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Khalid Halahleh
Department of Medical Oncology-Hematology, Bone Marrow Transplantation, King Hussein Cancer Center, Amman, Jordan, Kh.06314@khcc.jo

Dalia Al Rimawi
Biostatistics Unit, Research Office, King Hussein Cancer Center, Amman, Jordan

Amal Abu Ghosh
Department of Pediatrics, Medical Oncology-Hematology, King Hussein Cancer Center, Amman, Jordan

Isra Muradi
Department of Internal Medicine, University of Tripoli, Tripoli, Libya

Waleed Da'na
Department of Medical Oncology-Hematology, Bone Marrow Transplantation, King Hussein Cancer Center, Amman, Jordan

See next page for additional authors

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Khalid Halahleh, Dalia Al Rimawi, Amal Abu Ghosh, Isra Muradi, Waleed Da'na, and Mehdi Hamadani

LETTER TO EDITOR

The Impact of Post-Hematopoietic Stem Cell Transplant Tyrosine Kinase Inhibitors in Philadelphia-Positive Acute Lymphoblastic Leukemia

Khalid Halahleh [a,*], Dalia Al Rimawi [b], Amal Abu Ghosh [c], Isra Muradi [d], Waleed Da'na [a], Mehdi Hamadani [e]

[a] Department of Medical Oncology-Hematology, Bone Marrow Transplantation, King Hussein Cancer Center, Amman, Jordan
[b] Biostatistics Unit, Research Office, King Hussein Cancer Center, Amman, Jordan
[c] Department of Pediatrics, Medical Oncology-Hematology, King Hussein Cancer Center, Amman, Jordan
[d] Department of Internal Medicine, University of Tripoli, Tripoli, Libya
[e] Internal Medicine, Division of Hematology & Oncology, Medical College of Wisconsin, Wauwatosa, WI, USA

To the Editor

Post-allogeneic hematopoietic stem cell transplant (allo-HSCT) application of tyrosine kinase inhibitors (TKIs) has been shown to reduce the incidence of relapse and has contributed to better overall survival (OS) and leukemia-free survival in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) [1]. However, due to conflicting results of retrospective analyses [2–4] and lack of definitive prospective trials [5], their role remains a subject of controversy. Furthermore, there are no commonly accepted standards with respect to the choice of TKI, dosage, time of initiation, and treatment duration [1–5]. The sole randomized study of prophylactic imatinib with negative minimal residual disease (MRD) failed to demonstrate significantly superior OS. However, 70% of patients were unable to continue imatinib owing to intolerance [5]. Second- and third-generation TKIs can reduce relapse risk; however, intolerance is frequently encountered [1–4].

Herein, we reported our institutional experience with patients with Ph + ALL who received post–allo-HSCT maintenance TKIs; 20 patients were identified, of which 19 received maintenance treatment (January 2014 to December 2019). Patient, disease, and transplant-related characteristics are detailed in Table 1. Complete molecular remission and major molecular remission (MMR) were defined as more than 4.5-log reduction (>0.0032% IS), and a 4-log reduction in p190 Bcr-Abl1 to ABL1 ratio (0.01% IS) [6]. Survival outcomes were defined from diagnosis to death or last follow-up and calculated using Kaplan–Meier method. Cox regression models were used to evaluate prognostic variables. Variables significant at 0.1 level on univariate were included in multivariate analysis. All p values are two-sided and statistical significance was determined at the 10% level. The study was approved by the Institutional Review Board of King Hussein Cancer Center. SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA) was used for statistical analysis.

After a median follow-up of 38.2 months (range, 15–98 months), seven patients relapsed (36.8%) and eight patients died (42%). The 3-year OS was 49% (95% confidence interval [CI]: 0.24–0.73; median, 19.7 months) and event-free survival (EFS) was 38% (95% CI: 0.15–0.64; median, 11.25 months; Fig. 1A and B). Age $\leq$ 35 years improved EFS (hazard ratio [HR]: 1.05; 95% CI: 0.98–1.11; $p = .10$) in univariate and multivariate analysis (HR: 1.05; 95% CI: 0.99–1.11; $p = .05$), but not OS (HR: 1.07; 95% CI: 0.99–1.16; $p = .08$). The median OS was similar at 19.7 months ($p = .83$) for patients in first and second complete remission (CR1 and CR2), with trend

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* Corresponding author at: King Hussein Cancer Center, P.O. Box 1269, Aljubeiha, Amman 11941 Jordan.
E-mail address: Kh.06314@khcc.jo (K. Halahleh).

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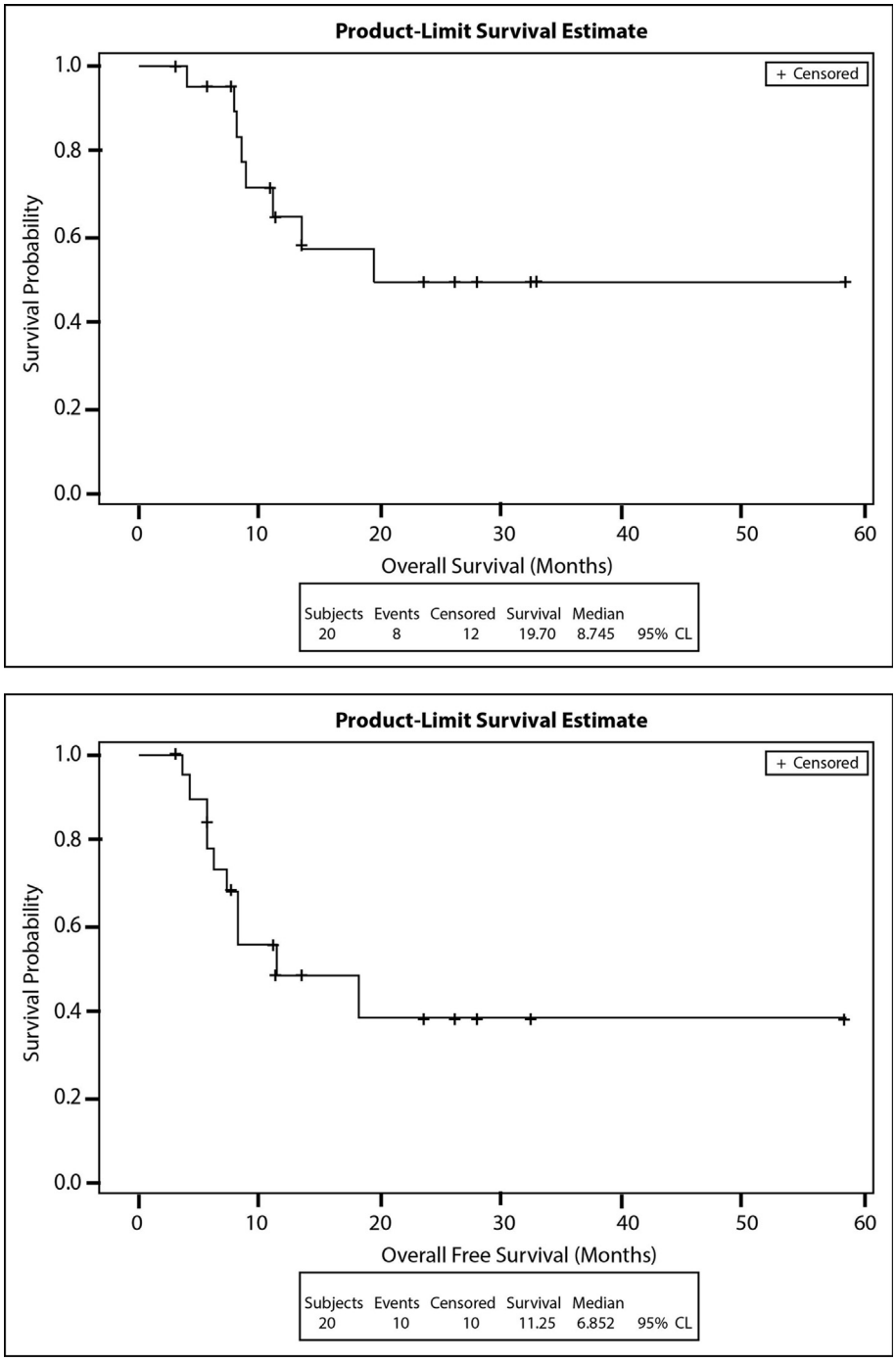

Fig. 1.

toward improved EFS, but not statistically significant probably due to small sample size (18 vs. 6.5 months, $p = .14$). Patients who achieved more than 4.5-log reduction (<0.0032% IS) had a trend toward improved OS ($p = .09$), but not EFS ($p = .40$).

To analyze outcomes of patients who did not experience early mortality or relapse, we did a 100-day landmark analysis in patients, who were alive and in remission at this time point ($n = 12$). Eight patients were excluded (1 patient had gut graft-versus-host disease, 7 patients had early relapses). The 3-year cumulative incidence of relapse (CIR) was 27% and 5-year OS was 80%. Remission status before allo-HSCT (CR1 vs. $\geq$ CR2; $p = .45$) and MRD (positive vs, negative; $p = .62$) did not affect OS or EFS. When we compared newer generations with imatinib, 3-year CIR was 27% versus 0% (95% CI: 0.02–0.61; $p = .39$). Patients who are alive and in > MMR at 3 months post

Table 1. Patient and treatment characteristics (n = 20).

Patient characteristics	Value	Number (%) or median (range)
Age (yr)		24.5 (6–47)
Sex	Male	12 (60.0)
	Female	8 (40.0)
White blood count at presentation	$>30 \times 10^9$	13 (65.0)
	$<30 \times 10^9$	7 (35.0)
ALL presentation	De novo ALL	16 (80)
	Relapsed ALL	4 (20)
Karnofsky score	>90	15 (75)
Induction chemotherapy prior to allo + TKI		20 (100)
Chemotherapy + imatinib		
Chemotherapy + dasatinib		16 (80)
Chemotherapy + 1TKI		4 (20)
		14 (70)
Remission status at allo-HSCT	CR1	13 (65)
	≥CR2	7 (35)
Presence of MRD by flow at allo-HSCT	Negative	15 (75.0)
	Positive	5 (25.0)
>MMR at allo-HSCT, BCR-ABL (RT-PCR)	Negative	15 (75)
	Positive	4 (15)
Time from diagnosis to allo-HSCT (mo)		14 (4.13–62.7)
Graft source	Peripheral blood	16 (80)
	Bone marrow	3 (15)
	Cord blood	1 (5)
Donor type	Matched related	16 (80.0)
	Haploidentical	3 (15)
	Cord blood	1 (5)
Conditioning regimen intensity	Myeloablative	18 (90.0)
	Reduced intensity	2 (10.0)
GvHD prophylaxis	CNI/PTcy	3 (15.0)
	CNI/Methotrexate/	16 (80.0)
	CNI/MMF	1 (5.0)
Day 100 work-up post allo-HSCT	>MMR + MRD	18 (90)
	Chimerism	20 (100)
TKI maintenance post-transplant use (n = 19)	Dasatinib/Imatinib	13 (68)/ 4 (21)
	Nilotinib/Ponatinib	1 (5.0)/ 1 (5.0)
Time from HSCT to TKI initiation (mo)		10.0 (1.34–52.33)
Duration of maintenance TKIs (mo)		13 (0.23–74)
Reasons for TKI's discontinuation	Disease relapse	6 (32)
	Disease relapse	5 (26)
	Completed ≥ 24 months	4 (21)
Follow-up (mo)		38.2 (15–98)

Note. ALL = acute lymphoblastic leukemia; allo = allogeneic; CNI = calcineurin inhibitor; CR = complete remission; GvHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation; MMR = major molecular remission; mo, months; MRD = minimal residual disease; TKI = tyrosine kinase inhibitor.

allo-transplant ($n = 12$) and continued maintenance for > 2 years had a trend toward decreased relapse compared with patients who stopped before 2 years (25% vs. 40%; $p = .32$). Only one out of four patients relapsed in the first group.

In conclusion, we observed reduced hematologic relapse at 100-day landmark analysis. Due to small sample size and inhomogeneous group of patients, we cannot draw any definite conclusions or recommendations on the use of post–allo-transplant TKI in Philadelphia-positive ALL from this analysis. Given the lack of a well-designed randomized trial, we believe this cohort study provides an important insight for TKI use in daily practice.

Authors' contributions

KH: wrote the first draft; MH: edited the final draft. All authors vouch for the content and approved the final version of the article.

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Conflicts of interest

None of the authors declare any relevant conflicts of interest.

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