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The evolution of treatment strategies for patients with chronic myeloid leukemia relapsing after allogeneic bone marrow transplantation: Can tyrosine kinase inhibitors replace donor lymphocyte infusions?

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Abstract

The optimal treatment for chronic myeloid leukemia (CML) relapsing following allogeneic bone marrow transplantation (alloBMT) is unknown. We performed a single-center retrospective analysis of 71 consecutive patients undergoing alloBMT for CML from 1995–2008. A multi-state model was used to quantify the cumulative incidences of complete molecular response (CMR) and death following alloBMT. The primary analysis was the comparison of three treatment interventions (tyrosine kinase inhibitor: TKI, donor lymphocyte infusion: DLI, and TKI+DLI) for relapsed disease post-alloBMT. Forty-five (63%) patients relapsed post-alloBMT (molecular

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Author Contributions

JFZ and BDS conceived and carried out the study, participated in the data collection and analysis, and drafted the manuscript; MZ and GLR performed the statistical analysis and assisted in drafting the manuscript; CDG and RJJ assisted with study implementation, data analysis and revised the manuscript.

Conflict of interest:

The authors declare no conflict of interest.

relapse: n=16, cytogenetic relapse: n=20, hematologic relapse: n=2, advanced phase relapse: n=7) and 40 patients underwent one of three treatments: TKI-only (n=13), DLI-only (n=11), or TKI +DLI (n=16). Although not statistically significant, the TKI-only group had the highest cumulative incidence of CMR and the lowest cumulative incidence of death compared to DLI and TKI+DLI. These data support the finding that TKI therapy is active in the post-alloBMT setting.

Keywords

chronic myeloid leukemia; relapse; allogeneic transplantation

Introduction

The management of chronic myeloid leukemia (CML) has undergone dramatic changes over the last decade secondary to the discovery and success of tyrosine kinase inhibitors (TKIs) directed at the *BCR-ABL1* fusion gene [1–3]. Prior to the discovery of these agents, allogeneic blood/marrow transplantation (alloBMT) was the goal for younger patients. However, the use of alloBMT for CML has subsequently decreased dramatically, with the procedure being reserved for patients with advanced disease, those who cannot tolerate TKI therapy, or show clinical resistance to multiple TKIs [4–6]. This change in the utilization of alloBMT for only those patients with the highest risk disease is likely to impact the overall success of alloBMT, which is known to have its best outcomes in patients undergoing alloBMT in first chronic phase, and in those responding to front-line therapy [4]. With higher relapse rates expected following alloBMT, optimizing the post-alloBMT management is vital to ensuring the best possible outcomes for patients with advanced CML.

Donor lymphocyte infusion (DLI) was considered the mainstay of treatment for CML patients relapsing post-alloBMT in the pre-TKI era [7,8]. Escalating doses of DLI can lead to cytogenetic responses in approximately 70% of patients, many of which are durable. DLI, however, has been associated with increased rates of graft-versus-host disease (GVHD), myelosuppression, and infection, leading to high rates of morbidity and mortality [7].

TKIs have recently been shown to have efficacy for patients who relapse post-alloBMT and are even commonly utilized prophylactically in the post-alloBMT period, particularly in high-risk patients [9–12]. There are also data supporting the combination of DLI and TKIs suggesting that the combination may lead to more rapid responses post-alloBMT [13]. Although TKIs have never been compared with DLI in a prospective trial for relapsed CML post-alloBMT, there is continued interest in utilizing TKIs post-alloBMT due to the more favorable toxicity profile.

We sought to understand the evolving treatment strategies for patients with CML relapsing following alloBMT based on patterns of care and outcomes at our institution. We report our thirteen-year retrospective longitudinal experience of patients with CML relapsing after alloBMT at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC).

Methods

Patients and Methods

Outcomes of 71 consecutive patients undergoing an alloBMT from 1995–2008 at the SKCCC were analyzed retrospectively. All patients had confirmed diagnosis of CML based on the presence of the Philadelphia chromosome by cytogenetics [t(9;22)] or RT-PCR (*BCR-ABL1*). Baseline patient characteristics included demographics, CML phase, and prior treatments. The cohort included both myeloablative and nonmyeloablative conditioning regimens as well as matched-related, matched-unrelated, and haploidentical donors. Myeloablative regimens included busulfan/cyclophosphamide (Bu/Cy), Cy/total body irradiation (TBI), Bu/fludarabine (Flu), or Bu/Cy/thiotepa [14–17]. Nonmyeloablative regimens included Flu/Cy/TBI or Flu/TBI conditioning [17]. All patients received harvested bone marrow transplants from healthy donors. Prior to 2006, cyclosporine and methotrexate were used for GVHD prophylaxis for all myeloablative alloBMTs. After 2006, post-transplant cyclophosphamide (PTCy) on days 3 and 4 was used as sole GVHD prevention for myeloablative matched-related alloBMTs [18]. Nonmyeloablative haploidentical alloBMTs utilized PTCy with tacrolimus (days 5–180) and mycophenolate mofetil on (days 5–35) for GVHD prevention [17]. General patient outcomes that were analyzed included relapse, treatment for relapse, secondary relapses, and GVHD.

Definitions

Standard definitions of CML disease status were used to classify patients into chronic phase (CP), accelerated phase (AP), and blast crisis (BC) [19]. Relapses following alloBMT were classified as: a) molecular (either persistence of *BCR-ABL1* by PCR for ≥ 6 months or reemergence of a positive PCR following a complete molecular response in two consecutive samples ≥ 4 weeks apart in the absence of cytogenetic relapse), b) cytogenetic (detection of t(9;22) by either FISH or traditional marrow cytogenetics- at any time point following alloBMT), and c) hematologic (persistently elevated white blood cell count $> 12 \times 10^9/L$ or platelet count $> 500 \times 10^9/L$ not related to infection and with concurrent cytogenetic relapse). The time to molecular relapse was calculated from the date of alloBMT to the first positive test beyond 6 months, or the date of the first emergence of *BCR-ABL1* positive test in patients previously undetectable. Institutional guidelines included monitoring patients post-alloBMT with *BCR-ABL1* RT-PCR (after 2004) every 3 months for the first year, and every 6 months thereafter.

Response criteria were defined as: a) complete molecular response (CMR), undetectable PCR in two consecutive samples at a limit detection of 0.05 copy *BCR-ABL1* per 1000 copies ABL; b) major molecular response (MMR), persistent *BCR-ABL1* PCR positivity, but < 1 copy *BCR-ABL1*/1000 copies ABL; c) complete cytogenetic response (CCyR), no evidence of Philadelphia chromosome by peripheral blood FISH or conventional bone marrow cytogenetics; and d) complete hematologic response (CHR), normalization of white blood cell and platelet count to $< 10 \times 10^9/L$ and $< 450 \times 10^9/L$ respectively.

BCR-ABL1 PCR Measurement

The t(9;22)(q34;q11) chromosomal translocation (reciprocal translocation of the ABL1 proto-oncogene and the BCR gene) is detected by a one-step real-time RT-PCR protocol using the Ipsogen FusionQuant FQPP-10 kit according to the manufacturer's directions, detected on the Taqman 7900 thermocycler (ABI). The relative standard curve method was used for quantitation with ABL1 as the internal control.

Treatment of Relapse Post-alloBMT

Patients undergoing alloBMT were monitored for relapse as defined above. We compared patients who received: 1.) TKI as a single agent (either imatinib, dasatinib or nilotinib at standard doses), 2.) DLI-only, or 3.) the combination of TKI and DLI, given either concurrently or sequentially.

Statistical Analysis

A multi-state model [20] was used to estimate cumulative incidence functions and current leukemia-free survival (CLFS) for 71 CML patients following alloBMT. This method of analysis was chosen to account for the changes in the risk of death as a function of the number of relapses and treatments at the time of relapse. For the multi-state model, states were transient or absorbing. Transient states allowed transitions to other states (e.g., treatment to relapse or remission), while absorbing states (e.g., death) did not allow exit transitions. The multi-state process in this study was Markovian [20], meaning that the future of the process depended only on the current state and the time since the date of alloBMT. Patients started in the initial state, alloBMT, and moved to one of three possible states: treatment with a TKI to prevent relapse, initial relapse, or death. Once a patient had an initial relapse, three treatments options were possible: TKI, DLI or TKI+DLI. Following each of these treatments, two additional states were possible: second CMR or death without a second CMR. An additional two states were possible after achieving a second CMR: second relapse and death following second CMR. Event history summaries based on the multi-state model are through transition probabilities or cumulative incidence functions. Transition probabilities were estimated with the nonparametric Aalen-Johansen estimator [20], which takes censoring into account. CLFS, defined as the probability that a patient is alive and leukemia-free either in first or second CMR, was estimated with the multi-state model and reported graphically for each treatment group [21].

A Lexis diagram [22] was used to display treatment practice patterns over time. Event-time distributions for overall survival (OS) of the entire cohort, measured from the date of alloBMT to the date of death or last follow up, as well as by treatment group were estimated with the Kaplan-Meier method [23].

All statistical computations were performed using R, version 2.14.1 [24]. The etm package [25] was used for nonparametric estimation of cumulative incidences. The Lexis diagram was created with the R packages Epi [26] and mstate [27]. Cumulative incidence functions for second CMR and for death by treatment group are displayed graphically with 95% confidence intervals.

Results

Patient Characteristics

Seventy-one patients received an alloBMT for CML from 1995–2008 (Table I). The median age at the time of alloBMT was 41 years (range, 10–67). Thirty-six (51%) patients received a TKI prior to alloBMT, and 54 (76%) patients remained in CP prior to alloBMT. The proportion of patients undergoing alloBMT in CP decreased proportionally from 1995–1999 (92%), to 2000–2004 (75%), to 2005–2008 (57%). The majority of alloBMTs utilized myeloablative conditioning with matched-related donors (66%). Ten (14%) patients received a nonmyeloablative haploidentical alloBMT. Twenty-eight (39%) patients had a T-cell depleted alloBMT, 43 (61%) patients had an unmanipulated graft, and 22 (31%) patients had PTCy on days 3 and 4 for GVHD prophylaxis. There were 33 (46%) deaths. The causes of death included: relapsed disease (n = 9, 27%), infection (n=8, 24%), GVHD (n=6, 18%), no engraftment (n=2, 6%), multi-organ failure (n=2, 6%), intracerebral hemorrhage (n=1, 3%), metastatic pancreatic cancer (n=1, 3%), and unknown causes (n=4, 12%).

Relapse Characteristics and Intervention

Of the original 71 patients undergoing alloBMT for CML, 45 (63%) patients relapsed. The characteristics of the patients who relapsed post-alloBMT are shown in Table II. At the time of relapse, 16 patients had a molecular relapse, 20 patients had a cytogenetic relapse, 2 patients had a hematologic relapse, and 7 patients relapsed with advanced phase.

Five of the 45 patients who relapsed did not receive treatment for relapse. All five patients had a molecular relapse and were observed serially. The outcomes of these 5 untreated patients were: lost to follow up after serial observation for 6 months (n=3), death due to GVHD (n=1), and continued observation for 1 year with fluctuating *BCR-ABL1* PCR levels (n=1). Two of these 5 untreated patients had ongoing GVHD that was being actively treated at the time of molecular relapse, with one of these patients dying of infection.

Forty of the 45 patients who relapsed post-alloBMT underwent one of three treatment interventions: TKI-only (n=13), DLI-only (n=11), or the combination of TKI and DLI (n=16) (Figure I). The TKI-only group represented patients who received imatinib (n=5), nilotinib (n=3), or a sequential combination of imatinib, dasatinib and/or nilotinib (n=5). The TKI+DLI group represented patients who received imatinib with DLI (n=10), nilotinib with DLI (n=1), or a sequential combination of imatinib, dasatinib, and/or nilotinib with DLI (n=5). Additionally, all patients treated with DLI-only for relapse had alloBMTs prior to 2002, and hence have the longest follow up of the three intervention groups. As TKIs were introduced into clinical practice, TKI-only and the combination of TKI+DLI became the favored approach for treatment. The average follow-up time from alloBMT to last follow-up or death was 4 years, 6.7 years and 6.1 years among the TKI-only, DLI-only and TKI+DLI treatment groups, respectively.

There were 4 patients from the original cohort who received a TKI prophylactically post-alloBMT in CMR to prevent relapse. Three of these patients had BC prior to alloBMT, and three of these patients relapsed post-alloBMT (molecular relapse: n=2, advanced phase relapse: n=1). Of the three patients who relapsed, one patient is still alive in MMR 2 years

(as of June 2012) after switching to a second-generation TKI due to a molecular relapse. The causes of death of these patients treated with a prophylactic TKI post-alloBMT were: progressive disease (n=2), and GVHD (n=1).

Outcomes of Intervention

The best response for the 40 patients treated for relapse post-alloBMT was CMR in 12 (30%) patients, MMR in 5 (13%) patients, and a CCyR in 10 (25%) patients. Intervention outcomes are listed in Table III.

In the TKI-only group (n=13), the overall responses were 4 CMRs (including 1 with AP relapse), 2 MMRs, 4 CCyRs, and 3 patients with either progressive disease or no response. There were 5 deaths in the TKI-only group: advanced disease (n=3), GVHD (n=1), and infection (n=1).

In the DLI-only group (n=11), the majority of relapses (8/11 or 73%) were cytogenetic relapses, as our molecular monitoring evolved over that time period. The responses after treatment with DLI-only were 2 CMRs, 2 MMRs, 2 CCyRs, and 5 patients with either progressive disease or no response in the DLI-only group. There were 5 deaths in the DLI-only group: advanced disease (n=2), GVHD (n=1), infection (n=1), and unknown cause (n=1).

In the TKI+DLI group (n=16), the responses were 6 CMRs, 1 MMR, 4 CCyRs, and 5 patients with either progressive disease or no response. There were 7 deaths in the TKI+DLI group: advanced disease (n=4), infection (n=1), metastatic pancreatic cancer (n=1), and unknown cause (n=1).

There were a total of 7 patients who relapsed with advanced phase (AP or BC) disease (4 treated with TKI-only, 1 treated with DLI-only, and 2 treated with TKI+DLI), with only 1 reaching a CMR (TKI-only group). Three of the 7 advanced phase relapses were treated with cytotoxic chemotherapy prior to the treatment intervention. All of the 7 patients relapsing in advanced phase died; the 1 patient achieving a CMR died of GVHD complications.

The median OS for the entire cohort was 100 months, with a median follow-up of 6.5 years. The median OS of the TKI-only group was not reached at the time of this manuscript (57.7% OS at 104 months). The median OS of the DLI-only group was 137 months, and the median OS of DLI + TKI was 100 months. The five patients not treated following relapse had an OS of 67% at 43 months.

At the end of follow-up, 19 patients were alive in CMR, 16 patients died in first or second remission, 17 patients died following relapse, and 19 patients remained in relapse. Estimates of CLFS were obtained from the multi-state model.. At 2 years post-alloBMT, the CLFS estimates are 33.0%, 31.6%, and 33.0%, for the TKI, DLI, and TKI+DLI groups, respectively. At 8.7 years these CLFS estimates are 19.7%, 15.0% and 20.3%, respectively.

Figures IIA and IIB show the treatment-specific cumulative incidence of being alive and in CMR and the cumulative mortality after treatment for relapse post-alloBMT. The TKI-only

group had the highest cumulative incidence of CMR after treatment for relapse: 50% (95% CI: 13%, 86%) at 104 months (8.7 years) (Figure IIA), and the lowest cumulative mortality after treatment for relapse: 33% (95% CI: 3%, 64%) at 8.7 years (Figure IIB). The cumulative incidences of CMR 8.7 years after alloBMT were 11% (95% CI: 0.0%, 30%) and 18% (95% CI: 0.0%, 50%) for the DLI and TKI+DLI groups, respectively. Cumulative mortality 8.7 years after alloBMT was 71% (95% CI: 51%, 100%) and 78% (95% CI: 42%, 100%) for the DLI and TKI+DLI groups, respectively.

Discussion

No cancer has experienced such changes in its therapeutic paradigm over the last two decades as has CML. While TKIs are clearly the primary therapy for newly diagnosed patients, the management of patients who progress following alloBMT remains less certain. This concern is magnified by the clinical practice of using alloBMT for only the most difficult to treat patients or those with advanced CML, as demonstrated in this cohort by the increasing proportion of AP/BC patients undergoing an alloBMT after 2000. Thus, higher rates of relapses are expected to occur post-alloBMT. TKIs are being increasingly incorporated into treatment algorithms for relapsed CML post-alloBMT and have completely replaced the use of DLI in some institutions. Yet, there are little data to support one intervention over the other.

Our single institution experience documents the evolution of treatment strategies for relapses post-alloBMT over the past decade. Currently, TKIs, either alone or in combination with DLI, are the most commonly utilized approach for relapsed CML post-alloBMT at our institution. The decision to add DLI to TKIs post-alloBMT was determined by physician preference, mostly based on the clinical status of the patient. The clinical activity of TKIs seemed to warrant this evolution in practice based on the finding that, although not statistically significant, the TKI-only group had the highest probability of being alive in CMR over time and the lowest probability of death when compared to the other two intervention arms (DLI-only and TKI+DLI). Our results and conclusions are similar when a multi-state model with only first chronic phase patients prior to BMT is considered. While these data should be interpreted cautiously given the shorter follow-up in the TKI-only group, Shanavas et al. [28] recently compared long-term outcomes of patients treated with DLI or TKI after CML relapse post-alloBMT, and also demonstrated inferior outcomes associated with DLI compared with TKIs, further suggesting that TKIs are active as a single-agent in the post-alloBMT setting. Together, these findings warrant further study in larger, randomized controlled trials, comparing TKIs and DLI for relapse management post-alloBMT.

A high relapse rate after alloBMT (63%) was found in this study. Although this relapse rate is higher than would be expected, contributing factors may be due to: 1) the stringent definition used to define molecular relapse, 2) an earlier programmatic goal of minimizing GVHD through T-cell depletion (39% of patients), 3) the use of PTCy in 31% of patients, and 4) approximately half of the patients (49%) in this cohort were not exposed to TKI's before alloBMT. As more institutions use molecular evidence of disease to define relapse,

and with higher risk patients making up the majority of CML patients receiving alloBMT, relapse strategies following alloBMT will need to be identified.

This single institution retrospective analysis does have limitations, including different types of alloBMT being performed, various stem cell sources, a transition between T-cell depletion of allografts to PTCy for GVHD prophylaxis, and the absence of randomization. However, there are several important components in this report of a “real-world experience” of our practice patterns. First, the data were collected uniformly over a thirteen-year time period. There was relative homogeneity in patient monitoring, follow-up and treatment patterns. Secondly, as fewer alloBMTs are being performed for CML, the ability to conduct large, prospective studies is poor. Given the relative dearth of data available for relapsed CML post-alloBMT, reporting of institutional experiences may help initiate large cooperative group randomized trials to determine an optimal strategy in relapsed CML post-alloBMT.

We utilize a multi-state model for the interpretation and analysis of post-alloBMT data. Multi-state modeling has a history of use in CML with a range of applications such as decision analysis, modeling of covariate effects, prediction, and estimation of the prevalence of intermediate conditions [29 – 33]. When the disease recovery process involves multiple events and disease states, the probability of the event of interest may need to take into account competing risks, time dependent covariates, or transitions into transient states (e.g. a treatment following relapse). In this study, we used the model to take multiple transient states into consideration. While sample size and the non-randomized retrospective design limited the opportunities for making inferences, it is hoped that this study will provide an example of how these statistical techniques can be applied and that the estimates might be useful for the design of randomized controlled studies to better determine the most effective treatment for CML relapse post-alloBMT.

In summary, this study documents the evolving treatment strategies for relapsed CML post-alloBMT over a thirteen-year time period. Although not statistically significant, we found that patients treated with TKI-only for relapse had a higher cumulative incidence of CMR and a lower cumulative mortality when compared with DLI-only, or the combination of TKI and DLI. Although the numbers of patients with CML undergoing alloBMT are small, particularly in CP, there are still a substantial number of patients who have undergone alloBMT and are at high risk of relapse. It would be ideal to form collaborations with other centers and groups to perform randomized controlled trials comparing different TKIs, with and without DLI, to determine the most effective strategy. Nonetheless, these data support the use of TKIs in the post-alloBMT setting, which may mitigate the unwanted toxicities seen with DLI.

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Figure I.

This schema highlights the cohort of 71 CML patients that underwent an alloBMT. Each box represents the transition of patients into respective categories based on the multi-state model.

Figure II.**Cumulative Incidence Analysis**

A) Cumulative incidence of being alive in CMR following alloBMT. The solid line on the cumulative incidence curves for each treatment group represents the actual probability, and the dotted lines represent 95% confidence intervals. Though not statistically significant, the TKI only group had the highest cumulative incidence of CMR compared to DLI and DLI + TKI; 0.50 (95% CI: 0.13, 0.86) at 104 months (8.7) years.

B) Cumulative incidence of death following alloBMT. The solid line on the cumulative incidence curves for each treatment group represents the actual probability, and the dotted

lines represent 95% confidence intervals. Though not statistically significant, the TKI only group had the lowest cumulative incidence of death compared with DLI and TKI+DLI; 0.33 (95% CI: 0.03, 0.64) at 104 months (8.7) years.

Table I**Patient Characteristics (n = 71)**

Patient Age: median, (range)	41, (10–67)
Pre-alloBMT TKI: n (%)	36 (51%)
Highest Stage Pre-alloBMT	n (%)
CP	54 (76%)
AP	5 (7%)
BC	12 (17%)
Dates of AlloBMT and Stage	n (%)
1995–1999	26/71 (37%)
CP	24/26 (92%)
AP	1/26 (4%)
BC	1/26 (4%)
2000–2004	24/71 (34%)
CP	18/24 (75%)
AP	2/24 (8%)
BC	4/24 (17%)
2005–2008	21/71 (30%)
CP	12/21 (57%)
AP	2/21 (10%)
BC	7/21 (33%)
GVHD Prophylaxis	n (%)
T-Cell Depletion	28 (39%)
Post-alloBMT Cyclophosphamide	22 (31%)
Conventional GVHD prophylaxis ^I	21 (30%)
AlloBMT Conditioning/Source	n (%)
Myeloablative, Matched Related	47 (66%)
Myeloablative, Matched Unrelated	14 (20%)
Nonmyeloablative, Haploidentical	10 (14%)
GVHD	n (%)
Acute (Grade 0, I, II)	19 (27%)
Acute (Grade III, IV)	14 (20%)
Chronic	5 (7%)

^I - Conventional GVHD prophylaxis refers to myeloablative conditioning without T-cell depletion and use of methotrexate and cyclosporine for GVHD prophylaxis.

Table II

Relapsed Patient Characteristics (n = 45)

Patient Characteristic	Total (%)
Pre-alloBMT TKI	
Yes	20 (44%)
No	25 (56%)
Pre-alloBMT Phase	
Chronic	36 (80%)
Accelerated	5 (11%)
Blast	4 (9%)
AlloBMT Conditioning/Source	
Myeloablative, Matched Related	31 (69%)
Myeloablative, Matched Unrelated	8 (18%)
Nonmyeloablative, Haploidentical	6 (13%)
GVHD Prophylaxis	
T-Cell Depletion	19 (42%)
Post-alloBMT Cyclophosphamide	14 (31%)
Conventional GVHD prophylaxis	12 (27%)

Table III**Outcomes of Intervention**

	TKI (n = 13)	DLI (n = 11)	TKI+DLI (n =16)
Molecular Relapse (n = 11)	5	1	5
Response to Intervention			
CMR	2	0	3
MMR	1	1	0
CCyR	1	0	0
No response	1	0	2
Cytogenetic Relapse (n = 20)	4	8	8
Response to Intervention			
CMR	1	2	3
MMR	1	1	0
CCyR	2	2	4
No response	0	3	1
Hematologic Relapse (n = 2)	0	1	1
Response to Intervention			
CMR	0	0	0
MMR	0	0	1
CCyR	0	0	0
No response	0	1	0
Advanced Phase Relapse (n = 7)	4	1	2
Response to Intervention			
CMR	1	0	0
MMR	0	0	0
CCyR	1	0	0
No response	2	1	2
Deaths	5	5	7