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Research paper

Canadian chronic myeloid leukemia outcomes post-transplant in the tyrosine kinase inhibitor era

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ABSTRACT

The majority of patients with TKI failure respond to HCT. However, the relapse risk remains high. This study has evaluated transplant outcomes in 223 CML patients with TKI failure due to resistance (n = 132) or intolerance (n = 29), as well as those that were TKI naïve/responding with advanced disease (n = 35) or with chronic phase (CP, n = 27). We studied outcomes according to post-transplant *BCR-ABL* transcript level within 3 months. With respect to transplant outcomes according to the post-transplant *BCR*/ABLtranscript level within 3 months, the group failing to achieve a 1.3 log reduction (n = 14, 12.4%) showed the highest relapse rate of 78.6% at 5 years, compared to 26.2% and 24.1% in the groups achieving 1.3–4.0 log reduction (n = 45, 39.8%), and ≥4.1 log reduction (n = 54, 47.8%) respectively ($p < 0.001$). Multivariate analysis confirmed that the group failing to achieve a 1.3 log reduction had a 2.3-fold higher risk of death and 6.6 times higher risk of relapse. Poor overall survival after HCT was associated with advanced disease at diagnosis, but not disease status prior to HCT. Of 61 patients who relapsed after HCT, 47 were treated with post-transplant TKI therapy; those receiving TKI after loss of MR2 or MMR showed higher rates of response and survival compared to those receiving TKI after hematologic relapse ($p < 0.001$). QPCR log reduction level within 3 months post transplantation is prognostic in this population.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (HCT) remains a potentially curative option for CML patients who have failed multiple tyrosine kinase inhibitors (TKI's) or progressed to advanced disease. In patients with TKI failure, the majority (89%) responded to HCT with 68% achieving at least a major molecular response (MMR) [1]. Disease phase, found to be a major prognostic factor affecting transplant outcomes in the pre-TKI era, remains significant in the TKI era. The 3-year survival rate has been reported as 91% in chronic phase (CP) vs 59% in advanced disease phase patients transplanted in the TKI-era [2]. However, the relapse risk remains high. Nair et al recently reported a 41% relapse rate post-transplant [3], emphasizing the need for better risk stratification of relapse risk after HCT. Prognostic factor analysis suggested two prognostic factors for long-term outcome namely CP1 status and complete molecular response (CMR) achievement prior to HCT [4]. Therefore, a need exists for individualized pre-emptive therapies to improve outcomes after HCT.

An early molecular milestone after initiation of TKI therapy, reduction to $10\%^{IS}$ of *BCR-ABL* transcript level within 3 months, has recently been incorporated into CML management recommendations [5]. This type of pre-emptive response-guided intervention could be implemented in the post-transplant management of high-risk patients before progression or relapse occurs.

The current study has evaluated transplant outcomes in 223 CML patients having received HCT in the TKI era in Canada. We have also analyzed the prognostic impact of the *BCR-ABL* transcript level within 3 months post-transplant on long-term outcomes in 113 patients with an

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Table 1
The demographics, disease characteristics and transplant procedure in 223 patients with chronic myeloid leukemia transplanted for TKI failure (n = 161), TKI responsive but advanced disease (n = 35) or TKI naïve or responsive chronic phase (n = 27).

No of pts (%)		TKI resistance N = 132 (59.2)	TKI intolerance N = 29 (13.0)	Advanced, TKI responsive N = 35 (15.7)	CP, TKI naïve or responsive N = 27 (12.1)	p-value
Age	Median (range, year)	43.5 (18–65)	43 (28–66)	40 (18–63)	40 (18–60)	0.166
Gender	(female:male)	44/88 (33.4/66.6)	17/12 (58.6/41.4.2)	15/20 (42.9/57.1)	13/14 (48.1/51.9)	0.120
Disease stage at diagnosis	CP/AP/BP	64/29/39 (48.5/22.0/29.5)	25/2/2 (86.2/6.9/6.9)	5/16/14 (14.3/45.7/40.0)	27/0/0 (100/0/0)	< 0.001
Disease stage at HCT	CP1/CP2-3/AP or BP	62/58/12 (47.0/43.9/9.1)	25/4/0 (86.2/13.8/0)	5/23/7 (14.3/65.7/20.0)	27/0/0 (100/0/0)	< 0.001
Cytogenetics at Dx	ACA/Ph+[a]	20/63 (51.6)	3/22 (13.6)	8/17 (47.1)	4/20 (20.0)	0.099
Cytogenetics at HCT	ACA/Ph+[b], CE/Ph-[c]	23, 4 (17.4,3.0)	0, 3 (0,10.3)	1, 0 (2.9,0)	0, 0 (0,0)	0.002,0.075
TKD Mutation[d]		17/131 (13.0)	0 (0)	0 (0)	0 (0)	0.005
Bcr-abl level within 3 months	≤1.3 log (n = 14; 12.4%)	11 (15.1)	1 (7.1)	1 (5.6)	1 (12.5)	0.743
	1.3–4.0 (n = 45; 39.8%)	27 (37.0)	5 (35.7)	8 (44.4)	5 (62.5)	
	≥4.1 log (n = 54; 47.8%)	35 (47.9)	8 (57.1)	9 (50.0)	2 (25.0)	
Previous treatment	Imatinib/Dasatinib	125/55 (94.7/41.7)	21/13 (72.4/44.8)	33/0 (94.3/0)	14/0 (53.8/0)	< 0.001/ < 0.001
	Nilotinib/Ponatinib	20/2 (15.2/1.5)	10/0 (34.5/0)	0/0 (0/0)	0/0 (0/0)	< 0.001/0.711
	Bosutinib/Omacet	1/2 (0.8/1.5)	0/0 (0/0)	0/0 (0/0)	0/0 (0/0)	0.877/-
Previous lines	1/2/3/4 lines	74/46/11/1 (56.1/34.8/8.3/0.8)	18/7/4/0 (62.1/24.1/13.8/0)	33/0/0/0 (94.3/0/0/0)	14/0/0/0 (53.8/0/0/0)	< 0.001 (0.484[***])
Conditioning	MAC/RIC	123/9 (93.2/6.8)	27/2 (93.1/6.9)	33/2 (94.3/5.7)	27/0 (100/0)	0.579
GVHD prophylaxis	T-cell depletion	37 (28.5)	15 (51.7)	5 (14.3)	4 (14.8)	0.003
Stem cell source	BM/PBSC/UCB	20/109/3 (15.2/82.6/2.3)	4/25/0 (13.8/86.2/0)	10/25/0 (28.6/71.4/0)	6/21/0 (22.2/77.8/0)	0.427
Donors	MRD/Others	59/73 (44.7/55.3)	14/15 (48.3/51.7)	19/16 (54.3/45.7)	25/2 (92.6/7.4)	< 0.001
HLA-disparity	One-allele mm	19 (14.4)	0 (0)	6 (17.1)	1 (3.7)	0.058

Abbreviations: TKI, tyrosine kinase inhibitor; TKD, tyrosine kinase domain; HLA, human leukocyte antigen; CP, chronc phase; AP, accelerated phase; BP, blastic phase; ACA, additional cytogenetic abnormalities; CE, clonal evolution; NA, not available; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; BM, bone marrow; PBSC, peripheral blood stem cell; UCB, umbilical cord blood; MRD, matched related donor; mm, mismatched.

[a] ACA/Ph+ at initial diagnosis was identified in 23 patients (14.3%); +8 (n = 4); double Ph+ (n = 2); t(9;22;11) (n = 1); t(9;22;12) (n = 1); t(8;9;22) (n = 1); t(1;22) (n = 1); t(17;20)(n = 1); t(1;11;8) (n = 1); t(5;17) (n = 1); t(12;17), t(16;16), +5, +8, +21 (n = 1); t(2;3) (n = 1); t(1;3;9) (n = 1); t(4;6), +X, +6, +8, +18, +19 (n = 1); inv(9) (n = 1); + 21 (n = 1); −Y (n = 1); +19 (n = 1); -7 (n = 1); +8, +9, +14 (n = 1).

[b] ACA/Ph+ at HCT was identified in 23 patients (14.3%); double Ph+ (n = 4); −Y (n = 2); −7 (n = 2); t(16;16), t(12;17), +8, +5, +21 (n = 1); t(3;12), −7, i17q (n = 1); t(3;21) (n = 1); t(4;6), +X, +6, +8, +18, +19, +de(22) (n = 1); t(8;9;22) (n = 1); t(1;3;9), +21 (n = 1); +8 (n = 1); +8, der (1;7), +1, +9 (n = 1); +8, i(17q) (n = 1); +9, i(17q) (n = 1); del 7p15 (n = 1); del(5)(q22), +8, inv (17p) (n = 1); del(8q11.2), r(7) (n = 1); del 5, −8, −14, −17, −18 (n = 1); inv (3)(q21q26)(n = 1).

[c] CE/Ph− at HCT was identified in 7 patients (4.3%); −7 (n = 3); +8 (n = 2); −7, +8 (n = 1); +6, +9 (n = 1).

[d] ABL1 KD mutation was identified in 17 patients (10.6%) prior to HCT; T315I (n = 9), D276 G (n = 1), E355 G (n = 1), E459 K (n = 1), F359 V (n = 1), G250E/E255 K (n = 1), E255 V/F359 V (n = 1), P402S (n = 1); Y253 H/V379I (n = 1).

*** p = 0.484 between TKI resistant group vs TKI intolerant group.

available *BCR-ABL* transcript level taken within 3 months post-HCT.

2. Methods

2.1. Patient groups

A total of 223 patients were reviewed. They were transplanted at 6 centers (Toronto, Vancouver, Calgary, Ottawa, Quebec, and Hamilton) between 2002 and 2014. Of these, 161 were transplanted due to TKI failure including TKI resistance (n = 132) or TKI intolerance (n = 29); of the latter, TKI response had been poor/suboptimal (n = 22) or good (n = 7). Sixty-two patients were transplanted during the same time period for TKI naïve/responsive CML in CP (n = 27) or with advanced disease responsive to TKI prior to HCT (n = 35) and are included for comparison. Advanced disease responsive to TKI was defined as achievement of hematological or cytogenetic response only as data on the molecular depth of response was not available. For the 161 patients with TKI failure, disease phase prior to HCT in the TKI resistance group (group A) includes CP1 (n = 62), CP2/3 (n = 58) or AP/BC (n = 12). Details on patient demographics and disease characteristics for all patients are summarized in Table 1.

This study was approved by the Research Ethics Board of the University Health Network, Toronto, Canada.

2.2. Transplant procedures

The data are summarized in Table 1. Patients received conditioning regimens prior to HCT infusion and GVHD prophylaxis per institutional protocols [3,6–11]. Unrelated donors of peripheral blood stem cells (PBSC) or bone marrow (BM) cells were identified through the One-Match Stem Cell and Marrow Donor Network. Unrelated cord blood was used in 3 TKI resistant cases.

2.3. BCR-ABL Transcript Monitoring following imatinib therapy and definition of groups based on BCR-ABL transcript level within 3 months post-transplant

According to each institution's policy, *BCR-ABL* transcript quantitative PCR (Q-PCR) testing was performed within 3 months post-transplant, usually beyond day 60 but before day 90, then usually every 3 months for the first 2 years [12,13]. *BCR-ABL* transcript levels were measured and reported using log reductions based on the international