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Authors
Stephens, Deborah M
Ruppert, Amy S
Weirda, William G
et al.

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Externally validated predictive clinical model for untreated del(17p13.1) chronic lymphocytic leukemia patients

Deborah M. Stephens[1], **Amy S. Ruppert**[2], **William G. Weirda**[3], **Jeffrey A. Jones**[2,4], **Jennifer A. Woyach**[2,4], **Kami Maddocks**[2,4], **Samantha M. Jaglowski**[2,4], **Leslie A. Andritsos**[2,4], **Joseph M. Flynn**[2,4], **Michael R. Grever**[2,4], **Gerard Lozanski**[5], **Constantine Tam**[6], **Susan O'Brien**[3], **Michael J. Keating**[3], **Natarajan Muthusamy**[2,4], **Lynne V. Abruzzo**[2,4], **Nyla A. Heerema**[2,7], **John C. Byrd**[2,4,8,*]

[1]Division of Hematology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

[2]Comprehensive Cancer Center, Ohio State University, Columbus, Ohio

[3]Division of Cancer Medicine, Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas

[4]Division of Hematology, Department of Internal Medicine, Ohio State University, Columbus, Ohio

[5]Division of Hematopathology, Department of Pathology, Ohio State University, Columbus, Ohio

[6]Division of Medicine, Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

[7]Division of Cytogenetics, Department of Pathology, Ohio State University, Columbus, Ohio

[8]Division of Medicinal Chemistry, College of Pharmacy, Ohio State University, Columbus, Ohio

Abstract

Little is known about outcomes of patients with chronic lymphocytic leukemia (CLL) with del(17p13.1) karyotype at diagnosis. We reviewed 114 de novo del(17p13.1) CLL patients seen at our institution. Using proportional hazards models to identify pretreatment clinical variables significantly associated with treatment-free survival (TFS) and overall survival (OS), we developed a simplified risk score for de novo del(17p13.1) CLL patients to predict TFS and OS based on these variables. These scores, particularly the very highest, can be utilized to identify high-risk patients for expedient enrollment on clinical trials. Our data support careful observation for low-risk patients, potentially preventing unnecessary use of aggressive therapies.

[*]**Correspondence to:** John C. Byrd, MD, 445D Wiseman Hall, 410 W 12th Ave, Columbus, OH 43210. john.byrd@osumc.edu.

Author Contributions

All authors critically revised the manuscript and approved the final submitted version. DMS and ASR acquired, analyzed, and interpreted data and drafted the manuscript. WGW, JAJ, JAW, KM, SMJ, LAA, JMF, MRG, GL, CT, SO, MJK, NM, LVA, NAH contributed to acquisition of data. NAH acquired and analyzed cytogenetic data. DMS and JCB developed the concept for the study.

Conflict of interest: The authors have no competing interests to disclose.

Introduction

Since the landmark cytogenetic analysis of chronic lymphocytic leukemia (CLL) patients by Dohner et al. [1], the subset (~10%) of patients with del(17p13.1) karyotype are recognized as a group commonly refractory to therapy with poor clinical outcomes. The unfavorable clinical course has been at least partially attributed to dysfunction of the tumor suppressor gene TP53, located on the p-arm of chromosome 17 [2]. Recent genetic analysis of CLL samples with whole-exome sequencing provided evidence that TP53 mutations can arise following therapy as subclonal driver mutations leading to adverse clinical consequences [3]. Little is known about outcomes of patients with del(17p13.1) karyotype at diagnosis. No publication describes large groups of these patients treated at a single institution. A multi-institution publication that investigated this population identified a subset (typically Rai Stage 0 and IgVH mutated status) of these de novo del(17p13.1) patients with a relatively indolent clinical course [4]. For these patients, current guidelines recommend early referral to clinical trials or aggressive therapy with hematopoietic stem cell transplant once therapy is required [5]. As these therapies can be highly toxic, we aimed to develop a risk score to classify patients with de novo del(17p13.1) CLL at high risk of early treatment or death versus those who may survive without therapy for an extended time.

Methods

We retrospectively reviewed records of 114 patients with CLL with del(17p13.1) who were seen for initial evaluation prior to receiving any therapy at Ohio State University (OSU) from 2002 to 2012. Research was performed in accordance with the Institutional Review Board-approved study 2014C0126. Stimulated cytogenetic and fluorescent in situ hybridization (FISH) analyses were performed on peripheral blood or bone marrow samples, as previously described [6,7]. 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 [8].

Response was assessed by IWCLL 2008 criteria [9]. Treatment-free survival (TFS) was calculated from date of first visit until date of first treatment or death, censoring patients alive and treatment-free at last follow-up. Overall survival (OS) was calculated from date of first visit until date of death or last follow-up. TFS/OS estimates were calculated using the Kaplan-Meier method. Proportional hazards models were fit using backwards selection to identify variables significantly associated with TFS and OS. A multiple imputation technique estimated missing data and combined results for 10 datasets [10]. Variables considered for inclusion in the multivariable models were age, sex, Rai Stage, ECOG performance status (PS), white blood cell count (WBC), absolute lymphocyte count, creatinine, albumin, total bilirubin, aspartate aminotransferase, lactate dehydrogenase, and beta-2 microglobulin levels, IgVH status, percentage of cells with del(17p13.1), and presence of trisomy 12, del(11q22.3), del(13q14.3), or complex karyotype. A risk score (RS) was calculated based on the variables and regression coefficients of the model. A simplified risk score (SRS) to be used in clinical practice was based on the strength of associations with clinical outcome when all variables had been categorized. To externally validate the SRS, a dataset of 129 de novo del(17p13.1) patients was obtained from MD Anderson

Cancer Center (MDA). Consistency in model coefficients used to derive the SRS and predictive power of the SRS using Harrell's c-index (*c*) were compared between the datasets [11].

Results

Comparison of the OSU and MDA patient sets demonstrated no significant difference in baseline patient characteristics that were included in models predicting clinical outcome ($P > 0.15$) for TFS and OS ($P > 0.10$) (Table I). Median TFS estimates were 16 months (95% CI = 6–27) and 6 months (95% CI = 3–12) for the OSU and MDA sets, respectively, while median OS estimates were 5.2 years (95% CI = 3.4–7.8) and 6.4 years (95% CI = 4.7 not reached).

Using the OSU set, a multivariable model for TFS included ECOG Performance Status (PS), Rai Stage, age, white blood cell (WBC), and del(11q22.3) (all $P < 0.017$, $c = 0.84$). A RS used the formula: 0.793 × (ECOG PS = 1: no = 0, 1 = yes) + 1.685 × (ECOG PS ≥ 2: no = 0, 1 = yes) + 1.488 × (Rai I/II/III/IV: no = 0, 1 = yes) + 0.053 × (age in years) + 0.0045 × (WBC) + 0.881 × [del(11q22.3): no = 0, 1 = yes). A SRS used the formula: 1 × (ECOG PS = 1: no = 0, 1= yes) + 2 × (ECOG PS ≥ 2: no = 0, 1 = yes) + 2 × (Rai Stage I/II/III/IV: no = 0, 1 = yes) + 1 × (age ≥65 years) + 1 × (WBC ≥50 × 10^9/L) + 1 × [del(11q22.3): no = 0, 1 = yes], with possible scores ranging from 0 to 7. TFS estimates at 2 years for SRS = 0/1, 2/3, and ≥4 were 85% (95% CI = 0.60–0.95), 51% (95% CI = 0.32–0.67), and 0%, respectively (Fig. 1A). In the MDA set, Rai Stage and WBC contributed significantly to the SRS, followed by ECOG PS, with little consistency in the impact of age or del(11q22.3) compared with the OSU set, leading to a loss in predictive power ($c = 0.66$). Still, the SRS was significantly associated with TFS ($P < 0.0001$), with 2-year estimates of 63% (95% CI = 0.39–0.79), 26% (95% CI = 0.15–0.39), and 16% (0.06–0.29) for SRS = 0/1, 2/3, and ≥4 (Fig. 1B).

Using the OSU set, a multivariable model for OS included ECOG PS, age, and lactate dehydrogenase (LDH; all $P < 0.03$, $c = 0.76$). A RS used the formula: 0.776 × (ECOG PS = 1: no = 0, 1 = yes) + 1.646 × (ECOG PS ≥ 2: no = 0, 1 = yes) + 0.042 × (age in years) + 0.447 × [LDH relative to upper limit of normal (ULN)]. A SRS used the formula: 1 × (ECOG PS = 1: no = 0, 1 = yes) + 2 × (ECOG PS ≥ 2: no = 0, 1 = yes) + 1 × (age ≥ 65 years) + 1 (LDH × 2ULN: no = 0, 1 = yes), with possible scores ranging from 0 to 4. The SRS was associated with OS ($P < 0.0001$, $c = 0.73$), with 2-year estimates of 89% (95% CI = 0.74–0.96), 66% (95% CI = 0.41–0.82), and 0% for those with SRS = 0, 2, and 4, respectively (Fig. 1C). In the MDA set, with the exception of ECOG PS = 1, the strength in association of all variables with OS was similar to what had been observed in the OSU set. The predictive ability of the SRS decreased in the MDA set ($c = 0.68$), but remained associated with OS ($P = 0.001$), with the highest score showing early, inferior OS (Fig. 1D). Estimates at 2 years ranged from 95% (95% CI = 0.83–0.99), to 80% (95% CI = 0.55–0.92) to 20% (95% CI = 0.01–0.58) with an SRS of 0, 2, and 3, respectively; no one had a SRS = 4.

Fifty-eight patients seen at OSU went on to receive therapy. Sixty percent of these patients received purine analogue-based therapy and 31% received therapy on a clinical trial. Of 57 evaluable patients, 25%, 37%, 9%, and 30% of the patients achieved complete response (CR), partial response, stable disease, and progressive disease, respectively. Of the 14 patients that achieved CR, 9 (64%) patients had received purine analogue-based therapies.

Discussion

In summary, these data detail the largest reported subgroup of de novo del(17p13.1) CLL patients treated at a single institution. Using statistical models, we identified variables significantly associated with TFS and OS, which were used to develop a SRS for use in clinical practice to identify those de novo del(17p13.1) CLL patients at highest risk of early treatment or death. Then, we validated this SRS on an independent set of similar patients from MDA.

When reported alone, the OSU data are limited by analysis of patients from a single institution with potential differences in referral base and clinician treatment management/ supportive care preferences when compared to other institutions. External validation with MDA patients, which showed no statistically significant differences in the noted baseline characteristics or survival, strengthens these data and supports a certain degree of generalizability.

The previous multi-institutional article which described another de novo del(17p13.1) population [4] reported an overall response rate (ORR) of 72% with a purine-analogue chemoimmunotherapy regimen. Even though our reported ORR estimate of 62% is slightly lower, it is not significantly different from the previously reported estimate with a 95% exact confidence interval ranging from 35% to 87%. Further, caution should be used in the interpretation of these data as they were collected retrospectively and without the ability to directly compare characteristics of these two distinct patient subgroups.

The same prior study identified two significant risk factors for progression; Rai Stage ≥1 and unmutated IgVH status [4]. Our study also identified Rai Stage ≥I as a risk factor for shorter TFS, in addition to ECOG PS ≥1, age ≥65 years, WBC ≥50 × 10^9/L, and concurrent presence of del(11q22.3). The prior study identified three factors associated with OS; Rai Stage ≥I, unmutated IgVH status, and del(17p13.1)% ≥25% [4]. Conversely, our study found ECOG PS ≥1, age ≥65 years, and LDH ≥2 × ULN to be associated with worse outcomes. In the OSU dataset, IgVH results were not available for 41% of the patients. Although the missing data were imputed and unmutated IgVH status was significantly associated with shorter TFS in a univariable analysis ($P = 0.02$), it did not provide significant additional information once other variables were accounted for in the multivariable models for TFS or OS ($P > 0.30$). The importance of IgVH status and its role in a risk score for TFS and OS in patients with del(17p13.1) may be better clarified if the data were collected prospectively.

In conclusion, pretreatment clinical characteristics can be used in a simplified score for de novo del(17p13.1) CLL patients to predict TFS and OS. These scores support careful

observation for low-risk patients and can be utilized to identify high-risk patients for expedient enrollment on clinical trials.

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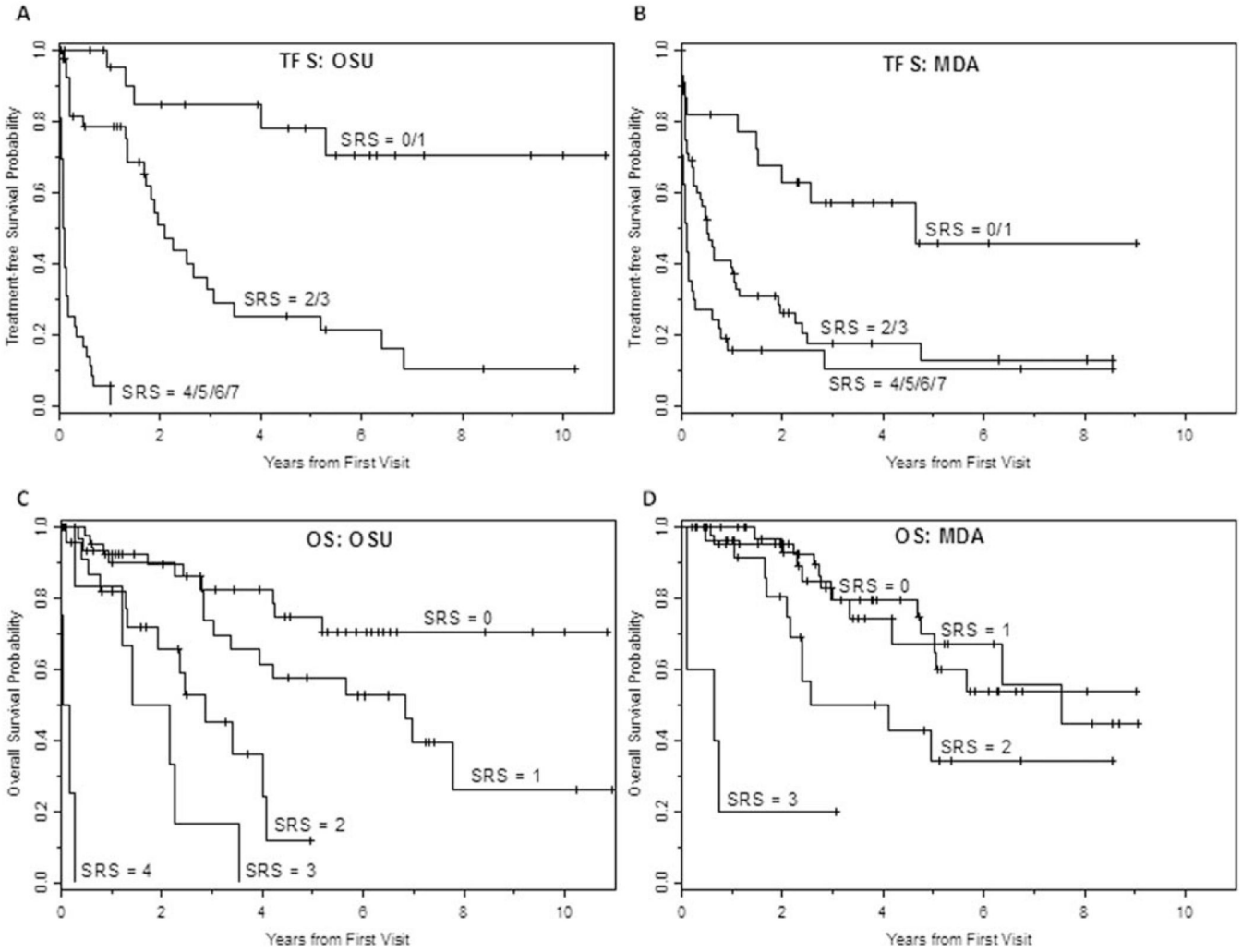

Figure 1.

Kaplan–Meier survival estimates for CLL patients with de novo del(17p13.1) karyotype based on our calculated simplified risk score (SRS). A: Treatment-free survival (TFS) for patients treated at Ohio State University (OSU); (B) TFS for patients treated at MD Anderson (MDA); (C) overall survival (OS) for patients treated at OSU; (D) OS for patients treated at MDA.

TABLE I.

Clinical Characteristics of De Novo Del(17p13.1) Chronic Lymphocytic Leukemia Patients Treated at Ohio State University Compared with Patients Treated at MD Anderson

Characteristic	MDA: *N* = 129	OSU: *N* = 114	*P*
Diagnosis until first visit date			0.46
Median, months	4.8 months	4.7 months	
Range	0 days to 12.4 years	0 days to 19.7 years	
Median age (years)	63	62	0.80
Range	40–85	40–92	
Rai stage at first visit, no. (%)			0.62
0	37 (29)	38 (33)	
I/II	66 (52)	52 (46)	
III/IV	24 (19)	24 (21)	
ECOG performance status, no. (%)			0.21
0	73 (60)	69 (61)	
1	43 (35)	33 (29)	
2+	6 (5)	12 (11)	
Median white blood cell, × 10^9/L	31.1	26.9	0.41
Range	3.8–604.1	2.4–446.6	
Unknown	3	1	
Median LDH Relative to ULN[a], U/L	0.95	0.89	0.16
Range	0.44–5.10	0.52–9.43	
Unknown	4	22	
Median 17p, %	54.4	32.1	0.17
Range	6.5–97.5	5.7–99.5	
Presence of del(11q), no. (%)	16 (12)	16 (14)	0.71
Complex Karyotype, no. (%)	26 (28)	41 (36)	0.30
Unknown	37	0	

[a]Upper limit of normal LDH = 190 U/L at OSU and 618U/L at MDA.

LDH = lactate dehydrogenase, MDA = MD Anderson, NR = not reached, OS = overall survival, OSU = Ohio State University, TFS = treatment-free survival, ULN = upper limit of normal.