Allogeneic stem cell transplantation for chronic myeloid leukemia in the tyrosine kinase inhibitor era

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Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by the production of mature granulocytes and their precursors that are dysregulated and uncontrolled. The presence of the Philadelphia chromosome (Ph) is the hallmark of CML; it encodes a chimeric protein with constitutive tyrosine kinase activity that leads to uncontrolled cell growth and eventually the development of CML. Tyrosine kinase inhibitors (TKI) revolutionized the management of patients with CML. Before TKIs, hematopoietic stem cell transplantation had a major role in the treatment of these patients, but currently, its use is limited to cases presenting in the advanced phase and patients in the chronic phase failing multiple TKIs. In this article, the author summarizes the data about hematopoietic stem cell transplantation use in chronic phase CML, reviews the published guidelines, and provides his opinion.

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Introduction

Chronic myeloid leukemia (CML) is driven by unregulated granulocyte proliferation caused by the chimeric-oncogene BCR-ABL1 (breakpoint cluster region and Abelson murine leukemia genes), which is the consequence of a balanced chromosome 9–22 translocation [1]. This translocation was first reported in 1960 and is a key characteristic of CML [2]. CML is a disease that mainly affects the elderly, with a range of age of 65–74 years at diagnosis. Most cases are diagnosed incidentally after a workup for elevated white blood cells and later identification of the pathognomonic Philadelphia chromosome [3]. In 2019, 8990 new CML cases were diagnosed and 1140 deaths were attributed to CML in the USA [4].

Once a diagnosis is made, the disease is classified into three phases: chronic (CP), accelerated (AP), or blast phase (BP). The prognosis of patients in CP is better as compared with those in AP, whereas patients with BP have the worst outcomes [5]. Untreated, the disease inevitably progresses from CP to AP and later to BP. Early detection and treatment initiation are critical to avoid this progression [6]. Since 2001, a number of tyrosine kinase inhibitor (TKIs) have been approved for the treatment of CP-CML, and the prognosis of patients with CML treated with TKIs is now comparable to that of the general population. A minority of patients with CP-CML will fail the current TKIs and require hematopoietic stem cell transplantation (HSCT), whereas the majority of patients with AP or BP-CML will require transplantation for long-term control. The author reviews the HSCT literature addressing transplantation for patients with CP-CML.

Treatment landscape of chronic phase-chronic myeloid leukemia

Regardless of the therapeutic approach used, the primary goals of TKI treatment are to achieve hematological remission or better and to prevent the disease from progressing to the advanced phases (AP and BP) while maintaining a quality of life. This aim should ideally be achieved with good quality of life and minimal safety issues, especially in patients with comorbidities or who are taking medicines that interact with TKIs. Achieving a deep remission to allow participation in a treatment-free trial may be the goal for a specific subgroup of patients. The response to TKIs seems to be the most important prognostic indicator in predicting long-term outcomes. A normal life expectancy is likely to result in patients achieving a complete cytogenetic response (CCyR) or a major molecular response at the expected time points [7]. If a patient fails to meet these milestones, particularly CCyR, a change in therapeutic strategy is required to minimize the risk of progression and death [8]. Treatment failures in CP-CML are well defined and can be primary or secondary. Some patients encounter treatment failure, necessitating a change in treatment, with most of these failures caused by intolerance, nonadherence, drug interactions, and resistance [9].

Interferon alpha followed by HSCT was the main therapy that provided long-term disease control and

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survival for patients with CP-CML [10,11]. With the advent of TKIs, HSCT is rarely performed nowadays until several TKIs fail. Currently, five TKIs have been licensed for use in the frontline treatment of CML [imatinib, nilotinib, dasatinib, bosutinib, and radotinib (only approved in South Korea)]. Table 1 summarizes the trials that led to the approval of different TKIs in frontline therapy for CP-CML [12–15]. When compared with imatinib, second-generation TKIs in frontline therapy offer faster and deeper responses with a lower risk of progression but no overall survival (OS) advantage. Patients with a high-risk disease score at baseline are more likely to be selected for second-generation TKIs in the frontline.

Treatment failures and the need to change therapy are becoming a health care problem as a result of improved survival, an increase in prevalence, and the established practice of indefinite treatment with TKIs. Table 2 outlines long-term efficacy data for second-generation TKIs after the failure of first-line imatinib for CP-CML. The CCyR for all of these trials was between 44 and 54%, indicating that almost 50% of the patients will fail to achieve a major milestone linked to the survival of patients with CP-CML [16,18–20].

The management of patients with CP-CML who failed a second-generation TKI is challenging, and it is dependent on several variables and factors

Table 1 Long-term efficacy data from phase III randomized trials for first-line tyrosine kinase inhibitor therapy in patients with newly diagnosed chronic phase-chronic myeloid leukemia

Trial	Study arms	No. of patients	Median follow-up	Conclusion	Disease progression [*n* (%)]	PFS (%)	OS (%)
IRIS [12]	Imatinib (400 mg once daily)	553	11 years	Imatinib is superior to IFN+Ara-C treatment with regard to hematological, cytogenetic, and molecular responses (imatinib is the 'standard of care' in CML	38 (7)	92	83
	Interferon-alpha+ low dose cytarabine	553			71 (13)	–	79
DASISION [13]	Dasatinib (100 mg once daily)	259	5 years	Dasatinib is superior to imatinib with regard to cytogenetic and molecular response	12 (5)	85	91
	Imatinib (400 mg once daily)	260			19 (7)	86	90
ENESTnd [14]	Nilotinib (300 mg twice daily)	282	5 years	Nilotinib is superior to imatinib with regard to cytogenetic and molecular responses	10 (4)	92	94
	Nilotinib (400 mg twice daily)	281			6 (2)	96	96
	Imatinib (400 mg once daily)	283			21 (7)	91	92
BEFORE [15]	Bosutinib (400 mg once daily)	268	12 months	Bosutinib is superior to imatinib with regard to cytogenetic and molecular response	4 (2)	–	–
	Imatinib (400 mg once daily)	268			6 (3)	–	–

CML, chronic myeloid leukemia; OS, overall survival; PFS, progression-free survival.
–, Long-term follow-up ongoing.

Table 2 Long-term efficacy data for second-generation tyrosine kinase inhibitor therapy after failure of first-line imatinib for chronic phase-chronic myeloid leukemia

Second-generation TKI	*N*	CHR, %	MCyR, %	CCyR, %	MMR, %	24-Month PFS, %	24-Month OS, %	Study
Dasatinib 70 BID	378	91	62	53	47	80	95	[16]
Dasatinib 70 BID	101	93	53	44	29	86	N/A	[17]
Dasatinib								
140 QD	167	87	63	50	38	75	94	[18]
70 BID	168	88	61	54	38	76	88	
100 QD	167	92	63	50	37	80	91	
50 BID	168	92	61	50	38	76	90	
Nilotinib 400 BID	321	76	59	46	N/A	N/A	88	[19]
Bosutinib 500 QD	288	85	59	46	35	81	91	[20]

BID, twice a day; CCyR, complete cytogenetic response; CHR, complete hematological response; MCyR, major cytogenetic response; MMR, major molecular response; N/A, not available; OS, overall survival; PFS, progression-free survival; QD, every day; START, SRC/ABL Tyrosine kinase inhibition Activity Research Trial; TKI, tyrosine kinase inhibitor.

(cytogenetics, mutation profile, comorbidities, age, transplant eligibility and donor availability, prior history of adverse effects with prior TKI therapy, and risk profile for adverse effects on specific TKIs). Patients with CP-CML who are intolerant or resistant to a second-generation TKI must undergo BCR-ABL1 mutational analysis and search for a suitable donor for allogeneic HSCT. Table 3 summarizes the response to second-generation TKIs in the third-line (or later) treatment of CP-CML [21].

'Ponatinib is the only third-generation TKI available on the market, and it is also the only TKI with activity against the BCR-ABL1 gatekeeper mutation T315I, which is resistant to all other approved TKIs' [27]. In contrast to the currently available TKI that targets the BCR-ABL1 adenosine triphosphate-binding site, asciminib (ABL001) is a novel TKI that targets the BCR-ABL1 myristoyl pocket and acts as a powerful and selective allosteric blocker. Asciminib is effective against both native and mutated BCR-ABL1, including the gatekeeper T315I mutation. In a phase 1 study of patients with CML who had previously failed more than or equal to two TKIs, asciminib was well tolerated and showed sustained efficacy in heavily pretreated patients with CML [28]. Omacetaxine mepesuccinate is a protein synthesis inhibitor with limited efficacy in patients with CML. Omacetaxine's activity is unaffected by mutations, and it has been licensed by the FDA for the treatment of CP-CML in patients who have failed at least two TKIs [29].

Allogeneic stem cell transplantation

Although TKIs have largely replaced transplants in the early treatment lines, allogeneic HSCT remains an important treatment option for CML [30]. Approximately 10% of patients with CP-CML will experience resistance or intolerance to multiple TKIs, making allogeneic HSCT the only curative option [31]. Table 4 summarizes the current guidelines' recommendation for transplant in CP-CML. Allogeneic HSCTs should be considered in patients at high risk for transformation as the transplant outcome after transformation is unfavorable [33].

After an allogeneic HSCT for CML, the probability of survival at 5 years could range from more than 90% to less than 5%. The probability of survival depends on some factors, such as disease stage at transplant, the European Group for Blood and Marrow Transplantation (EBMT) risk score, and achieving a complete molecular response before HSCT [30]. The probability of treatment-related mortality (TRM) depends on many factors, such as patient age, donor origin (related vs. unrelated), degree of human leukocyte antigen (HLA) compatibility, patient CMV status, the strength of conditioning regimens used, and institutional expertise. Between 1980 and 1990, more than 2600 patients in Europe underwent allogeneic HSCT for CML in the pre-TKI era. The TRM was 40%, with 20-year OS rates of 40, 20, and 10% for CP, AP, and BP, respectively [36]. As a result of the allogeneic HSCT, there will be early

Table 3 The response to second-generation tyrosine kinase inhibitors in the third line (or later) treatment of chronic phase-chronic myeloid leukemia [21]

TKI	Cumulative CCyR rate, %	Cumulative MMR rate, %	Median follow-up, months (range)	OS	Study
Dasatinib in CP-CML (*N*=16)	31	13	13 (0.5–41) (all pts)	Median OS: 20 months (all pts)	[22]
Nilotinib in CP-CML (*N*=9)	11	33			
Dasatinib (*N*=5) or Nilotinib (*n*=13)	13	24	52 (7–75)	5-year OS: 86%	[23]
Dasatinib (*N*=30), Nilotinib (*N*=18), or Bosutinib (*N*=5)	21	NA	21 (1–67)	2-year OS: 67%	[24]
Nilotinib in CP-CML (*N*=39)	24	NA	12 (NA) (all pts)	18-month estimated OS: 86%	[25]
Dasatinib or Nilotinib	35	19	21.5 (6–46.5)	30-month OS: 47%	[26]

CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP, chronic phase; MMR, major molecular response; NA, not available; OS, overall survival; TKI, tyrosine kinase inhibitor.

Table 4 The guidelines' recommendations for transplantation in chronic phase-chronic myeloid leukemia

NCCN 2019 [32]	ESMO [33]	ELN-2013 [34]	ELN-2020 [35]
Resistant to TKIs	CP-CML who have failed at least 2 TKIs	Resistant or intolerant to at least one second-generation TKI	resistant or intolerant to multiple TKIs
Intolerant to all TKIs	T315I mutation (after trial of ponatinib therapy)		In resource-poor countries
			T315I mutation (after trial of ponatinib therapy)

CML, chronic myeloid leukemia; CP, chronic phase; ELN, European Leukaemia Net; ESMO, European Society for Medical Oncology; NCCN, Current National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

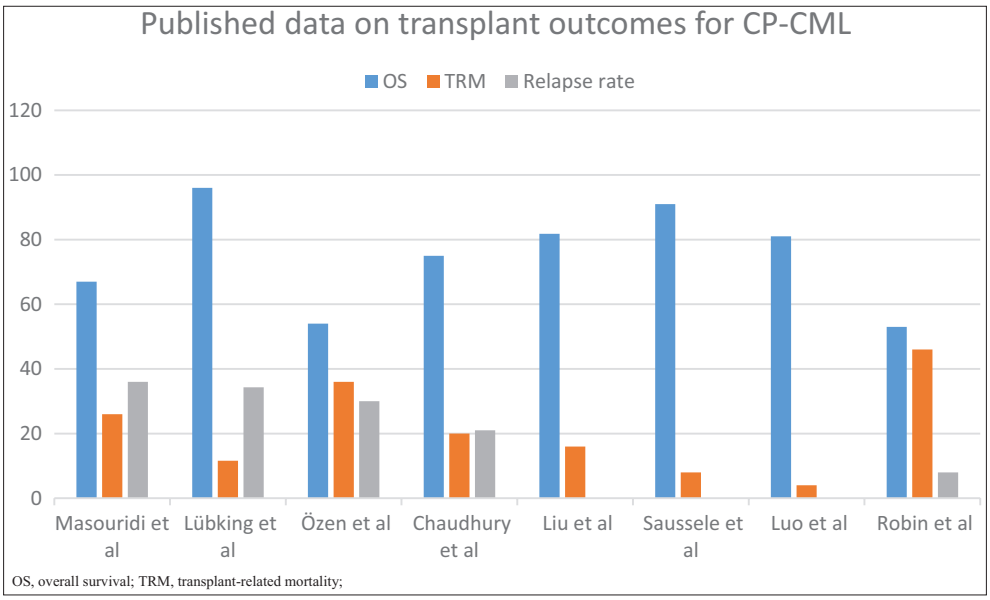
mortality but a later survival benefit that balances for the lost early years of life. TRM has decreased and transplant outcomes have improved as a result of advances in transplant procedures and supportive measures. The Center for International Blood and Marrow Transplant Research reported 1 and 2-year survival rates of 79 and 72%, respectively, for HSCT performed between 1999 and 2004 [37], and the most recently transplanted patients in the German CML study IV showed even better results, with a 3-year OS exceeding 90% [38]. Table 5 and Fig. 1 summarize published data on transplant outcomes for CP-CML. A recent retrospective study in Sweden evaluated 118 patients with CML transplanted in the TKI era, where 56 (47%) of these patients underwent allogeneic HSCT in the first CP. TKI resistance was the most

Table 5 Published data on transplant outcomes for chronic phase-chronic myeloid leukemia

References	No. of patients	OS	EFS/DFS	TRM	Relapse rate	Regimen (%)	Pre-HSCT TKI (%)	Type of the study	Transplant period
Masouridi-Levrat *et al.* [39]	139	67% (5y)	56% (5y DFS)	26% (5y)	36% (5y)	71% (MAC)	100%	Prospective Multi-center study (EBMT)	2009–2013
Lübking *et al.* [5]	56	96% (5y)	NR	11.6% (NRM)	34.3% (5y)	44.6% (MAC) 5.4% (RIC)	97%	Retrospective Multi-center study	2002–2017
Özen *et al.* [40]	116	54% (5y)	47% (5y)	36% (5y)	30% (5y)	92% (MAC) 8% (RIC)	0%	Retrospective single-center study	1989–2002
Chaudhury *et al.* [41]	449	75% (5y)	59%(5y DFS)	20% (5y)	21% (5y)	Variable	53%	Retrospective Multi-center study (CIBMTR)	2001–2010
Liu *et al*. 2011 [42]	91	81.8 (5y)	74.8%(5y DFS)	16% (5y)	NR	MAC	NR	Retrospective single-center study	1997–2009
Saussele *et al.* [38]	56	91% (3 y)	NR	8%	NR	Variable	NR	Prospective multi-center study	2003–2008
Luo *et al*. [43]	28	81% (3y)	67% (3y DFS)	4%	NR	RIC	100%	Retrospective single-center study	2005–2007
Robin *et al.* 2005 [44]	102	53% (15y)	NR	46% (15y)	8% (15y)	MAC	0%	Retrospective single-center study	1982–1998

CIBMTR, Center for International Blood and Marrow Transplant Research; DFS, disease-free survival; EBMT, European Group for Blood and Marrow Transplantation; EFS, event-free survival; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative; NR, not reported; NRM, nonrelapse related mortality; OS, overall survival; RIC, reduced-intensity conditioning; TKI, tyrosine kinase inhibitor; TRM, transplant-related mortality.

Figure 1



Illustrates published data on transplant outcomes for CP-CML. CP-CML, chronic phase chronic myeloid leukemia; OS, overall survival; TRM, transplant-related mortality.

common reason for transplantation in CP1, followed by T315I mutation in 12% and TKI intolerance in 9%. The likelihood of undergoing allogeneic HSCT within 5 years in patients diagnosed with CP-CML was 9%. An unrelated donor and a peripheral blood source were used in the transplantation of the majority of patients. When transplanted in CP, AP, or blast crisis, overall 5-year survival rates were 96, 70, and 37%, respectively. OS was significantly affected by the phase of disease at the time of transplantation. Patients who had TKI resistance and were transplanted in CP1 had a 5-year survival rate of 97%. The OS of AP/BP patients was significantly lower than that of CP1 transplant patients, even when they had reached the CP at the time of allogeneic HSCT. Both an EBMT score greater than 2 and reduced-intensity conditioning were risk factors for relapse. Patients transplanted in CP had a nonrelapse mortality rate of 11% [5].

It has been observed that having an EBMT score of more than 2 and advanced phase disease can have a negative effect on transplant outcomes. However, it is not obvious whether the amount of TKIs administered before transplantation affect OS after transplant [45–47]. The recommended preparation regimens for allogeneic HSCT in CML are myeloablative conditioning regimens, such as intravenous busulfan and cyclophosphamide (BU/CY). For older patients (>60 years) or those with medical comorbidities, reduced-intensity conditioning or nonmyeloablative regimens are good options to overcome high TRM [48]. The preferred donor source is a HLA-matched sibling donor given the better clinical outcomes after transplantation (less GVHD), readiness, and cost-effectiveness. A matched unrelated donor allogeneic HSCT is an acceptable alternative for patients without a matched sibling donor. Other sources of donors have been used in patients without an HLA-matched sibling or an unrelated donor [49,50]. The ideal graft source (bone marrow vs. peripheral blood) is determined by numerous factors, including donor (related versus unrelated), disease phase (chronic versus advanced), and donor preference.

The Blood and Marrow Transplant Clinical Trials Network has compared the outcomes of bone marrow versus peripheral blood from unrelated donors [51]. Many centers have adopted bone marrow as a donor source for patients with CP-CML who had allogeneic HSCT with a related or unrelated donor, as it has been associated with lower rates and severity of chronic GVHD. In advanced-stage disease, mobilized peripheral blood progenitor cells would be preferred owing to higher graft-versus-tumor effects. Maintenance TKI therapy after allogeneic HSCT was well tolerated and reduced the risk of relapse, particularly in patients transplanted while molecular remission was not achieved, with nonmyeloablative conditioning regimens, or transplanted in an advanced phase [52].

It is important to monitor the patient's disease status on a regular basis after transplantation. Molecular testing should be performed by quantitative reverse transcriptase PCR every 3 months for 2 years and then every 3–6 months thereafter. Early detection of BCR-ABL1 transcripts after allogeneic HSCT may help predict early frank relapse, allowing early use of alternative therapies such as TKI or donor lymphocyte infusion (DLI) therapy [32]. Reduced immunosuppression, DLI, and TKI treatment are all options for relapsed CML after allogeneic HSCT [53,54]. The best approach for patients with molecular relapse who are not on TKI is to reintroduce TKI and closely monitor their progress. Patients with cytogenetic or hematological relapse may benefit from resuming TKI with DLI. Late complications of allogeneic HSCT occur after 1 year of transplantation and can affect any organ system. Late complications in allogeneic HSCT survivors may include secondary malignancies, organ-specific toxicity, infections, psychosocial concerns, fertility concerns, and financial toxicity. The late effects in CML HSCT survivors were similar to those seen in other malignant HSCT survivors.

Conclusion

Allogeneic HSCT remains an important treatment option for CP-CML. It is recommended that patients at high risk for transformation (such as those who have been resistant or intolerant to multiple TKIs, those who live in resource-limited countries, and those who have the T315I mutation after trial of ponatinib therapy) be considered eligible for allogeneic HSCT as the outcome of transplantation after transformation is unfavorable.

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Conflicts of interest

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