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Ibrutinib Dose Adherence and Therapeutic Efficacy in Non-Hodgkin Lymphoma: a single center experience.

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Abstract

Background: As oral targeted agents, such as ibrutinib, become more widely used understanding the impact of suboptimal dosing on overall and progression-free survival outside of clinical trials is imperative.

Methods: Data on ibrutinib discontinuation, dose reductions and treatment interruptions were collected on 170 non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL n=115, 64%) patients treated with ibrutinib at a single institution. Ibrutinib dose adherence was calculated as the proportion of days in which ibrutinib was administered out of the total number of days ibrutinib was prescribed in the first 8 weeks. Kaplan-Meier curves and log-rank tests were used to compare conditional survival outcomes beyond 8 weeks in patients 80% dose adherence and patients <80% dose adherence.

Results: Median overall survival among those that discontinued for progression was poor (n=51, 1.7 months, 95% CI 0.3–3.7). Lower dose adherence (<80%) was associated with significantly worse progression-free (p=0.002) and overall survival (p=0.024). However, among CLL patients, lower dose adherence was only associated with worse progression-free survival (p=0.043). Patients with early dose reductions had significant worse PFS (p=0.004) and OS (p=0.014). Patients with dose interruptions lasting > 1 week had worse PFS (p=0.047) but not OS (p=0.577).

Conclusion: In this observational study, NHL and CLL patients demonstrated poor outcomes after discontinuing ibrutinib for disease progression. The inferior survival related to suboptimal dose adherence of ibrutinib was predominantly due to early dose reduction. These data confirm poor survival in CLL and lymphoma patients alike after ibrutinib discontinuation and support recommendations for full dose at treatment initiation.

Microabstract:

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Conflicts of Interest: None

Orally administered targeted therapies, including ibrutinib, are increasingly used to treat non-Hodgkin lymphoma, however, little is known about the clinical impact of suboptimal dosing. Data on reasons and timeframes for ibrutinib discontinuation, dose reductions and treatment interruptions were collected on 170 non-Hodgkin lymphoma and chronic lymphocytic leukemia patients treated with ibrutinib at a single institution. Discontinuation of ibrutinib therapy was associated with poor outcome as previously reported. We also show that discontinuation of therapy for reasons other than progression and reduction of ibrutinib dose were associated with poor outcome. Patients also demonstrated poor progression-free and overall survival related to suboptimal dose adherence of ibrutinib which was predominantly due to early dose reduction rather than temporary dose holds. These data support recommendations for full dose at treatment initiation and allowing for short duration dose holds as needed.

Keywords

non-Hodgkin lymphoma; chronic lymphocytic leukemia; ibrutinib; targeted therapy; tyrosine kinase inhibitor

Introduction

Treatment paradigms for non-Hodgkin lymphoma are shifting toward orally administered targeted therapies. While these therapies are well tolerated in clinical trials, data from real-world use continue to emerge reporting high frequencies of dose reductions, dose holds, and discontinuations^{1–3}. Data are limited, however, about the combined impact of overall dose holds and reductions on survival outcomes.

Ibrutinib, is an oral inhibitor of Bruton tyrosine kinase (BTK) which is currently approved for treatment of chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma, and marginal zone lymphoma. While ibrutinib therapy is generally well tolerated across multiple indications, dose reductions are required in 6–26% of patients and treatment discontinuation rates are reported in 4–24% of patients^{1, 2, 4, 5}. Further, patients need to interrupt ibrutinib therapy for invasive procedures due to bleeding risk⁶ and may be non-adherent to their prescribed therapy.

Previous studies have demonstrated that adherence to oral tyrosine kinase inhibitors is critical to achieving efficacy^{7, 8}. In CLL patients, once daily dosing of 420mg resulted in complete BTK active-site occupancy for 24 hours⁹. Fewer patients are able to maintain BTK occupancy at lower doses¹⁰ and dose interruptions may reverse the biological effect of ibrutinib. Poor adherence and reduced dosing are a significant concern given the possibility of treatment resistance.

Current understanding of the impact of ibrutinib dose adherence on clinical effectiveness is conflicting and potentially dependent on disease characteristics. We examined the impact of ibrutinib discontinuation and dose adherence on overall and progression-free survival in all non-Hodgkin lymphoma and chronic lymphocytic leukemia patients treated with this drug at a single institution. We hypothesized that early discontinuation and lower dose adherence would be associated with worse survival outcomes.

Methods

All CLL and non-Hodgkin's lymphoma patients treated with ibrutinib at the University of Rochester Wilmot Cancer Institute between January 1, 2014 and December 1, 2016 were eligible for inclusion in this study. Data to date suggests that the addition of rituximab to ibrutinib does not improve long term progression free survival (PFS) and overall survival (OS) outcomes in CLL. We therefore included patients receiving this combination¹¹. In this study, which was approved by the University of Rochester's institutional review board, medical records were carefully reviewed for demographic and clinical data pertaining to the subject's ibrutinib use. A lymphoma clinic specialty pharmacist routinely followed all standard of care patients on ibrutinib therapy at planned intervals in clinic and by telephone. Reasons and timeframes for dose reductions and treatment interruptions required for surgical procedures and other indications, both self-reported by patients and prescribed in the medical record, were carefully documented. This monitoring provided consistent and detailed data on ibrutinib adherence, drug interactions, adverse events, dose reductions, and treatment interruptions that was prospectively recorded in the medical record. The frequency of permanent discontinuation over the entire study period and reasons for discontinuation were examined. Kaplan-Meier curves were used to graphically summarize OS after ibrutinib discontinuation, and the log-rank test was used to compare survival between those who did and did not discontinue due to progressive disease.

Dose adherence was calculated to incorporate data on dose interruptions, dose reductions and permanent discontinuations in the first eight weeks. Dose adherence was calculated as the proportion of days in which ibrutinib was administered as prescribed out of the total number of days ibrutinib was prescribed in the first 8 weeks post-initiation. Calculating dose adherence in the first 8 weeks post-initiation of ibrutinib allows for analysis of conditional survival beyond 8 weeks, stratified by adherence in the first 8 weeks. Survival outcomes included overall survival (OS) and progression-free survival (PFS). OS was defined as the time from 8 weeks post-initiation of ibrutinib to death from any cause, and PFS was defined as the time from 8 weeks post-initiation to cancer progression or death, whichever occurred first. Patients who died (n=4) or were lost to follow up (n=3) within the first eight weeks were not included in OS or PFS analyses. Additionally, 6 patients progressed in the first eight weeks and were excluded from progression-free survival analyses. Previously, a dose adherence of <80% was reported to be associated with worse PFS in CLL³. Therefore, we primarily used the cut point of <80% to define poor adherence.

To determine which was contributing more to the effect of poor dose adherence, additional analyses were done separately examining the effect of dose reductions or permanent discontinuations in the first eight weeks and the effect of dose interruption longer than 7 days or permanent discontinuations in the first eight weeks. Holding ibrutinib for 7 days for a surgery/procedure was relatively common and we sought to examine the effects of longer dose interruptions on PFS and OS.

Kaplan-Meier curves were used to graphically summarize conditional PFS and OS beyond 8 weeks, and the log-rank test was used to compare survival between strata defined by dose adherence, dose reductions, and dose interruptions in the first 8 weeks of ibrutinib therapy.

Given the large number of CLL patients included in our sample we performed a planned subset analysis of this population.

Results

Patient Sample

Clinical and demographic characteristics for patients included in this analysis are shown in Table 1. The sample largely consisted of patients with CLL (n=115), WM (n=23), and MCL (n=21). Patients median age at ibrutinib initiation was 68 years. Median treatment duration at the time of analysis was 14.3 months, with 33.5% of patients receiving ibrutinib as a first line therapy. Of the CLL patients, 59 (51.3%) had traditionally defined high-risk disease defined as having any of the following: deletion of 17p or a TP53 mutation (24% (n=27/113)), deletion 11q (18.6% (n=21/113)), unmutated IGHV genes (74% (n=32/43)), NOTCH1 (23% (n=6/26)) or SF3B1 (19% (n=5/26)). Notably, not all CLL patients had complete testing therefore, this may be an underestimate. The frequency of reductions and interruptions was high, with 49 patients (28.8%) having at least one dose reduction and 98 patients (57.6%) experiencing at least one transient dose interruption (of any length) over the entire study period.

Treatment discontinuation

Fifty-one patients permanently discontinued ibrutinib during the entire time period studied (30%). The majority of discontinuations were due to adverse events/comorbidities (n=28, 54.9%) or disease progression (n=18, 35.3%). Specific adverse events leading to treatment cessation included infection (n=7), bleeding (n=4), myalgia/arthritis (n=4), fatigue (n=2), anemia (n=2), renal failure (n=2), and single patients with peripheral edema, headache, nausea, diarrhea, dyspnea, cough, rash, paresthesias, or muscle weakness. Two patients discontinued therapy at physicians discretion for unrelated events. The median overall survival after discontinuation of ibrutinib due to disease progression was short (1.7 months, 95% CI 0.3 – 3.7 months) (Figure 1a). Patients stopping therapy for other reasons had a better overall survival after discontinuation (p=0.0008; median not reached, 95%CI 9.6 months, not reached) than those stopping for disease progression. CLL specific survival after discontinuation (Figure 1B) was similar to the larger group with patients who stopped ibrutinib for disease progression having slightly worse OS than those who stopped for adverse events (p=0.097, progression: 1.8 months, 95%CI 0.3 months, not reached; adverse events: not estimated, 95%CI 13.3 months, not reached).

Dose adherence

In effort to evaluate the effect of reduced adherence on subsequent clinical outcomes, we focused on patients requiring early dose reduction or interruption (within the first 8 weeks of starting therapy). To be consistent with previous analyses, outcomes were compared using an adherence cut-off of 80%³. Twenty patients had a dose adherence <80% within the first eight weeks. Dose adherence of <80% was significantly associated with worse progression free survival (p=0.002) and overall survival (p=0.021) (Figure 2). When examining CLL patients specifically, dose adherence <80% was significantly associated with worse PFS but not OS (p=0.043 and 0.816).

Dose reductions

We next attempted to examine the impact of dose reductions within the first eight weeks independently. Of the 5 patients who required a dose reduction within the first eight weeks of therapy, the lowest ibrutinib dose was 280 mg in 2 patients and 140 in 2 additional patients. In addition, one patient with mantle cell lymphoma reduced from 560mg to 420 mg daily. Reasons for dose reduction included thrombocytopenia, febrile neutropenia, anemia, rash and a medication interaction in 1 patient each. These patients who required an early dose reduction had a significantly worse PFS ($p=0.004$) and OS ($p=0.014$) compared to those who maintained dosing (Figure 3). Their outcomes appeared somewhat similar to those permanently discontinuing ibrutinib although formal comparison of these 2 groups is limited by the sample size.

Dose interruptions

In a similar manner, we evaluated the impact of temporarily holding ibrutinib within the first eight weeks. Ten patients required a dose interruption lasting more than 1 week but subsequently restarted therapy. Reasons included febrile neutropenia, anemia, gastrointestinal bleeding, headache, rash, heart palpitations, surgical procedure and medication interactions in 1 patient each and pneumonia in 2 patients. While these patients demonstrated an inferior PFS ($p=0.047$), OS ($p=0.577$) was similar to those who continued on therapy without an early interruption and appeared significantly better to patients discontinuing ibrutinib. (Figure 4)

Discussion

Ibrutinib has dramatically changed treatment paradigms for CLL, MCL and WM as it is highly effective and has a low toxicity profile, however, it requires continuous administration. Frequent dose interruptions or alterations prompt concerns of disease progression and the potential for therapeutic resistance. Our results demonstrate that discontinuation of ibrutinib after an adverse event is associated with a poor overall survival in lymphoma and CLL patients. Further, patients with a reduced adherence shortly after treatment initiation have inferior outcomes. Specifically, early dose reduction appears to correlate with an inferior survival.

The discontinuation rates reported here are similar to previous studies in both CLL and WM populations^{1, 2, 4, 13}. However, our rate of discontinuation is smaller than a recently reported discontinuation rate in a community based CLL study, which also saw much lower frequency of discontinuation due to progression (10.7% vs. 35% in this study) potentially indicating a less heavily pre-treated and lower risk population¹⁴. Similar to analyses of CLL patients and WM on clinical trials, patients who discontinued ibrutinib for progression had a worse overall survival compared to those who discontinued for other reasons^{1, 4}. Among CLL patients that discontinued for progression median overall survival was 54 days. This is shorter than OS estimates reported in two other studies of CLL patients (16 and 17.6 months) however these estimates did not include transformed disease (2.3 and 3.5 months) which was included as progression in our analyses^{2, 4}. Outcomes for non-progression discontinuation in these analyses have been reported to be somewhat better with a median

overall survival of 1–3 years for patients with relapsed CLL. Our findings are similar, with 67% of the entire group and 80% of CLL patients remaining alive after 1 year. Not surprisingly, survival following discontinuation for a severe infection is poor while discontinuation for ibrutinib intolerance is more favorable. Cumulatively, these results suggest ibrutinib discontinuation after disease or treatment related toxicity continues to predict for poor survival despite earlier use and the availability of effective agents available for salvage therapy. As such, treating physicians need to be aware of these outcomes when initiating therapy on patients with high-risk CLL or lymphoma as well as those with significant comorbidities or immune deficiencies.

In addition to stopping ibrutinib, our findings suggest that poor early dose adherence is also associated with poor survival. Despite excluding early disease progression, patients able to continue ibrutinib but with suboptimal dosing had a 1 year survival of 67.3%. Results from our CLL patients are similar to findings previously published suggesting poor dose adherence was associated with worse PFS but a comparable OS³. In sensitivity analyses we explored PFS and OS in other subtypes, including mantle cell lymphoma where poor dose adherence was significantly associated with worse PFS and OS (data not shown). Together, these analyses raise concerns for the development of therapeutic resistance for patients receiving suboptimal ibrutinib dosing. However, bias may arise as reduced adherence early in the treatment course may also be related to underlying illness limiting adherence or influencing physician prescribing.

Exploring this further, we found early dose reduction to be associated with an inferior progression free and overall survival for the entire cohort and with an inferior progression free survival only for CLL patients. The effect of temporary dose holds appeared less detrimental overall. A similar pattern of findings was reported in a large cohort of CLL patients receiving first line ibrutinib¹⁵. This would suggest that the ideal treatment strategy would be to recommend initiation of therapy at standard dosing and interruption as needed as directed in the FDA label. Two studies have reported no negative impact for patients requiring dose reductions^{16, 17}, however differences may be attributable to population differences and timing of reductions. The present analyses focus on patients with early incomplete adherence and possibly represents a group that is at greater risk of poor adherence and subsequent poor outcomes. Despite our results and those obtained within the context of a clinical trial³ demonstrating transient disease progression related to temporary dose holds, this appears to be reversible with re-initiation of therapy¹⁶.

The current study is limited by the small number of non-CLL patients, future larger multicenter studies should examine the role of dose adherence and survival in patients who have MCL specifically, as our exploratory analyses suggests this subgroup may be driving the association between dose adherence and poor OS. These results are also limited by the relatively small number of dose reductions and holds within the first eight weeks and results should be interpreted cautiously. Nonetheless, meaningful differences are reported in PFS that are consistent with other larger studies. Additionally, our analyses cannot truly differentiate between poor adherence and the cause for poor adherence. Still, many patients experienced poor adherence due to known AEs that resolved with altered dosing supporting a causal role for poor adherence. This study is also constrained by the inherently subjective

nature of date adherence data. As ibrutinib is administered independently by the patients, dose reductions/hold were prescribed by the physician, and missed doses were self-reported to the specialty pharmacist or prescribed by the physician, we cannot be sure of a patients' true dosing. However, patients were systematically questioned about their adherence so if underreporting exists the survival estimates reported here are underestimates. Recognizing the limitations of assessing adherence, this study contributes to the increasingly important discussion of the threshold of nonadherence that results in poor outcomes¹⁸. Lastly, dose adherence in the first eight weeks was examined to maintain consistency with other reports, however, we recognize that their may be clinical utility in examining the predictive potential of other time frames. Future larger studies with longer ibrutinib treatment duration should be designed to examine other exposure periods (e.g. six months). Ideally these studies would also be able to account for residual confounding by line of therapy, ibrutinib therapy combinations, and underlying disease risk (particularly for CLL). Understanding which time periods and patient characteristics influence patient compliance, drug resistance, and ultimately survival outcomes will be informative in launching interventions to improve adherence.

In conclusion, we found survival to be significantly inferior for patients discontinuing ibrutinib for disease progression and treatment related toxicity. Further, these findings suggest that maintaining optimal dosing of ibrutinib early in the treatment course is critical to preventing disease progression. The population unable to maintain optimal adherence are at risk for particularly poor outcomes.

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Clinical Practice Points (Original Studies, Case Reports)

Previous studies have demonstrated an inferior survival for patients discontinuing ibrutinib for CLL progression or histologic transformation and to a lesser degree for discontinuation due to intolerance or toxicity. Analyses of reduced ibrutinib adherence have produced mixed results. Here we confirm poor outcomes after discontinuation for CLL and NHL patients alike despite the increasing availability of salvage therapy and for patients requiring early dose reductions. These findings allow treating physicians to identify patients at risk for poor survival and guide ibrutinib prescribing when faced with patients experiencing disease or treatment related side effects.

Figure 1:

A) Survival from time of discontinuation (all diagnoses) comparing discontinuation due to progression vs. other causes, and B) Comparing survival after discontinuation among CLL patients comparing discontinuation due to progression vs. other causes

Figure 2:

A) Conditional overall survival stratified by $< 80\%$ adherence in first 8 weeks of ibrutinib therapy, and B) Conditional progression-free survival stratified by $< 80\%$ adherence in first 8 weeks of ibrutinib therapy, C) Conditional overall survival in CLL patients stratified by $< 80\%$ adherence in first 8 weeks of ibrutinib therapy, and D) Conditional progression-free survival in CLL patients stratified by $< 80\%$ adherence in first 8 weeks of ibrutinib therapy

Figure 3:

A) Conditional overall survival stratified by dose reductions and discontinuations, and B) Conditional progression-free survival stratified by dose reductions and discontinuations

Figure 4:

A) Conditional overall survival stratified by dose holds and discontinuations, and B) Conditional progression-free survival stratified by dose holds and discontinuations

Table 1:

Demographic and clinical characteristics.

	Entire Cohort
N (%)	170 (100%)
Demographics:	
Age at diagnosis (years, median (min, max))	61.35 (34.25,91.71)
Male	118 (69.4)
White	158 (92.9)
Clinical Characteristics:	
Time From Diagnosis to Ibrutinib (months, median (IQR))	55.87 (0.26,423.00)
Cancer Diagnoses: ¹	
CLL	115 (63.7)
Other	55 (36.3)
WM/LPL	23
Mantle Cell Leukemia	21
Hairy Cell Leukemia	1
B-cell prolymphocytic leukemia	3
Other	7
Ibrutinib Use Characteristics	
Age at Ibrutinib Initiation (years, median (min,max))	67.90 (41.00,92.30)
Treatment Duration (months, median (min,max))	14.28 (0.36,65.77)
Treated on Clinical Trial	39 (22.9)
First Line therapy	57 (33.5)
Concurrent Therapy	35 (20.6)
Rituxumab	26 (74.3)
Bendamustine and rituxumab	2 (5.7)
Other	7 (20.0)
Reason for Initiation ¹	
Clinical or Symptomatic Disease	136 (80.0)
Cytopenia	70 (41.2)
Other	5 (2.9)
Discontinued Ibrutinib:	51 (30.0)
Reasons for Ibrutinib Discontinuation	
Adverse Event	19 (37.2)
Progression	17 (33.3)
Comorbidities	9 (17.6)
Patient Choice/Other	6 (11.9)
Progressed after discontinuation (n=32)	15 (46.9)
Response to Ibrutinib	

	Entire Cohort
N (%)	170 (100%)
Responder	137 (81.0)
Stable disease (never responded)	22 (13.02)
Progression (never responded)	10 (5.92)
1 Dose Reduction 1st 8 weeks	8 (4.7)
1 Dose Interruption 1 st 8 weeks	28 (16.5)
Dose Adherence (mean)	
<80% adherence in 1 st 8 weeks (n=163)	20 (12.27)

CLL: chronic lymphocytic leukemia, WM/LPL: waldenstrom macroglobulinemia or lymphoplasmacytic lymphoma

¹Not Mutually Exclusive