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Ibrutinib in the real world patient: many lights and some shades

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With an estimated incidence of about 4.92 cases per 100,000/year in Europe[1] and 14,620 new cases in 2015 in the USA,[2] chronic lymphocytic leukemia (CLL) is the most frequent leukemia in Western countries. While a minority of patients may attain long-lasting responses with chemoimmunotherapy,[3,4,5] relapse and treatment-resistant diseases develop in the majority of cases; infections, progressive disease and second primary tumors being the most frequent causes of death.[5] The first-in-class inhibitor of Bruton's tyrosine kinase (BTK), ibrutinib, was welcomed in 2013 as a new paradigm for the treatment of relapsed or refractory CLL, as it produced responses in 71% of the cases in a heavily pre-treated patient population who had few, if any, alternative treatment options.[6,7] After a median observation of 3 years,[8] exceptional overall survival (OS) and progression-free survival (PFS) rates were reported (79% and 69%, respectively), along with a low (12%) discontinuation rate due to adverse events. Following the publication of excellent efficacy data in patients with 17p deletion (del(17p)) or *TP53* mutations,[9,10] high expectations were generated in the belief that this drug was able to produce durable responses in the majority of patients, irrespective of the presence of unfavorable prognostic factors.[11]

However, the median age of the patients in the trials was 64 years[8] and only 32% of them had a Cumulative Illness Rating Scale (CIRS) score of >6.[12] This reflects the inclusion criteria in the clinical trials, which required that the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, with adequate liver and kidney function, no significant neutropenia or thrombocytopenia and who did not require warfarin or strong CYP3A4/5 inhibitors. Because CLL is diagnosed at a median age of 70-72 years and the majority of patients carry several comorbidities,[13] the efficacy and safety data published in the literature were obtained in a patient population which did not reflect the typical patient found in everyday practice.

Two papers in this issue of Haematologica[14,15] describe the efficacy and toxicity of ibrutinib in 315 and 95 real-world patients treated in the UK and in Sweden, respectively, within a named patient scheme or a compassionate use program. Both studies adopted rigorous methods, minimizing biases inherent in retrospective studies. The baseline characteristics of the enrolled patients are summarized in Table 1, along with the salient outcome measures.

Overall, these two studies are reassuring with regards to the excellent efficacy of this new class of inhibitors, even when utilized in routine clinical practice without the many constraints and controls typical of clinical trials. Though the follow up is still short (around 1-1.5 years), objective outcome measures, i.e., median discontinuation-free survival and PFS, remain in the comfort zone, with PFS values of 77% after 10 months among the Swedish patients, and not yet reached in the UK series. These PFS values also include *TP53* disrupted patients, and, in particular, those patients with del(17p), who make up one third

Table 1. Salient results of published studies of ibrutinib in relapsed refractory chronic lymphocytic leukemia (CLL).

Patients' characteristics and outcome measures	Patients enrolled in trials Byrd *et al.* (2015)[8]	UK CLL forum[14]	Swedish CLL group[15]	Real world patients Mayo Clinic series[16]	Moffitt Cancer Center series[17]
N. of patients	101	315	95	124	54
Median age	64	69	69	65	60
Median follow-up (months)	36	16	10.2	6,4	9,1
Progression free survival	69% at 30 months	NR	77% at 10 months	NR	NR
Overall survival	79% at 30 months	83,8% at 12 months	83% at 10 months	NR	NR
Cases with dose reduction	12%	44,4%	22%	NR	NR
Cases with permanent discontinuation due to AEs	12%	17,7% at 12 months	11%	10% at 6 months 22% at 12 months	15%

NR: not reported; AEs: adverse events.

of all cases in the UK cohort and >50% in the Swedish group. Unfortunately, both real life studies were categorically able to demonstrate that even among the most advanced countries in Europe, testing for *TP53* mutations in all CLL patients before starting any line of therapy remains a difficult goal to reach. Having said that, the efficacy of ibrutinib in CLL with *TP53* disruption was also confirmed in these two studies, even though the affected patients experienced more discontinuations and earlier progression than the remaining individuals. It seems likely that a more advanced age and the number of previous treatments were the contributing factors to a less favorable prognosis.

This is probably also one of the possible explanations for the unexpectedly higher discontinuation rate, which ranged between 24-26% after 10-12 months, in contrast with the more reassuring percentage of patients (33% at 3 years) discontinuing ibrutinib treatment in published trials. Although disease progression was one of the reasons for discontinuing treatment, most patients, in particular in the UK study, stopped the drug because of adverse events. In general, the median age, which was 69 years in both studies, was higher than that reported in the registration trials, and 1/4 patients had poor performance status, thus providing, at least in part, an explanation for the discrepancies in drug tolerance. It is also worth noting that in the past, in the case of immunochemotherapy, the fludarabine, cyclophosphamide, and rituximab (FCR) regimen when used in routine clinical practice was associated with more dose reductions than previously reported.[18] A worrisome possibility would be that, in contrast to the colleagues enrolling patients in clinical trials and who can be assisted by written guidelines or medical monitoring, hematologists in everyday life may not feel fully at ease in managing the typical non-hematological toxicity of the drug, resulting in earlier discontinuation. In line with this, a higher percentage of patients also reduced the dose, but this did not appear to be associated with poorer outcome, at least in the larger UK series. Long (>14 days) dose interruptions were associated with inferior outcome, and it is likely that this observation might be simply due to a selection bias for those patients with comorbidities or with more advanced disease.

Interestingly, the efficacy of ibrutinib was similar irrespective of the number of prior lines of therapy. This observation in everyday life is at variance with the *ad hoc* analysis within the RESONATE study,[19] and requires longer follow-up and maybe sequential study in order to confirm the correct placement of the drug in the treatment history of our CLL patients.[20,21]

In conclusion, ibrutinib confirmed its efficacy and tolerability in over 400 patients treated outside clinical trials, without unexpected adverse events, but with infection being cited as a frequent cause of discontinuation. Dose reductions did not appear to influence outcome which also remained very good in patients with TP53 disruption, though less favorable in those with reduced performance status, more likely resulting in prolonged treatment breaks.

Along the same line, it becomes relevant to underscore that while initial reports suggested that most patients with relapsed or refractory CLL who discontinued ibrutinib had poor outcomes,[22] more recent studies clearly show that switching to another kinase inhibitor[23] or to venetoclax[24] may rescue up to 70% of the cases, especially when discontinuation was prompted by an adverse event. Therefore, there is life with ibrutinib, but also after it.

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