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Editorial

What is the place of single-agent ibrutinib in the current landscape of CLL?

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Abstract

Ibrutinib is a disease-altering therapy. It has widespread and increasing use because of its better tolerability than other available therapies. Many studies showed the high efficacy of ibrutinib in CLL, however, its follow-up has remained quite short. Many questions have remained unanswered about long-term ibrutinib tolerability, the features of those patients who stop treatment on the long run, predictors of response as well as how ibrutinib favors immune recovery.

Abbreviation: CLL: chronic lymphocytic leukemia; TN: treatment-naïve; PFS: progression-free survival; BTK: Bruton's tyrosine kinase; ORR: overall response rate

Introduction

Ibrutinib is a highly effective therapy in all categories of chronic lymphocytic leukemia (CLL) patients, the most prevalent adult leukemia. It is better tolerated than other available therapies [1] and is well tolerated in the heavily pretreated populations [2]. Ibrutinib has a direct antitumor effect via targeting of BTK. Ibrutinib is likely to interfere with other pathways associated with migration, adhesion, and egression [3]. It also modulates the immunosuppressive CLL microenvironment through inhibition of the STAT3 pathway. By suppressing STAT3, the drug inhibits CLL B10 function and induces down regulation of PD-1/PD-L1 expression, thus potentially enhances antitumor immune responses [4]. Ibrutinib does not cure CLL. Its efficacy is dependent upon chronic BTK inhibition. At present, ibrutinib is thought to require indefinite administration to ensure continued clinical benefit [5].Many studies have confirmed the high efficacy of ibrutinib in CLL, however, its follow-up has remained quite short [1]. Follow-up of patients who discontinue ibrutinib without disease progression, as well as systematic investigation of time-limited therapy, including use of novel combination approaches, is clearly warranted with the goal of maximizing ibrutinib benefit and minimizing its toxicity [1].

The Influence of Ibrutinib Treatment Duration on the Patient Outcome

After one Year Follow-Up

The quality of response to ibrutinib gradually improves with treatment duration. Best responses increase gradually during prolonged treatment [3]. Continuous ibrutinib therapy (excepting minimal breaks) throughout the first year is required for optimal outcomes [6]. At 1 year, the DFS and OS rates for responding patients who had no dose reductions and no treatment break of >14 days were excellent, with 95% (152/160) of patients are alive and continuing on ibrutinib treatment [6]. The prolonged lymphocytosis induced during ibrutinib treatment does not appear to associate with an increased risk of progression [3]. Patients with persistent lymphocytosis at 1 year have improved PFS and OS similar to those with PR or CR [7]. As regards the effect of prior lines of therapy on 1 year outcomes of ibrutinib treatment, the RESONATE updated abstract presentation suggested that patients treated with 1 prior line of therapy had a statistically meaningful PFS advantage at 12 months compared with those receiving 2+ prior lines of therapy (94% vs. 82%). Perhaps, this may be related to the presence of poorer prognostic features such as poorer performance status (PS) and higher levels of 17p deletion in the more heavily pre-treated patients [6].

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After Three Years Follow-Up

PCYC-1102 and the extension study PCYC-1103 demonstrated that continuous single-agent, ibrutinib in treatment-naïve (TN) and in previously treated CLL patients ≥65 years showed improved quality and frequency of responses over time leading to durable remissions. Daily ibrutinib was continued in 81% of TN patients at 3 years follow up. No further relapses were detected over 2 years in R/R patients. The genomic aberrations del (17p) in heavily pretreated population appear to affect PFS [7]. Modest toxicities were observed. Furthermore, toxicities such as cytopenias, fatigue, diarrhea, and infections and toxicity leading to ibrutinib discontinuation diminished with continued treatment [7].There is gradual decrease of infection complications during the 3 years of treatment, despite the persistence of circulating tumor cells. Grade ≥3 infections are virtually absent in TN patients. This is explained by ibrutinib inhibition of immunoregulatory interleukin-10 production by activated CLL cells in vitro. In addition, ibrutinib inhibits interleukin-associated T-cell kinase, which can promote T helper cell type 1 CD4 T-cell outgrowth. Continuous ibrutinib treatment was associated with recovery of humoral immunity, with an increase in serum immunoglobulin levels, predominantly the IgA isotype. CLL cells can also act as regulatory B cells [3].

After Five Years Follow-Up

The remissions were lasting and even improved in many cases from partial to complete remissions including some patients who achieved minimal residual disease negativity with ibrutinib treatment continuation for almost five years [8].

After Seven Years Follow-Up

The ORR for single agent ibrutinib treatment was 89% for all CLL/SLL patients after up to seven years follow–up. The ORR rates were similar in previously untreated (87%) and the R/R patients (89%). CR rates were higher in previously untreated patients (32%) than in R/R patients (10%). PFS was also better for R/R patients treated with ibrutinib after one or two prior lines of therapy as compared with those treated with three or more lines of prior therapy. Median duration of response was 57 months for R/R patients while it was not reached in previously untreated patients. No new or unexpected AEs were observed. The occurrence of most grade 3 or higher AEs and serious AEs decreased over time with the exception of hypertension [9]. From all these mentioned results, it can be suggested that the best efficacy for ibrutinib treatment over the long term can be obtained when ibrutinib is started as early as possible and the best outcomes may be seen when ibrutinib is administered as first-line rather than salvage therapy in CLL [7].

Is Lower-Dose Ibrutinib is Effective as the Standard Dose of 420 mg Daily?

A small retrospective study supported the concept that patients on reduced dose of ibrutinib for clinical reasons had a similar PFS as compared with those who remained at full dose of 420mg daily. To test this hypothesis, Chen et al [10] designed a pilot study of ibrutinib dose reduction from 420mg to 280 mg and then 140mg over the first three 28-day cycles of treatment and examined the pharmacokinetics and pharmacodynamics at all dose levels [11].Although plasma and intracellular ibrutinib levels were lower at lower doses, mean BTK occupancy remained >97% at the farthest time point of dosing, which was cycle 3 day 28 at 24 hours [11].

Is Ibrutinib Dose Reductions/Breaks Influences Treatment Effectiveness?

Dose reductions/breaks were reported in the RESONATE trial (4% of patients) and in the Ohio State series (10%). In the UK/Ireland cohort, 26% had dose reduction of ibrutinib (with or without treatment breaks), and 19% of patients had treatment breaks (temporary and permanent) with no dose reductions [6]. The inclusion of poorer PS patients was likely a contributing factor for the high rates of dose modifications. Infection, cytopenias, bleeding issues, and gastro-intestinal toxicity were the recurring reasons cited for both temporary and permanent dose reductions and therapy breaks [6]. Immediate depletion of all CLL cells by ibrutinib is not necessary [3]. Ibrutinib induces death of 2.7% CLL cells per day in the lymph node, it is likely that the subgroup of cells with higher immunoglobulin (Ig)M and higher CXCR4 are subjected to ibrutinib-induced cell death.A numerable fraction of cells is forced to exit and remain in the circulation [3]. Those circulating cells may go back to tissue, making the disease more aggressive when ibrutinib is discontinued [3]. Patients who re-started ibrutinib by the 1 year time point after previous treatment breaks had inferior outcomes both at 1 year, and beyond 1 year [6].

Comparison between the Durability of CLL Remission for Patients Who Stopped Ibrutinib While in a Deep Incomplete Remission versus Those Who Continue Ibrutinib

The durability of remission after ibrutinib treatment discontinuation in CLL patients may ultimately differ based on the duration of therapy, depth of response, and CLL prognostic factors, but as yet, it remains unanswered question, with almost no data [1]. A short OS (median survival was 95 days) after stopping ibrutinib within the first year of treatment is a notable feature. The lack of access to alternative non-chemotherapy treatments after ibrutinib discontinuation could be a contributing factor [6].

Why Ibrutinib Discontinuation and Survival Rates are Likely Worse in A Real-World Setting Than In A Clinical Trial?

Patients treated outside of a clinical trial are more likely to have poorer PS and more comorbidities. Pre-treatment PS (2+) is significantly associated with reduced discontinuation-free and overall survival (16.2% and 9.3% lower at 1 year, respectively). Patients treated within a clinical trial have more stringent rules for dose modifications/dose interruptions that are likely to translate into higher levels of drug compliance [6].

Conclusion

From these data, it can be suggested that starting ibrutinib treatment as early as possible and its administration as first-line rather than salvage therapy results in the best outcomes and the best efficacy over the long term.

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