients with CLL as well as for frontline therapy of patients with CLL and a 17p deletion. All four of these drugs have been approved in both the USA and Europe.

## Antibodies

The approval of the two immunotherapies was based on randomized clinical trials. Obinutuzumab and chlorambucil were compared with chlorambucil alone, as well as rituximab and chlorambucil, in patients with significant comorbidities Cumulative illness rating scale (CIRS $\geq 6$) as well as renal dysfunction (creatinine clearance 70 mL/min [1]). The initial data compared single-agent chlorambucil to both the antibody arms and showed that combining chlorambucil with either antibody produced better results than were noted using chlorambucil alone. In the subsequent analysis, the two antibody combinations were compared; obinutuzumab and chlorambucil produced a significantly longer progression-free survival (PFS) of 26.7 months versus 15.2 months with rituximab and chlorambucil. Another trial, the COMPLEMENT 1 trial, compared chlorambucil alone with ofatumumab and chlorambucil [2]. The PFS with the ofatumumab combination was 22.4 months versus 13.1 months with chlorambucil alone. Both of these trials were designed for patients who would be considered too high risk to receive more standard regimens such as fludarabine, cyclophosphimide and rituximab (FCR) or bendamustine and rituximab (BR).

A recent trial performed by the German CLL Study Group compared FCR versus BR as frontline therapy for patients with better physical fitness (CIRS $< 6$) and good renal function [3]. This trial was designed as a non-inferiority trial and involved over 500 patients. The overall response rate (ORR) was high in both arms at 95%, but FCR produced a significantly higher complete response (CR) rate of 39.7% versus 30.8% with BR. Importantly, the rate of minimal residual disease negativity at the end of treatment was doubled with FCR as compared with BR. PFS was also significantly different at 55.2 months with FCR versus 41.7 months with BR. One notable difference in the patient characteristics is that the patients with an unmutated immunoglobulin heavy chain variable region were more frequent in the BR arm at 67.8% versus 55.3% in the FCR arm. This could potentially account for the shorter PFS with BR as mutation status is a very important predictor of outcome. However, when the patients within the unmutated group were compared, the FCR arm still produced a significantly better PFS of 42.7 months versus 33.6 months with BR. Currently, there is no difference in survival, but the follow-up is short with few events. Of note, and not unexpectedly, the incidence of neutropenia and the rate of infection were higher with the FCR arm. No prophylactic growth factor support was used in this trial.

## B-cell receptor inhibition

The two novel agents that have been approved (ibrutinib and idealisib) are both B-cell receptor inhibitors. Ligation of the B-cell receptor provides a strong proliferative and survival signal to the cell. Thus, interrupting such signalling could potentially have a positive effect on the disease. There are multiple kinases in the B-cell receptor pathway that could be targeted. The first drug approved, ibrutinib, targets the BTK. Ibrutinib was initially approved based on a phase 2 trial in patients with relapsed CLL [4]. The most recent update at ASCO 2014 showed that the ORR was 89% [5]. There were two groups of patients treated in the phase 2 trial: one group were patients that were relapsed or refractory to prior therapy; the other group of patients were treatment naïve, over the age of 65 years, but requiring therapy for their diseases. In the relapsed/refractory population, the ORR was 90% with 6% CR. In the previously untreated group, the ORR was 87% with 13% CR. Of note is a recently defined response designated PR-L, which stands for partial remission with lymphocytosis. All of the B-cell receptor inhibitors have a common pattern of response wherein there is rapid reduction of lymphadenopathy but a simultaneous increase in the baseline lymphocyte count, which generally peaks at 1–2 months and then slowly declines. The patients achieving a PR-L meet all the criteria for a PR except for the fact that the baseline lymphocyte count has not decreased by 50%. Many of these patients actually have 80–90% reduction in lymph nodes and organomegaly but may be slow to clear lymphocytosis. As of ASCO update, 5% of patients still had a PR-L with a median follow-up of about 3 years. The median PFS had not been reached for the relapsed/refractory population; the only group in whom a median PFS had been reached was patients with deletion 17p where it was 28.1 months. I discuss this population further in the succeeding text. The median PFS for patients with 11q deletion was not reached but was 74% at 30 months, and in patients who did not have a deletion 17p or 11q, the 30-month PFS was 89%[v]. Median survival had not been reached. In the treatment naïve population, only one patient had relapsed, and the 30-month PFS was 96% with a 30-month overall survival of 96.6%.

A major advantage of the use of B-cell receptor inhibitors is that they are not myelosuppressive. Myelosuppression and infections are the most common complication of treating patients with CLL with chemoimmunotherapy. In addition, these patients are often immunosuppressed or myelosuppressed already on the basis of prior therapy and/or bone marrow involvement. Not only is ibrutinib not myelosuppressive, but there is rapid improvement in baseline cytopenias in the majority of the patients who receive this drug.

The initial approval for relapsed/refractory patients based on the phase 2 data was an accelerated approval. Final approval was based on the RESONATE phase 3 study in which ibrutinib, at the standard dose of 420 mg once daily, was compared with IV ofatumumab given as described in the package insert [6]. The primary endpoint was PFS. Initially, no crossover was allowed, but later in the trial, the protocol was amended to allow crossover. There was a dramatic difference in PFS with the median PFS not reached with ibrutinib versus 8 months with ofatumumab, representing a 78% reduction in the risk of progressive disease or death. There was also a difference in the overall survival, although this was probably based on the fact that the initial patients were not allowed to crossover.

The toxicity seen on the phase 2 trial was predominantly diarrhoea, which was usually mild and often self-limited. Other toxicities include rash, arthralgia and bruising. Ibrutinib does interfere with one of the platelet aggregation pathways mediated by glycoproteins. However, it does not interfere with other aggregation pathways, the likely reason why most of the bleeding seen on the trials is related to bruising rather than major bleeding.

Of note, on the randomized trial was the incidence of atrial fibrillation. There were 10 episodes of atrial fibrillation on the ibrutinib arm and only one on the ofatumumab arm. Only one patient needed to discontinue ibrutinib. Many had predisposing risk factors such as a prior history of atrial fibrillation, but nevertheless, this was a clear difference and suggests a real signal with a development of atrial fibrillation on ibrutinib. Bleeding-related adverse events were most commonly petechiae and ecchymoses and were significantly more common with ibrutinib at 44% versus ofatumumab at 12%. However, there was no difference in severe/major bleeding events; there were two in the ibrutinib arm and three in the ofatumumab arm.

Although the response rate and durability of response to ibrutinib is impressive, the reality is that if patients stay in PR with residual disease, resistance may develop. A recent publication in the New England Journal of Medicine looked at patients with acquired resistance to ibrutinib after being on drug for 388–868 days [7]. All patients had a C481S mutation in BTK or a R665W mutation in PLCgamma (PLC 2), a downstream kinase. Most of these patients had high-risk disease with extensive prior therapy and complex karyotype or 17p deletion. This is not a surprising finding; if we extrapolate from the treatment of chronic myelogenous leukaemia with tyrosine kinase inhibitors (TKIs), we know that approximately 50% of the patients will become resistant through developing mutations, which inhibit binding of the TKI. This stresses the need to achieve CR and eradicate disease in CLL.

Recently, ibrutinib was approved by the Food and Drug Administration as initial therapy of patients with 17p deletion. As noted earlier, in the relapsed/refractory population, those patients with 17p deletion had a median PFS of 28 months. This compares favourably to the median PFS



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| Recently Approved Agents for the Treatment of CLL | | | | |
|---|---|---|---|---|
| **Agent** | **Type of Molecule** | **FDA Indication for CLL** | **Schedule** | **Black Box Warning** |
| Obinutuzumab | Type 2<br>anti – CD20<br>monoclonal antibody | In combination with chlorambucil in previously untreated CLL | 100mg IV $C_1D_1$<br>900mg IV $C_1D_2$<br>1000mg $C_1D_8$ + s<br>1000mg $C_{2-6}D_1$ | Hepatitis B reactivation<br>PML |
| Ofatumumab* | Type 1<br>anti – CD20<br>monoclonal antibody | In combination with chlorambucil in previously untreated CLL where fludarabine-based therapy is inappropriate | 300mg IV $D_1$*<br>1000mg IV weekly x7, then 1000mg monthly x 4 | Hepatitis B reactivation<br>PML |
| Ibrutinib | BTK<br>inhibitior | -Relapsed CLL post at least 1 prior therapy<br>-CLL and 17p deletion | 420mg (140x3) daily PO | N/A |
| Idelalisib | P13K$^{\delta}$ inhibitor | Relapsed CLL, in combination with rituximab, in whom rituximab alone would be considered appropriate due to comordities | 150mg PO BID | -fatal and/or severe: hepatotoxicity<br>-diarrhea or colitis<br>-pneumonitis<br>-intestinal perforation |
| *prior approval for patient refractory to fludarabine and alemtuzumab | | | | |

**Figure 1.** New agents approved for the treatment of chronic lymphocytic leukaemia in the past year

for frontline therapy of patients with 17p deletion with either FCR or alemtuzumab. In both cases, the PFS was 11 months. It was a very logical decision for the Food and Drug Administration to give such an approval, albeit there is little data on the efficacy of ibrutinib in the frontline population with 17p deletion, a group that only comprises about 5–10% of patients initially receiving therapy for CLL.

Idelalisib targets a different kinase in the B-cell receptor pathway, namely, PI3K . The delta isoform is the most important one in haematological malignancies, and the typical pattern of response with this drug as a single agent is a rapid reduction in lymph nodes along with a rise in the lymphocyte count. The registration approval for this drug is in combination with rituximab in relapsed patients with CLL.

Like ibrutinib, marked improvement in baseline cytopenias is seen with idelalisib. A common side effect is elevation of transaminases. If grade 3–4 elevation is observed, the drug is held and dose-reduced on reinitiation. However, re-escalation of the dose is frequently possible. In the phase I trial of single-agent idelalisib, the median PFS in relapsed/refractory patients receiving 150 mg BID or higher (150 mg BID now being the standard dose) was 31 months [8].

The approval of idelalisib was based on a randomized trial comparing idelalisib and rituximab to placebo and rituximab in patients with relapsed/refractory CLL [9]. Rituximab was given initially at 375 mg/m$^2$ and then 500 mg/m$^2$ every 2 weeks for 4 weeks, and then 500 mg/m$^2$ every 4 weeks for three more weeks. Idelalisib was continued indefinitely until either progression or toxicity. The primary endpoint was PFS, and at the time of progression, patients could crossover to an extension study. If they had not received idelalisib, they could go on to receive it at the standard dose of 150 mg twice daily; if they had been on that dose of idelalisib, they could increase the dose to 300 mg twice a day. The eligibility for this trial was quite variable but in essence defined a population that would be considered too high risk to receive chemotherapy. Some of the eligibility criteria included high CIRS score, reduced renal function, baseline cytopenias and increased Karnofsky score. The study was stopped at the first interim analysis when there was a dramatic difference in PFS, being 5.5 months with placebo and rituximab and not reached in the idelalisib and rituximab arm.

Idelalisib has also been used as therapy in treatment naïve patients ≥65 years old, again in combination with rituximab [10]. Sixty-four patients were treated; almost all patients responded and the median PFS has not yet been reached with a median follow-up of 2–3years. The most common reason for treatment discontinuation was late diarrhoea/colitis with a median time to onset of 9 months. After initially holding the drug and treating with IV steroids or non-absorbable steroids, some patients were able to be retreated. Idelalisib is not yet approved for initial therapy of CLL.

These are exciting times in research for CLL. There are already next generation SYK, PI3K and BTK inhibitors in clinical trials. There is also promising data with the BCL2 inhibitor ABT-199, which may be the next drug approved for the treatment of CLL.

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