

The Impact of Age on Survival in CLL Patients Receiving Ibrutinib as Initial Therapy

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Introduction: Recent randomized trials have demonstrated the efficacy of ibrutinib-based therapy in the treatment of patients with CLL. In Alliance A041202, a higher than expected number of unexplained deaths were reported with front-line ibrutinib in a patient population aged at least 65 years compared to ECOG 1912, which included patients up to 70 years of age.

Methods: Therefore, we conducted a retrospective analysis to investigate whether ibrutinib was associated with a greater mortality in older patients outside of a clinical trial setting. This multicenter analysis was performed by investigators at 20 academic and community practices.

Results: Amongst the 391 patients included, there was no correlation between age and response rate, PFS, or OS. However, there was a trend to higher rate of deaths in patients >65-years-old (8.7% vs 3.8%, $p=0.097$), with an increased number of early deaths (13 vs 4, $p=0.3$).

Conclusion: These data suggest greater intolerance, and possibly mortality, with ibrutinib in an older population. Patients should be educated regarding the potential complications related to ibrutinib and symptoms of concern to report.

Keywords: CLL, ibrutinib, elderly

Introduction

Recently published cooperative group studies, Alliance A041202 and ECOG E1912, have established the role of ibrutinib over chemoimmunotherapy for the front-line treatment of chronic lymphocytic leukemia (CLL).^{1,2} Notably, Alliance A041202, which evaluated patients ≥ 65 -years-old receiving ibrutinib with or without rituximab or the combination of bendamustine and rituximab (BR), reported a higher than expected number of deaths in both of the ibrutinib-containing arms.¹ Ten unexplained/unknown deaths occurred among the 361 patients receiving ibrutinib; whereas 1 such event occurred in the BR arm ($n=176$). These data were in contrast to ECOG E1912 in which ibrutinib plus rituximab was associated with an improvement in overall survival (OS) compared to FCR (fludarabine, cyclophosphamide, rituximab) in patients less than 70 years of age.² Together, these data suggest ibrutinib may be associated with significant adverse events (AE) and greater mortality in an elderly CLL population. We sought to investigate this hypothesis in previously untreated patients who received commercially available ibrutinib as initial therapy for CLL.

Methods

This multicenter retrospective analysis was performed by investigators at 20 academic and community practices. The study was approved by the institutional review board at

each participating institution ([Supplementary Materials](#)). Informed consent was waived because the research involved no more than minimal risk to the patient. In compliance with the Declaration of Helsinki, patient confidentiality was maintained through de-identified data collection practices. Patients were considered eligible for inclusion if they received ibrutinib for the front-line treatment of CLL through commercial sources. Medical chart review via diagnostic codes was performed to identify all CLL patients at each institution. Investigators utilized chart review, electronic medical records, and related databases to obtain required information. Patient demographics, prognostic markers, ibrutinib dosing administration, and clinical outcomes data were collected. The International Workshop on Chronic Lymphocytic Leukemia (iwCLL, 2008) criteria were used to define response and progression of disease.³

The primary endpoint was OS as determined by the Kaplan Meier method.⁴ OS was defined as time from initiation of ibrutinib to death. Comparisons of survival were made using COX regression analyses.^{5,6} All other comparison analyses were descriptive. Early deaths were defined as a death from any cause occurring within 12 months of ibrutinib treatment initiation. Secondary endpoints included response rates, progression-free survival (PFS), discontinuation rates, and reasons for discontinuation. PFS was defined as time from ibrutinib initiation to progression or death from any cause. Patients were otherwise censored at the time of last follow-up. Statistical analyses were performed using STATA 10.1 (Stata Statistical Software: Release 10, 2007; StataCorp LP, College Station, TX). All tests were two-sided at the 5% level.

Results

Of the 391 patients identified, 59% were 65 years or older (≥ 65 YO). The median age at initiation of ibrutinib was 63 years (range 36–96). Patient characteristics are detailed in [Table 1](#). Poor risk prognostic features were similar in patients stratified by age at start of ibrutinib (≥ 65 YO and < 65 YO cohorts, respectively): del 17p (29%, 30%), TP53 mutation (21%, 19%), IGHV unmutated (71%, 64%), and complex karyotype (25%, 21%).

The median time from diagnosis to initiation of ibrutinib was 35 months for patients ≥ 65 YO and 25 months for those < 65 YO. Eleven percent of older patients were initiated on a lower than standard dose of ibrutinib (420 mg daily) in contrast to 2% of younger patients ($p=0.02$). In older patients, 20% required dose reduction compared to 13% of younger patients ($p=0.07$). Dose interruptions occurred in 46% of older

Table 1 Patient Characteristics

	<65 YO (n=160)	≥ 65 YO (n=231)
Sex		
M	63%	62%
F	37%	38%
Race		
Caucasian	90%	94%
Other	10%	6%
del 17p	(n=158)	(n=211)
Absent	70%	71%
Present	30%	29%
TP53 mutation	(n=102)	(n=117)
Absent	81%	79%
Present	19%	21%
del 11q	(n=158)	(n=209)
Absent	79%	86%
Present	21%	14%
Complex Karyotype	(n=122)	(n=157)
Absent	79%	75%
Present	21%	25%
IgVH	(n=102)	(n=119)
Unmutated	64%	71%
Mutated	36%	29%

and 36% of younger patients ($p=0.04$); the median duration of dose interruption was 13 and 10 days, respectively ($p=0.49$). Ibrutinib discontinuation occurred in similar frequency for older and younger patients (25%, 22%). Intolerance was the most common reason for discontinuation in both age groups ($n=36$ and 20 , respectively), followed by CLL progression ($n=6$, 6), and Richter's transformation ($n=5$, 4).

Investigator assessed overall and complete response rates for ibrutinib were 79% and 15% in patients ≥ 65 YO and 85% and 20% in those < 65 YO. There was no difference in PFS based on age (HR 1.13, $p=0.69$), [Figure 1](#). At a median follow up of 13.8 months (range 1–76 months), a total of 26 deaths were observed. There was a higher proportion of deaths in the older cohort (8.7% vs 3.8%, 20 deaths vs 6 deaths), though difference in OS did not reach statistical significance (HR 2.1, $p=0.097$). [Figure 1](#). The number of early deaths, defined as occurring within the first 12 months of therapy, was 13 in patients ≥ 65 YO compared to 4 in patients < 65 YO, $p=0.3$.

Conclusion

In this cohort of nearly 400 patients who received single agent ibrutinib for the front-line treatment of CLL, age did

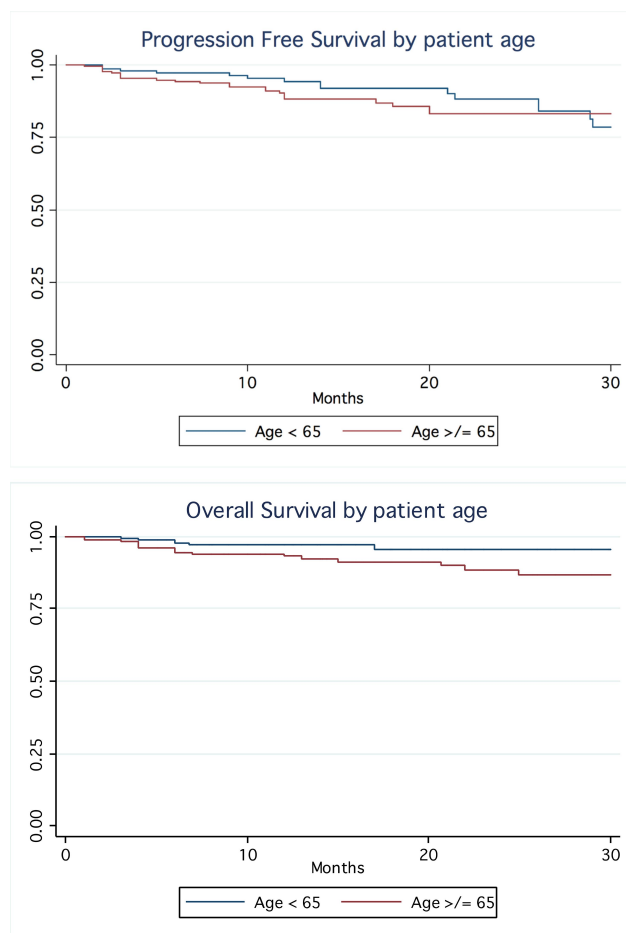


Figure 1 Survival by age.

not correlate with response rates, progression-free survival, or overall survival. Nevertheless, a greater than two-fold increase in death was noted in patients ≥ 65 -years-old compared to the younger cohort. Similar to the data reported in the Alliance A041202 study, where the majority of unexplained deaths with ibrutinib occurred within the first two years of treatment, early deaths in our analysis appeared to occur more frequently in the older patient population.¹ These data support our initial hypothesis that ibrutinib may be associated with a greater early mortality in an older CLL population.

In this analysis, nearly 50% of the older population required dose interruptions and 20% required dose reductions suggesting issues with drug tolerability related to AEs. Furthermore, it appears that practitioners anticipated an increase in AEs in the older population as they more frequently prescribed lower than standard doses of ibrutinib at initiation of therapy. Alternatively, this may represent decreased experience with the drug in the early days of approval. Despite these findings, the incidence of

ibrutinib discontinuation was relatively comparable between the different age groups. Additionally, intolerance to ibrutinib remained the most common reason for discontinuation of therapy in all patients.

When comparing the grade 3–5 adverse events that occurred with ibrutinib in the older Alliance A041202 and younger ECOG E1912 populations, the most notable differences are the increased rates of cardiovascular toxicity, specifically atrial fibrillation (9% vs 3%) and hypertension (29% vs 7%).^{1,2} A recent retrospective analysis of 562 patients receiving ibrutinib at the Ohio State University also noted a marked incidence of new hypertension of 72%.⁷ Major cardiac events were noted in 17% of patients and occurred more frequently in those with new or worsening hypertension (19%). In a separate aggregated data set of over 1000 patients receiving ibrutinib, 10 events of sudden death or cardiac arrest were identified.⁸ The HELIOS study of BR with or without ibrutinib was included in this analysis; 7 events of \geq grade 3 ventricular arrhythmia, cardiac arrests, and sudden deaths were found in the ibrutinib-containing arm compared to 0 with BR alone.⁹ The higher incidence of these toxicities raises suspicion for a cardiac event as a potential etiology for the unexplained, early deaths noted in both Alliance A041202 and this analysis; however, investigators were unable to confirm this impression. It is also noted that early death is not necessarily the same as sudden death. Unfortunately, a critical limitation of our analysis is that the individual causes of death were not captured uniformly as part of this retrospective data review, nor were the past cardiac histories. We were unable to identify which, if any, adverse events occurred in patients who experienced an early death or assign attribution to drug. However, given the marked efficacy of ibrutinib and the ability of patients to be effectively salvaged after progression, one may assume that toxicity may be a key contributing factor.

Given the quickly evolving treatment landscape for CLL, one of the more complicated decisions oncologists will face is determining the most appropriate novel therapeutic for their individual patient. Ibrutinib is certainly a highly effective therapy for patients of all ages, ensuring a lengthy PFS and OS in elderly patients with high-risk disease. However, as the majority of patients with CLL are elderly and many have comorbidities, ensuring tolerability is crucial. While our data are hypothesis generating only, these findings in combination with those of Woyach et al suggest close monitoring of elderly patients treated with ibrutinib is warranted for toxicity, particularly in the first

12 months of therapy.¹ In addition, patients should be educated regarding the potential complications related to treatment and symptoms of concern to report.

Fortunately, a number of effective agents have or will become available to patients in the near future. The CLL-14 study of venetoclax and obinutuzumab recently secured the B-cell lymphoma (BCL)-2 inhibitor a role in the front-line setting.¹⁰ The safety of venetoclax in an elderly population with comorbidities, including decreased renal function, was demonstrated in this study. However, 5 fatal adverse events were noted during treatment, primarily due to infection, as well as 4 fatal infection events which occurred after completion of venetoclax. The incidence of severe neutropenia was 53% in this study, highlighting the importance in supporting and monitoring patients appropriately both during and after therapy. Additionally, there are second-generation Bruton tyrosine kinase (BTK) inhibitors in development, including acalabrutinib and zanubrutinib, which may be associated with less atrial fibrillation.^{11,12} Their relative risk of early deaths will be forthcoming with the results of Phase III trials. The combination of a BTK inhibitor and a BCL-2 inhibitor has also demonstrated remarkable efficacy with a shorter required treatment duration and thus less time for drug exposure.¹³ Whether fixed duration combination strategies will result in less toxicity or early deaths is unknown. Moving forward, although the correlation between age and survival was not shown to be statistically significant, we do feel a greater effort must be focused on understanding whether the cause of early mortality in older patients receiving ibrutinib is related to the drug or the patient; additionally, how best to mitigate this problem which may limit the use of this highly effective agent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to

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