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Single-Agent Ibrutinib Versus Allogeneic Hematopoietic Cell Transplantation for Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and del(17p)

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OBJECTIVE

To provide comparative data of allogeneic hematopoietic cell transplantation (aHCT) versus ibrutinib treatment in patients with relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and del(17p)

CONCLUSION

This retrospective analysis suggests that ibrutinib treatment may offer improved overall survival and progression-free survival outcomes over aHCT in patients with relapsed/refractory CLL/SLL and del(17p)

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https://www.congresshub.com/ASH2024/Oncology/Ibrutinib/Awan

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INTRODUCTION

- Prognosis and treatment outcomes are inferior for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with del(17p) compared with patients without this abnormality.[1] Historically, these patients would undergo allogeneic hematopoietic cell transplantation (aHCT) early in the disease course[1]
- The introduction of targeted agents such as ibrutinib has significantly improved the survival rates for patients with CLL/SLL, but differences in outcomes between patients with and without high-risk genetic features have been observed[2–6]
- To date, outcomes with ibrutinib versus aHCT have not been directly compared in patients with del(17p)

METHODS

Data Source

- This study used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) observational registry and randomized clinical trials, RESONATE (NCT01578707) and RESONATE-17 (NCT01744691)

Study Design and Population

- This retrospective analysis includes adults with relapsed/refractory CLL/SLL with del(17p) who received either aHCT (reported to CIBMTR in 2008–2017) or single-agent ibrutinib (420 mg/day; enrollment dates: RESONATE, June 2012–April 2013; RESONATE-17, January 2013–June 2013)
- Inclusion criteria for patients who received ibrutinib or aHCT included age ≥18 years, diagnosis of CLL/SLL, and confirmed del(17p)
  - Additional inclusion criteria for patients in the ibrutinib cohort: Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, adequate organ function, and ≤5 prior lines of therapy
  - Additional inclusion/exclusion criteria for patients in the aHCT cohort: transplant received from human leukocyte antigen (HLA)–identical related donor, HLA–mismatched related donor, and HLA–matched or mismatched unrelated donor; all sources of grafts, all conditioning regimens, and all graft-versus-host disease (GVHD) prophylactic approaches permitted; and exclusion of syngeneic donor transplantation and prior ibrutinib therapy

Study Outcomes

- The main outcomes measured for patients who received aHCT or ibrutinib were overall survival (OS) and progression-free survival (PFS); cumulative incidence of relapse/progression, nonrelapse mortality (NRM), and GVHD were reported for patients with aHCT

Statistical Analysis

- PFS and OS were analyzed according to the Kaplan-Meier method
- Baseline covariates were compared between the 2 treatment groups using a 2-sample t-test or Mann-Whitney U test for continuous variables; Fisher exact or Chi-squared tests were used for categorical variables, as appropriate
- Outcome comparisons were estimated by the average treatment effect on treated inverse propensity score weighting (ATT-IPSW) to balance key confounders: age, sex, race, bulky disease, Rai stage, prior treatment, ECOG performance status score, time from diagnosis to treatment, del(11q), del(13q), and trisomy 12
- A sensitivity analysis was conducted using an E-value to assess the minimum strength of association that an unmeasured cofounder would need to impact the treatment and outcome to explain a treatment-outcome association[7]

RESULTS

- Among qualified patients with relapsed/refractory CLL/SLL and del(17p), the median follow-up was capped at 60 months for the aHCT cohort (n=145); median follow-up for ibrutinib (n=196) was 64 and 33 months for RESONATE (n=53) and RESONATE-17 (n=143), respectively

Baseline Demographic and Clinical Characteristics Differed Between Ibrutinib and aHCT Cohorts

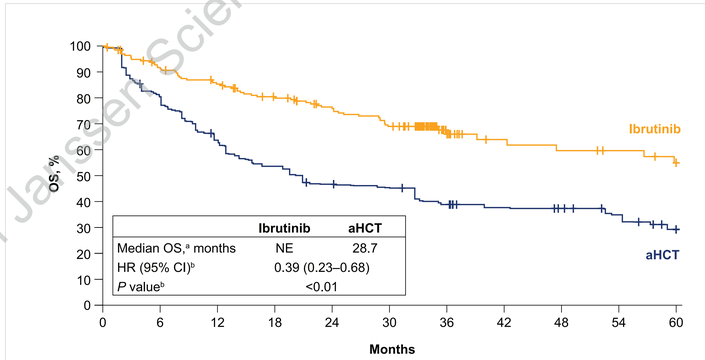
Characteristic	Ibrutinib Cohort N=196	aHCT Cohort N=145	*P* Value[a]
Age, median (range), years	65 (30–89)	59 (32–73)	<0.01
Women, n (%)	67 (34)	47 (32)	0.73
ECOG, n/N (%)			<0.01
0–1	195/196 (99)	134/137 (98)	
Race, n (%)			0.06
White	177 (90)	124 (86)	
Black	10 (5)	17 (12)	
RAI stage, n (%)			<0.01
3–4	123/196 (63)	31/106 (29)	
del(13q), n/N (%)	125/188 (66)	75/123 (61)	0.32
del(11q), n/N (%)	34/194 (18)	30/145 (21)	0.46
Trisomy 12, n (%)	36/182 (20)	25/145 (17)	0.56
Time from diagnosis to treatment, n (%)			0.02
<1 year	182 (93)	123 (85)	
Number of prior treatments, n (%)			<0.01
≥2	136 (69)	110 (76)	
Bulky disease ≥5 cm, n/N (%)	102/194 (53)	26/124 (21)	<0.01
GVHD prophylaxis, n/N (%)			NA
None	NA	1/144 (1)	
CNI + MMF[b]	NA	59/144 (41)	
CNI + MTX[b]	NA	62/144 (43)	
Others	NA	22/144 (15)	

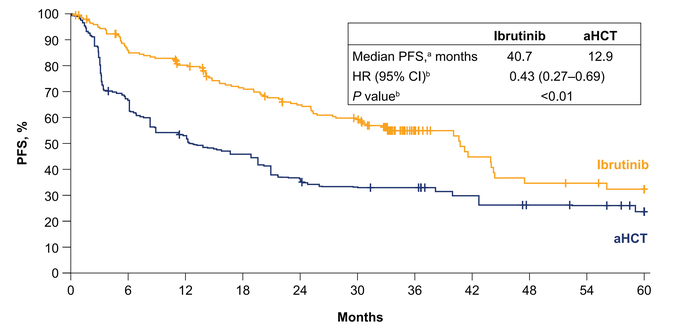
CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX; methotrexate; NA, not applicable.

[a]Calculated with 2-sample t-test for the age variable, Fisher exact test for the race and ECOG variables, and Chi-squared test for the remaining variables.

[b]With or without other prophylaxis.

Patients Treated With Ibrutinib Had Significantly Longer OS and PFS Compared With Patients Who Received aHCT





HR, hazard ratio; NE, not estimable.

[a]Estimated by Kaplan-Meier method with unweighted full analysis set.

[b]Estimated using unstratified Cox proportional hazard model using full analysis set with IPSW population and adjusted for confounders.

- At 36 months, the OS rates (95% CI) in ibrutinib and aHCT cohorts, respectively, were 66% (58–73) and 39% (23–55); PFS rates (95% CI) were 55% (47–62) and 33% (19–47)
- At 60 months after aHCT, the cumulative incidences (95% CI) of both disease relapse and NRM were 37% (0.29–0.45), 53% (0.45–0.61) for grade 2–4 acute GVHD, and 67% (0.59–0.74) for chronic GVHD (**Supplemental Information**)

Causes of Death in the Ibrutinib and aHCT Cohorts

Cause of Death, n (%)	Ibrutinib Cohort N=196	aHCT Cohort N=145
Primary disease	37 (19)	43 (30)
Infection	15 (8)	16 (11)
GVHD	1 (1)	18 (12)
Organ failure	4 (2)	6 (4)
Other	1 (1)	8 (6)
Hemorrhage	1 (1)	3 (2)
Not reported	2 (1)	2 (1)
Cardiovascular	3 (2)	0 (0)
Interstitial pneumonitis	0 (0)	1 (1)
Secondary malignancy	0 (0)	1 (1)
Vascular	0 (0)	1 (1)

- Sensitivity analysis for unmeasured confounding factors performed on the full analysis set determined an E-value (95% CI) of 2.95 (1.86–4.35), implying that considerable unmeasured confounding would be needed to negate the effect estimate

Limitations

- Data collection strategies and study time spans varied due to use of different data sources for the 2 cohorts (ie, clinical trials data vs real-world database)
- Due to clinical trial enrollment criteria, patients in the ibrutinib cohort were older, had more comorbidities, and had longer time from diagnosis versus those in the aHCT cohort. The propensity score model was applied to mitigate this imbalance
- A multiple imputation method was applied to account for missing baseline covariates
- Unmeasured confounders for the IPSW method are possible; however, sensitivity analyses indicate that only relatively strong unmeasured confounders would nullify the treatment effects
- Extreme weights from the propensity scores can bias the estimation of treatment effects and decrease the balance of covariates. In this study, weighting was truncated at 10 (99th percentile)

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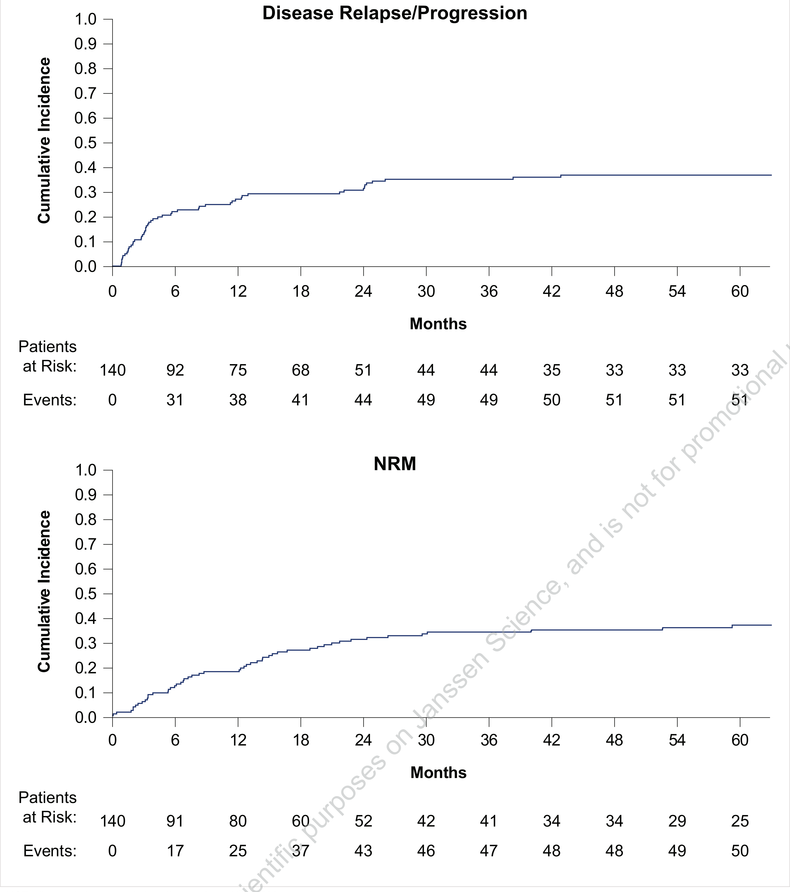
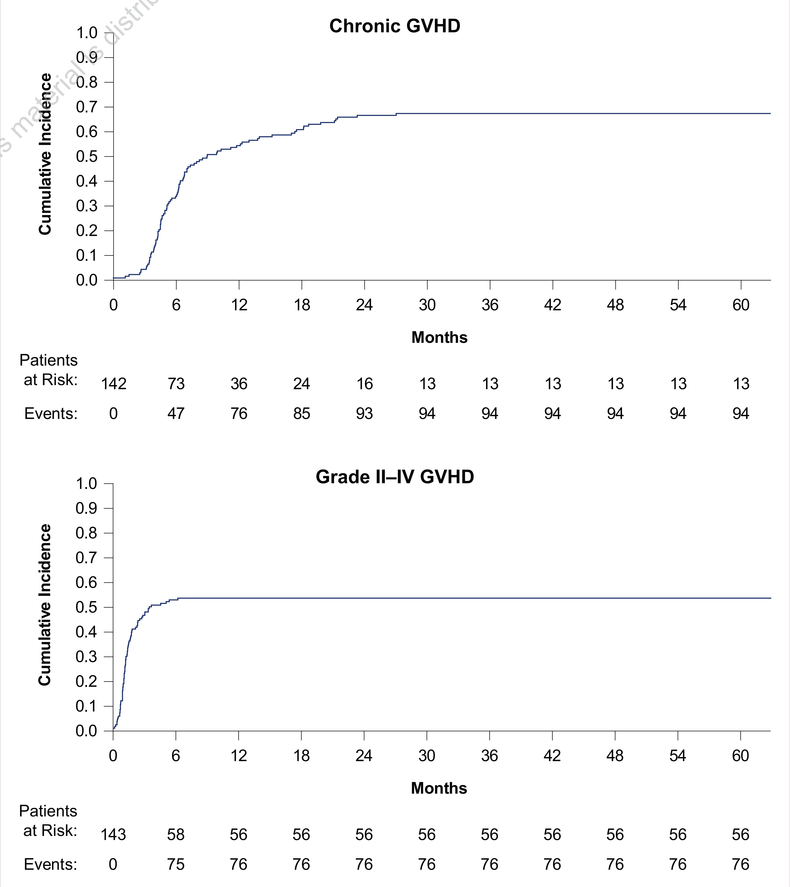
SUPPLEMENTAL INFORMATION

Cumulative Incidence of Disease Relapse/Progression and NRM Among Patients Who Received aHCT



aHCT, allogeneic hematopoietic cell transplantation; NRM, nonrelapse mortality.

Cumulative Incidence of Chronic and Grade II–IV Acute GVHD Among Patients Who Received aHCT



GVHD, graft-versus-host disease.