Efficacy of Ibrutinib in the Treatment of First Early Relapses of CLL

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Context

Up to 25% of CLL patients relapse within 24 months after first line fludarabine and bendamustine-containing immunochemotherapy (early relapses). Historically before new targeted drugs became available, post-salvage event-free survival (EFS) was only 6-18 months and overall survival (OS) was only 13-47 months in these patients. Nowadays, ibrutinib is widely used in this patient group. However, efficacy of ibrutinib in first early relapse setting is relatively poorly characterized because most ibrutinib trials included relapsed/refractory patients with several lines of therapy in anamnesis. Leukemic cells with del17p might be more prone to develop mutations, associated with resistance to ibrutinib, due to genomic instability. Thus, we hypothesized that del17p monitoring by FISH may provide clinically useful information as increase in relative del17p clone size would be an early marker of developing resistance.

Objective

To evaluate efficacy of ibrutinib in CLL patients with first early relapse as compared to other patients, to characterize ibrutinib safety profile, to analyze relative del17p clone size by FISH during therapy and make correlations with prognosis.

Patients

We retrospectively analyzed 31 CLL patients treated with ibrutinib alone (N = 15), in combination with rituximab (N = 14) or R-BAC regimen (N = 2). Ibrutinib was given in initial dose of 420 mg QD until PD or intolerance. Dose was modified in 3 patients due to adverse events or comorbidities (HCV infection-associated hepatic failure, atrial fibrillation). Median number of previous lines of therapy was 2 (range 1-10). 28 (90%) patients had previously received bendamustine or fludarabine-containing regimens. 16 (51%) patients received ibrutinib after first early relapse (tab. 1) and 15 (49%) after ≥2 lines of therapy. 9 (34%) patients had del17p as assessed by FISH method. To estimate del17p clone dynamics, in 5 patients interphase FISH was repeated at least every 12 months during treatment on flow-sorted peripheral blood B cells (CD45+CD19+, FACSAria III cell sorter).

Table 1. Baseline early relapse patients characteristics.

N	Sex	Age	1st line therapy	IGHV mutation status	FISH	Duration of therapy, months	Response
1	F	58	BR	Unmut	Del17p	20	CR
2	F	70	BR	Unmut	Del17p	23	PR
3	M	67	B+Ga	Unmut	Unknown	23	CR
4	F	75	BR	Unmut	Del17p, del11q	21	PR
5	F	70	BR	Unknown	Not done	23	CR
6	M	62	BR	Unmut	Not done	22	PR
7	F	68	BR	Unmut	Del17p	23	CR
8	M	54	BR	Unmut	Del17p, tri12	23	CR
9	M	59	BR	Unknown	Del11q	21	PR-L
10	M	57	FCR	Unknown	Not done	11	CR
11	F	54	FCR	Unknown	Del11q	7	CR, MRD-
12	M	67	FCR	Unknown	Del17p	10	PR
13	M	51	Chl+Ga	Unknown	Del11q	18	PR
14	M	64	BR	Unmut	Del17p	28	PR
15	M	71	BR	Unknown	Del11q	9	SD
16	M	62	FC	Unknown	Unknown	13	PD

Response to therapy and toxicity

Median follow-up was 18 months (range 7-42). At the time of analysis 77% patients didn't experience any events and 84% were alive with 5 deaths. Although median EFS and OS were not reached, survival was significantly longer in first early relapse patients vs others by log rank test (EFS: p=.034, OS: p=.02, fig. 1-2) despite higher incidence of del17p. There was only 1 bone marrow MRD-negative remission (first early relapse, without del17p, treated with R-BACx4+I). Three patients developed PD: 1 had CLL progression after 11 months of therapy (first early relapse, del17p), 2 developed Richter syndrome (DLBCL and Hodgkin Lymphoma). Most common toxicities were grade 1–2 hemorrhagic purpura (30%), grade 1–2 diarrhea (10%), paroxysmal atrial fibrillation (10%) and arterial hypertension (10%). Severe infections were seen in 3 patients (10%), all of them successfully resolved with combined antibacterial and antifungal therapy. Causes of death were CLL progression (including Richter syndrome) in 3 pts and comorbidities in 2 pts (HCV infection, pancreatic cancer).

Figure 1. Event-free survival (N = 31).

Figure 2. Overall survival (N = 31).

Del17p clone size dynamics

Median percent of del17p positive cells at baseline was 65% (range 7-88). 4/5 (80%) patients had increase of del17p relative clone size at 12-18 months of therapy (up to 100% of cells) (fig. 3). However, in all cases clone size subsequently decreased at 24 months (fig. 4) and 2/5 (40%) patients achieved lower levels compared to baseline. Median percent change of clone size was +16% at 12-18 mos and +2% at 24 mos compared to baseline level. None of the 5 patients progressed to date, which makes correlations with prognosis impossible.

Figure 3. Changes in del17p clone size by FISH on flow-sorted B cells during treatment (N = 5).

Figure 4. Decrease in del17p clone size at 24 mos compared to 12-18 mos of therapy (N = 5).

Conclusions

- First early relapse patients respond well to ibrutinib and achieve better EFS and OS compared to patients with several lines of therapy prior to ibrutinib. This is consistent with other observations showing better ibrutinib efficacy in patients with less lines of therapy in anamnesis.
- R-BAC+I combination was highly effective in 1 patient.
- Toxicity profile of ibrutinib was acceptable in our cohort.
- Increase of percent of del17p cells in PB at 12-18 months might be associated with their increased propensity to redistribute to PB or slower depletion compared to other leukemic cells.
- Utility of del17p relative clone size monitoring by FISH requires further analysis.

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