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Impact of Targeted Therapy on Outcome of Chronic Lymphocytic Leukemia Patients with Relapsed Del(17p13.1) Karyotype at a Single Center

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Letter to the Editor

Chronic lymphocytic leukemia (CLL) patients with del(17p13.1) exhibit short survival once disease progression necessitates therapy and respond poorly to traditional treatments compared with other cytogenetic subgroups (1). Poor outcome associated with del(17p13.1) is at least partially linked to malfunction of the tumor suppressor gene TP53 [located on 17p (2)], which inhibits apoptosis induced by chemotherapy (3-5). Therefore, despite general advances in CLL therapy with chemoimmunotherapy, progress in this subgroup has been limited. Current guidelines suggest allogeneic stem cell transplant as part of initial therapy (6), as salvage treatment for del(17p13.1) portends an even graver prognosis. Recently, novel therapeutic agents have demonstrated promising clinical activity in del(17p13.1) patients, specifically, cyclin-dependent kinase inbibitors (CDKis; flavopiridol and dinaciclib) and a Bruton's tyrosine kinase inhibitor (BTKi; ibrutinib)(7-9). To elucidate potential impact of CDKi and BTKi in this population, we examined outcomes of consecutive relapsed/refractory del(17p13.1) patients seen at Ohio State University (OSU), who received salvage therapy with one of these agents or alternative therapy. Our data

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Authorship Contributions

All authors critically revised the manuscript and approved the final submitted version. DS and AR acquired, analyzed and interpreted data and drafted the manuscript. JJ, JW, KM, SJ, LA, JF, MG, GL, AJ, NM, and NH contributed to acquisition of data. NH acquired and analyzed cytogenetic data. DS and JB developed the concept for the study.

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The authors have no significant conflicts of interest to disclose.

demonstrate significant impact of both classes of these agents on outcomes of del(17p13.1) patients.

We examined 174 consecutive relapsed/refractory del(17p13.1) CLL patients for outcome following initial salvage treatment given at OSU (OSUTx1) from 2002-2013. Patients were treated on previously reported clinical trials or received standard-of-care treatment according to NCCN guidelines. Patients provided informed consent for data collection through the Institutional Review Board-approved study OSU-0025. Stimulated cytogenetic and FISH analyses were performed on blood or bone marrow samples (previously described (10, 11)). FISH analyses probed for the chromosome 12 centromere, ATM (11q22.3), D13S319 (13q14.3), and TP53 (17p13.1) (Abbott Molecular; Des Plaines, IL). Karyotypes with ≥3 independent aberrations were defined as complex (12).

Response was assessed by IWCLL 2008 Criteria (13). Progression-free survival (PFS) was calculated from date of OSUTx1 until progression/death, censoring patients at date of second institutional treatment prior to progression or last contact, if alive and progression-free. Overall survival (OS) was calculated from date of OSUTx1 until date of death. Patients who underwent transplant or later ibrutinib (IB) were censored at that time; other patients were censored at last follow-up or administratively censored at 48 months since extended follow-up data were not available in those receiving IB and most events occurred in the CDKi and other (O; included both standard and investigational therapies) group within that timeframe. Logistic regression or proportional hazards models evaluated the impact of treatment group on outcome, controlling for other prognostic variables ($p<0.05$), where a multiple imputation technique estimated missing data and combined results for 10 datasets (14). Variables other than treatment group considered for inclusion in the multivariable models were age, sex, Rai Stage, ECOG performance status (PS), number of prior therapies, white blood cell count (WBC), creatinine, albumin, lactate dehydrogenase levels, percentage of cells with del(17p13.1), and concurrent presence of del(11q22.3), del(13q14.3), or complex karyotype (CK).

At OSUTx1, 16% (n=27), 33% (n=58), and 51% (n=89) of patients received IB-based therapy, CDKi-based therapy, or other therapies (O; includes standard and investigational therapies), respectively. Clinical and molecular characteristics were not statistically different across groups except the IB and CDKi groups had more patients with ≥3 prior therapies (70% in IB versus 64% in CDKi versus 42% in O), and as expected, the median WBC was lowest in the CDKi group since many CDKi clinical trials prohibited WBC >200K/uL to prevent tumor lysis syndrome (15) (Table 1). Overall response to OSUTx1 significantly differed among groups ($p<0.01$), where 56%, 45%, and 24% of patients in the IB, CDKi, and O groups, respectively, achieved at least a partial response (PR), and 85%, 64%, and 53% achieved at least stable disease (SD). Likewise, PFS was significantly extended with IB and CDKi compared to O ($p<0.0001$), and PFS was longer with IB compared to CDKi ($p=0.002$); 12-month estimates were 77% (95%CI=0.56-0.89), 38% (95%CI=0.25-0.52), and 17% (95%CI=0.10-0.26) in the IB, CDKi, and O groups, respectively (Figure 1A). OS was also significantly extended with IB and CDKi compared to O ($p=0.01$ and $p=0.04$, respectively) with 12-month estimates of 81% (95%CI=0.61-0.92), 78% (95%CI=0.64-0.87), and 58% (95%CI=0.46-0.68), although by 48 months, estimates for

CDKi and O were similarly low (Figure 1B). With a 12-month median follow-up, no large differences in OS between IB and CDKi were yet observed (p=0.49).

In a multivariable analysis for response, treatment group was significantly associated with achieving at least PR (p=0.0005) independent of number of prior therapies [≥3 vs <3 prior therapies: odds ratio (OR)=0.47 (95%CI=0.23-0.96; p=0.04)], and presence of del(13q) [yes vs no: OR=0.45 (95%CI=0.23-0.87; p=0.02)]. The odds of response were higher with IB and CDKi compared to O, but not significantly different between IB and CDKi [all pairwise odds ratios: IB vs O=5.66 (95%CI=2.12-15.08); CDKi vs O=3.38 (95%CI=1.57-7.31); IB vs CDKi = 1.67 (95%CI=0.65-4.32)]. In a multivariable analysis for PFS, treatment group was significantly associated with PFS (p<0.0001) independent of number of prior therapies [≥3 vs <3 prior therapies: hazard ratio (HR)=1.55 (95%CI=1.08-2.24; p=0.02)], albumin [each 1 g/dL increase: HR=0.56 (95%CI=0.37-0.85; p=0.007)], and CK [yes vs no: HR=1.65 (95%CI=1.12-2.43; p=0.01)]. The risk of progression/death decreased by 90% and 60%, respectively, with IB or CDKi compared to O, with a significantly larger decrease in risk with IB compared to CDKi [HR: IB vs O=0.10 (95%CI=0.04-0.22); CDKi vs O=0.40 (95%CI=0.27-0.60); IB vs CDKi = 0.24 (95%CI=0.11-0.54)]. In a multivariable analysis for OS, treatment group was significantly associated with OS (p=0.003) independent of number of prior therapies [≥3 vs <3 prior therapies: HR=1.73 (95%CI=1.06-2.82; p=0.03)], albumin [each 1 g/dL increase: HR=0.33 (95%CI=0.19-0.56; p<0.0001)], CK [yes vs no: HR=1.94 (95%CI=1.18-3.19; p=0.01)], ECOG PS [≥1 vs 0: HR=1.93 (95%CI-1.07-3.48; p=0.03)], and WBC [each 50×10^9/L increase: HR=0.82 (95%CI=0.68-0.99; p=0.04)]. Risk of death decreased by 73% and 47%, respectively with IB and CDKi compared to O, with no significant difference between IB and CDKi [HR: IB vs O=0.27 (95%CI=0.11-0.66); CDKi vs O=0.53 (95%CI=0.31-0.89); IB vs CDKi=0.52 (95%CI=0.21-1.29)]. Notably, age did not correlate with response or PFS/OS.

Herein, we describe the largest cohort of relapsed/refractory del(17p13.1) CLL patients treated at a single institution with specific attention to two promising new classes of agents that have demonstrated activity in this cohort. These data demonstrate that del(17p13.1) patients treated with IB- or CDKi-based regimens have improved response, PFS, and OS, compared to similar patients receiving alternative investigational or traditional therapies. Further, ibrutinib significantly increased response rates and extended PFS compared to treatment with CDKi. Difference in response rates between these two treatment groups became more pronounced when patients who achieved at least SD were included, as standard response criteria (13) do not fully capture the clinical benefit achieved by patients receiving ibrutinib, which can cause persistent lymphocytosis (7).

Notably, a higher proportion of patients with ≥3 prior therapies were treated in the IB and CDKi groups. Historically, heavily pre-treated patients are less likely to respond to therapy and may be excluded from clinical trials. In multivariable models, it was also noted that these patients were less likely to respond and had higher risk of progression/death; however, the relative benefit of treatment with IB and CDKi was irrespective of the number of prior therapies. For example, in patients who had received <3 prior therapies, response rates (at least PR) were 75%, 52%, and 29% with IB, CDKi, and O, respectively, while response rates in patients with ≥3 prior treatments were 47%, 41%, and 16%.

Although multivariable analyses were performed to adjust for potentially important variables, our analyses are limited by the retrospective nature of the study and could be confounded by unmeasured baseline differences in the patients who enrolled on a clinical trial versus those who were given standard therapy and differences in the enrollment criteria between trials. Factors previously associated with poor CLL patient survival such as un-mutated IgVH mutational status and elevated β2-microglobulin levels, were not included in our analyses as these were only available for a small proportion of the patients. However, an over-representation of patients with these risk factors in one of the groups could contribute to decreased survival in that group. As the treatments were given over a period of ten years, an improvement in supportive care may contribute somewhat to improved outcomes in patients on the most recent clinical trials.

Additionally, our OS analysis is limited by a shorter follow-up period in the IB group (median: 12.5 months). Regardless, OS is currently significantly longer with IB compared to O, and if the trend continues, may show a significant improvement in OS with IB compared to CDKi once follow-up matures. OS estimates in the CDKi and O groups become similar at approximately four years following therapy despite significant improvement in response rate with CDKi, indicating better initial clearance of the disease and short-term survival but not necessarily long-term survival.

In summary, treatment of relapsed del(17p13.1) CLL patients with IB and CDKi at OSU have demonstrated improved response, PFS, and OS when compared with patients treated with other therapies. Future efforts should focus on continued prospective investigation of these effective agents in attempt to further improve the outcome of these patients.

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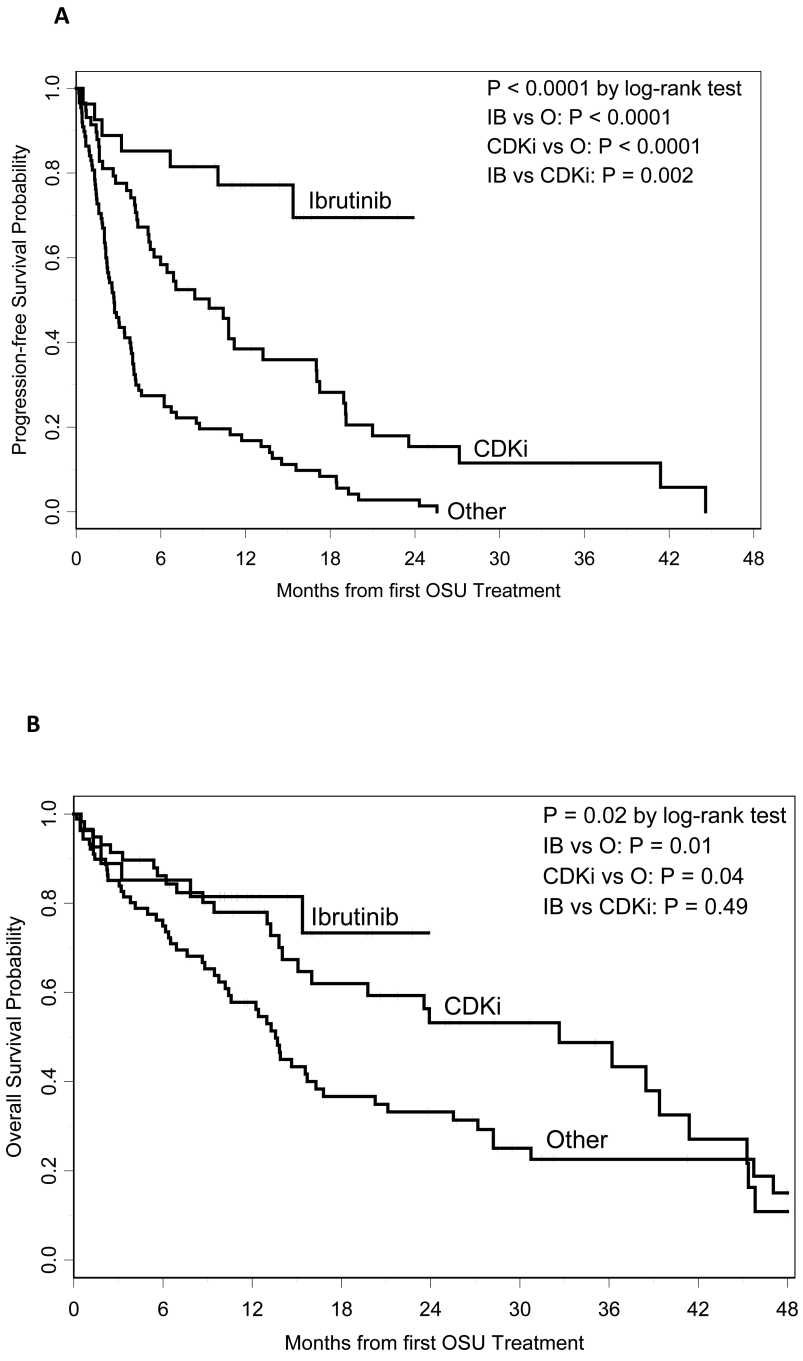

Figure 1.

(A) Kaplan-Meier curves of progression-free survival and (B) overall survival for relapsed/refractory chronic lymphocytic leukemia (CLL) patients with del(17p) karyotype treated with either ibrutinib-based regimens, cyclin-dependent kinase inhibitor (CDKi)-based regimens, or all other regimens.

Table 1

Pretreatment Characteristics of Chronic Lymphocytic Leukemia Patients with del(17p) Karyotype Evaluated at Ohio State University

Characteristic	Overall N=174	Ibrutinib N = 27	CDKi N = 58	Other N = 89	P*
Median Age, years	63	64	63	63	0.60
Range	39-83	50-77	39-81	42-83	
Female Sex, no. (%)	60 (34)	8 (30)	16 (28)	36 (40)	0.25
White Race, no. (%)	160 (93)	25 (93)	55 (95)	80 (92)	0.85
Unknown	2	0	0	2	
Rai Stage, no. (%)					1.00
0/I/II	49 (29)	8 (30)	17 (29)	24 (28)	
III/IV	121 (71)	19 (70)	41 (71)	61 (72)	
Unknown	4	0	0	4	
ECOG PS, no. (%)					0.12
0/1	150 (89)	26 (96)	53 (93)	71 (84)	
2/3	19 (11)	1 (4)	4 (7)	14 (16)	
Unknown	5	0	1	4	
Prior Therapies ≥3, no. (%)	93 (53)	19 (70)	37 (64)	37 (42)	0.005
Median Prior Treatments, no.	3	4	3	2	0.001
Range	1-10	1-9	1-10	1-7	
Median WBC Count, × 10^9/L	17.9	18.8	12.1	25.5	0.04
Range	0.4-289.1	1.3-289.1	1.2-144.5	0.4-287.0	
Unknown	7	0	0	7	
Median Creatinine, mg/dL	0.95	1.06	0.94	0.96	0.09
Range	0.47-2.70	0.47-2.09	0.47-1.76	0.50-2.70	
Unknown	13	0	0	13	
Median Albumin, g/dL	3.8	3.8	3.9	3.8	0.80
Range	1.9-5.0	2.6-4.8	2.7-4.5	1.9-5.0	
Unknown	18	0	1	17	
Median LDH†, U/L	221	200	221	235	0.11
Range	78-1091	120-1091	97-687	78-1007	
Unknown	17	0	0	17	
Median 17p, %	74	74	70	77	0.44
Range	6-100	7-99	6-97	6-100	
FISH‡, no. (%)					

Characteristic	Overall N=174	Ibrutinib N = 27	CDKi N = 58	Other N = 89	P*
Del(11q)	36 (21)	8 (30)	15 (26)	13 (15)	0.10
Del(13q)	100 (57)	16 (59)	34 (59)	50 (56)	0.93
Trisomy 12	28 (16)	6 (22)	9 (16)	13 (15)	0.66
CK, no. (%)	121 (70)	22 (81)	38 (66)	61 (69)	0.32

LDH=lactate dehydrogenase; WBC=white blood cell; PS=performance status; CK=complex karyotype.

*P-values result from testing the association between treatment group and categoric or continuous variables, respectively, using Fisher's exact or the non-parametric Kruskal-Wallis test.

†Upper limit of normal LDH is 190 U/L.

‡Aberrations are not mutually exclusive.