The Role of Hematopoietic Stem Cell Transplantation in CML

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11.1 Introduction

The introduction of tyrosine kinase inhibitors (TKI) has changed the outlook for patients with chronic myeloid leukemia (CML), a previously uniformly fatal disease, and spearheaded the introduction of "precision medicine" for this and other malignant diseases [1–13]. The success of the TKI not only changed the course of the disease but also its treatment algorithms over a very short period of time, no better evidenced than with the dramatic decline in the use of hematopoietic stem cell transplantation (HSCT) for CML (Fig. 11.1). HSCT lost its former importance as the "only curative therapy" [14–17] and was rapidly consigned to use only as a last resort when everything else had failed and often when the patient had experienced disease progression. However HSCT remains a powerful intervention with the potential for "cure." As the use of TKI has been optimized over the past 20 years so has the outcome of HSCT considerably improved over the same period, with more sophisticated tools for donor and patient selection, a reduction in the intensity of preparative regimens, better supportive care, and the introduction of quality standards for transplant units ([18–20]). With this new knowledge it is now possible to integrate HSCT into the treatment of the small but nevertheless important cohort of patients who do not respond to TKI but may achieve long-term survival with HSCT if recognized early in their disease course.

The use of HSCT for CML has been a role model for all other diseases amenable to transplant, and it is worth reflecting on the lessons learnt to understand how the technology may be utilized in the future.

11.2 Evolution of HSCT for CML

11.2.1 Historical Perspective

The first report of a successful HSCT from a syngeneic donor to a patient with CML was more than 50 years ago and introduced a new concept into the treatment of the disease [21]. There followed the discovery of circulating leukemia progenitors in the peripheral blood and the start of the autografting era. Using progenitors collected from the bone marrow [22] or blood during the chronic phase [23], patients were treated at the time of blast transformation by high dose chemo- or chemoradiotherapy followed by infusion of cryopreserved chronic phase cells. The aim was

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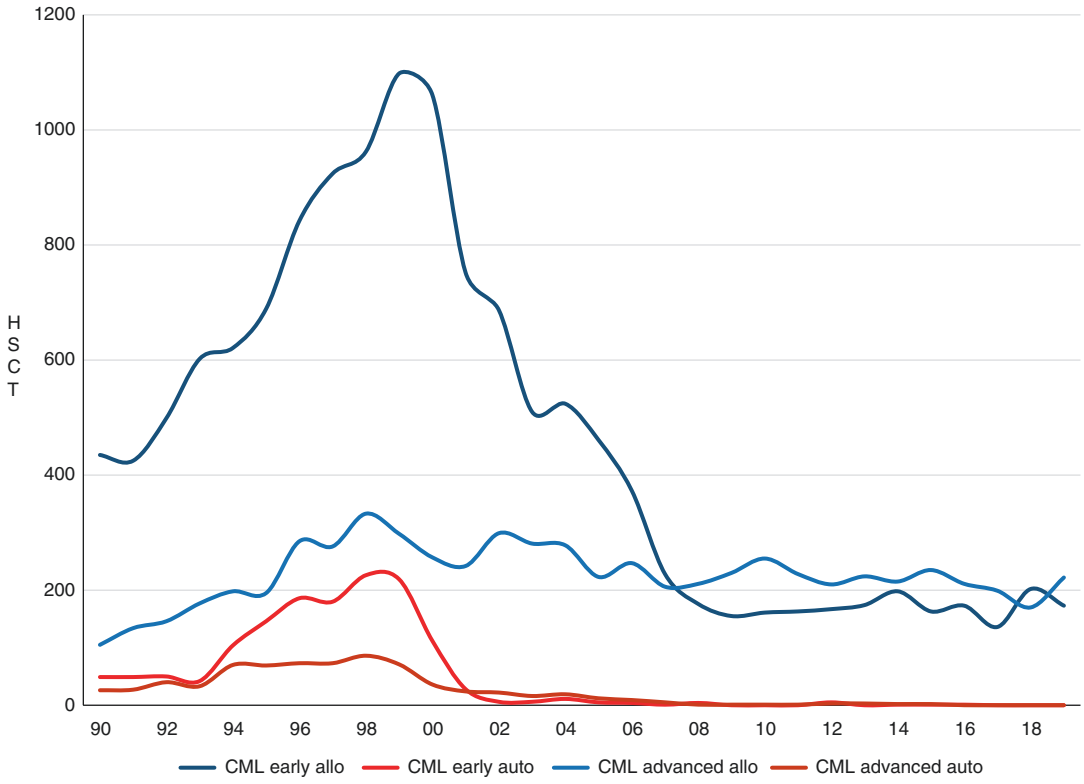

Fig. 11.1 Numbers of transplants performed for CML in Europe 1990–2019

to restore the chronic phase and prolong survival. Although the impact on survival was hard to judge, an important finding was that the majority of patients recovered Ph-negative (and putatively normal) hemopoiesis that persisted for variable lengths of time. The ability to restore normal hemopoiesis in patients with CML, albeit temporarily, through the use of high-dose chemotherapy was further confirmed by treatment with AML-like combination chemotherapy [24]. The same year saw the first series of patients who underwent transplantation with bone marrow from their identical twins who were clinically well 22–31 months later. In contrast to the previous strategies, Ph-negative hemopoiesis was consistently and durably achieved [25]. Transplantation from HLA-identical sibling donors followed rapidly thereafter [26–29].

The first autologous transplants for CML were reported to the EBMT database in 1979–80 from France and by the1990s this was a popular strategy to attempt to improve survival in selected patients. A number of prospective randomized trials were designed in Europe [30, 31] but none was completed as they coincided with the introduction of TKI. A retrospective meta-analysis of six multicenter trials in Europe and the United States showed no advantage of autologous HSCT compared to concurrent drug treatment [32]. This together with the success of TKI resulted in a rapid decrease in autologous transplant numbers since 2006, although it is fair to say that their potential role remains unclear [16] (Fig. 11.1).

The first allogeneic HSCT for CML was reported to the European Group for Blood and Marrow Transplantation (EBMT) database in 1975 from France, soon to be followed in 1978 by a patient from Switzerland and by 10 patients in 1979 from France, Italy, and the UK (personal communication; EBMT database, Leiden NL). CML soon became the most frequent indication for an allogeneic HSCT in Europe and worldwide (Fig. 11.1) [16, 33].

11.2.2 Lessons Learnt from Allogeneic HSCT for CML

The experience gained from HSCT for CML has been instructive in many ways, most of which are applicable to all hematological malignancies [34].

11.2.2.1 Disease Stage

An early observation was the importance of disease phase, rather than tumor bulk in determining outcome. Splenectomy, considered initially as essential, showed no advantage neither did splenic irradiation [35]. In contrast data from the Center for Blood and Marrow Transplant Research (CIBMTR) relating to 138 patients treated between 1978 and 1982 showed 3-year survivals of 63%, 56%, and 16% after transplant in the chronic, accelerated, and blast phases, respectively. Relapse rates for transplant in the chronic phase were remarkably low at 7% [17].

11.2.2.2 Expansion of Unrelated Donor HSCT

Only 30%–35% of patients who could benefit from allo-SCT have an HLA-identical family donor and in order to expand the applicability of transplant to more patients the next step was to utilize matched unrelated volunteer donors. In adults, the first successful unrelated allo-SCTs were reported for acute leukemia in 1980 and later for CML [36, 37]. Further development of the unrelated donor registries during the 1980s led to expansion of transplantation with CML becoming the commonest indication throughout the world [38]. With the introduction of high-resolution HLA typing, the outcomes of allografting using stem cells from matched unrelated donors are now comparable with those of HLA-matched siblings. The use of cord blood as the donor source has been successful in children but experience in adults is more limited. The largest series came from the Japan Cord Blood Bank Network, who described the outcome of transplant in 86 patients of median age 39 years. The 2-year survival for patients in chronic phase (n = 38), accelerated phase (n = 13), and blast crisis (n = 35) was 71%, 59%, and 32%, respectively ($P = 0.0004$). Results of multivariate analysis indicated that older patients (>50 years) had a higher incidence of transplant-related mortality and advanced-disease stage, and lower doses of nucleated cells were significantly associated with lower leukemia-free-survival (LFS) [39]. The Valencia group reported an LFS of 41% in 26 adults with CML of whom only 7 were in the first chronic phase at the time of a single-unit transplantation. All 8 patients transplanted in the advanced phase died [40].

11.2.2.3 GvHD and GvL

The major barrier to successful HSCT was then, as now, graft versus host disease (GvHD). The 1980s saw the introduction of T-cell depletion, which was effective in decreasing both the severity and frequency of GVHD, but was associated with higher frequencies of graft failure and relapse. The increased rate of relapse after T-cell depletion was more obvious in chronic phase CML than in other malignancies [41], and it provided direct evidence of the T-cell–mediated GVL effect of HSCT. The observation of an increased relapse rate in recipients of cells from identical twins compared with HLA-matched siblings further supported a graft versus leukemia (GvL) hypothesis [42]. The final proof of the necessity of an alloimmune effect came with the ability of additional donor lymphocyte infusions (DLI) at the time of relapse to restore remission [43, 44] in 60–90% of patients with CML who were transplanted and relapsed in the chronic phase. Optimization of the use of DLI through dose escalation minimized the risk of GvHD [45, 46].

11.2.2.4 The Advent of Reduced Intensity Conditioning

The realization that the curative power of allogeneic HSCT lay in large part in this alloimmunity paved the way for reduced intensity conditioning (RIC) which permits the expansion of transplant practice to older patients and/or those with comorbidities. Although RIC approaches with preemptive (based on chimerism) or early (based on molecular monitoring of MRD) use of DLI might have been predicted to be most effective

in CML [47], the introduction of TKI into clinical practice abrogated the immediate need for randomized studies of RIC versus myeloablative conditioning, and the question of the best conditioning regimen for CML in the chronic phase remains unresolved. An early attempt to combine RIC, immunotherapy, and TKI was reported in a study of 22 patients who were transplanted using a RIC regimen and in vivo T-cell depletion to minimize non-relapse mortality. To mitigate against the expected increase in relapse rate, imatinib was given at engraftment and continued for 12 months. After this time, any patient with residual or recurrent disease was treated with DLI. At 36 months, 19 patients were alive and 15 were in molecular remission [48].

Retrospective comparisons of the outcome of myeloablative and reduced intensity approaches are always confounded by the fact that the two patient groups are not matched for factors such as age, disease phase, donor type, or comorbidity that directly impact transplant outcome. In CML an early attempt at a retrospective study showed a reduction in the early treatment mortality but failed to demonstrate significantly improved 3-year survivals in patients with EBMT scores of 0–2. Survival was improved albeit with relatively short follow-up in scores of >3 < 6 [49].

11.2.2.5 The Introduction of MRD Monitoring

The recognition that donor lymphocyte infusions were most effective at the time of minimal residual disease (MRD) burden identified the need for a technology to identify early relapse and led directly to the development of MRD detection through reverse-transcriptase polymerase chain reaction (RT-PCR) assays for BCR-ABL1 [50]. The subsequent value of this technology to measuring response to TKI cannot be under-estimated.

11.2.2.6 Risk Assessment in HSCT

CML also provided the first example for risk assessment with the EBMT risk score [51, 52]. The EBMT score is based on five variables: donor type, disease phase, recipient age, donor/recipient sex combination, and interval from diagnosis to transplantation, from which can be derived the probabilities of non-relapse mortality and overall survival. The EBMT score was later tested in patients with various hematological disorders and was also shown to stratify risks of mortality after allogeneic HCT for diseases other than CML. More than two decades on there are recognized limitations of the EBMT score. It was derived at a time where allogeneic HSCT was rarely applied to individuals over the age of 50 years, when HLA-matching had historically not used high-resolution technology and before the introduction of reduced intensity conditioning regimens. The level of risk according disease stage does not take into account cytogenetic or molecular markers of prognosis, although these may be less relevant in CML than in acute leukemia. For CML in particular, the effect of a delay to transplant may no longer be a risk in the era of TKI. It is highly unlikely that any patient with chronic phase CML will come to transplant less than 12 months from diagnosis as most will have received at least three TKI before referral to the transplant unit. The EBMT has presented an analysis demonstrating that time to HSCT is no longer an adverse risk factor for patients previously treated with imatinib [53].

A risk score for the effect of 17 relevant comorbidities on transplantation outcome [54] has provided additional information to assist in the prediction of survival post-transplant. The HCT-CI provides specific information about patient tolerability to the transplant process and assesses the risk of non-relapse mortality. Although the score has wide applicability in hematological malignancies other than CML, in conjunction with the EBMT score, it may help to reassure patients with none or few co-morbidities of the value of HSCT if their response to TKI is less than optimal (for a fuller review of the current risk assessment tools please see [55]).

11.2.2.7 The Impact of Macroeconomics

Last but not least, in no other disease became the impact of macroeconomic factors on use of HSCT as clear as in CML. Rates of HSCT for CML dropped already in the year 2000, 2 years before

the release of imatinib in high-income countries, illustrating how expectations drive medical decision making. Until very recently they remained at a stable level in middle- and low-income countries where costs of drug therapy became higher than costs for a transplant [33, 56–59].

11.3 HSCT for CML in 2021

Data from the EBMT activity survey from 2018, the last completed and validated year, report a total of 372 allogeneic HSCT, 202 in early phase of the disease, 170 in advanced phase, and no autologous HSCT [60]. Allogeneic HSCT was performed in 35 of 51 participating EBMT countries. Their distribution over disease stage, donor type, and stem cell source, together with the near final figures from 2019, is illustrated in Table 11.1. Total numbers have remained stable for several years. There continue to be some differences in transplant rates (numbers of HSCT per ten million inhabitants) between reporting countries although these differences have diminished over recent years (Fig. 11.2). Of note, bone marrow was used as primary stem cell source for allogeneic HSCT in the first chronic phase in only 25 of 150 HLA-identical sibling and volunteer unrelated transplants, despite its survival advantage.

These consistent numbers over the past decade represent 10–15% of the numbers performed for CML in the late 1990s, i.e., shortly before the introduction of TKI into clinical practice and when CML was the commonest indication for HSCT. In fact this number fits well with models that predict the proportion of patients who will fare poorly with TKI irrespective of whether they commence treatment with first- or second-generation drugs (Fig. 11.3a, b).

Further evidence for the on-going need for HSCT in CML comes from the impressive Swedish population-based registries of all cancers [62]. The CML registry comprises 98% of all cases, 97% of which have a cytogenetically confirmed diagnosis. One hundred and eighteen patients diagnosed from 2002 to 2016 had received allogeneic HSCT by August 2017. Almost every patient (114/118) had received a TKI prior to transplant. Per 5-year periods, 34–43 patients underwent HSCT, and this number was stable during successive 5-year periods. The estimated probability that a newly diagnosed patient under the age of 65 years would receive a transplant was 9.7%. Equal numbers were transplanted in chronic and more advanced phases but most patients transplanted in the advanced phase had been diagnosed in the chronic phase, highlighting the possibility that the need for transplant in some of these patients might have been recognized before progression. Indeed the most frequent indication for HSCT in chronic phase was TKI resistance. Of the 48 patients in a second or subsequent chronic phase at time of transplant, 31 had received chemotherapy and 15 a TKI alone.

Predictably, 5-year survival was higher in early-phase disease with survivals of 96.2%, (91.4–100%),

Table 11.1 Number of HCT for CML reported to EBMT for 2018 (full data) and 2019 (near final data). Information provided by Helen Baldomero on behalf of EBMT

	Numbers of HCT in Europe 2018 by indication, donor type, and stem cell source												
	Number of patients												
Disease	Family									Unrelated			Total
	HLA-identical			Twin	Haplo ≥2MM		Other family						
	BM	PBSC	Cord	All	BM	PBSC	BM	PBSC	Cord	BM	PBSC	Cord	
2018													
CML	12	107	0	0	13	34	0	1	0	21	176	8	372
CML CP1	8	60			6	15		1		17	90	0	202
CML > CP1	4	47			7	19		0		4	86	3	170
2019													
CML	7	103	1	1	6	46	0	0	0	20	209	2	395
CML CP1	3	54	1	0	2	13	0	0	0	7	91	2	173
CML > CP1	4	49	0	1	4	33	0	0	0	13	118	0	222

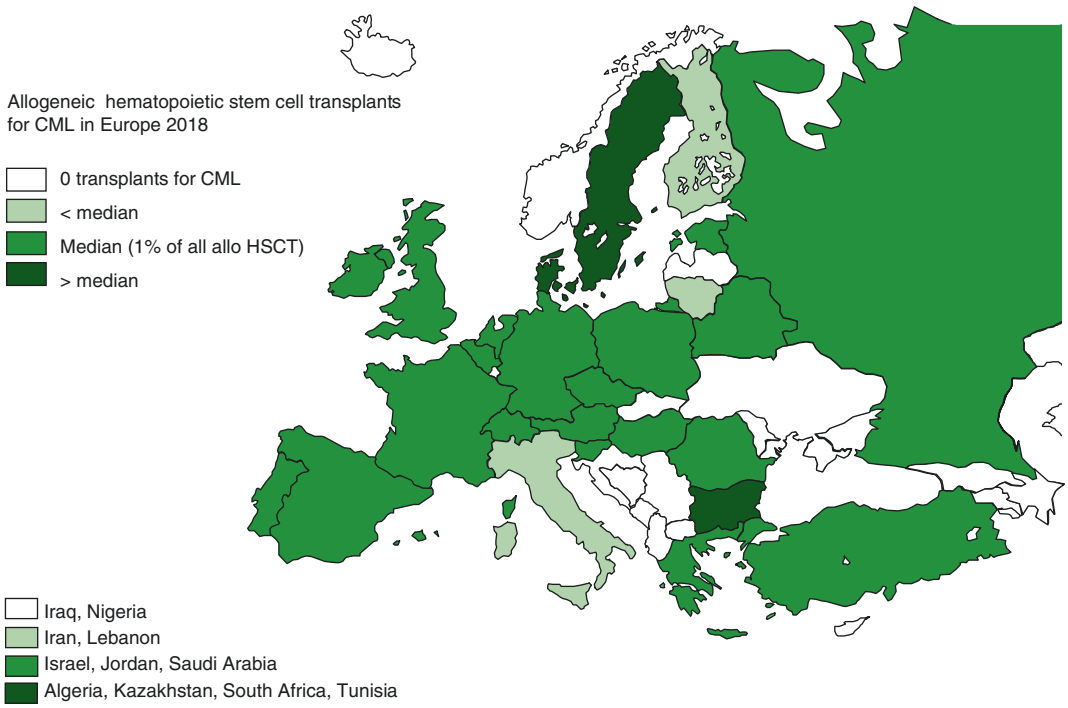

Fig. 11.2 Transplant rates for CML in Europe in 2018. The figure depicts number of HSCT for CML per ten million inhabitants for each country and depicts heterogeneity between countries. Data adapted from [61]) and kindly updated by Helen Baldomero, EBMT activity survey office

70.1% (57.4–85.5%), and 36.9% (17.7–76.8%) in the first chronic phase (CP1), second, or subsequent chronic phase (CP > 1) or advanced phase (AP – includes both acceleration and blast crisis). The excellent results achieved in the chronic phase are an important reminder of the value of HSCT in TKI non-responders. Twelve of the 56 patients transplanted in first chronic phase relapsed, most frequently detected by cytogenetic or molecular studies, and if destined to relapse, 66.7% did so within the first 2 years. Notably, 10 of 12 patients in this group achieved MR3 with TKI and/or DLI. All 7 patients transplanted in blast crisis relapsed within 6 months. Risk factors for relapse were an EBMT score > 2 and reduced intensity conditioning.

11.3.1 Factors Associated with Outcome

Risk assessment in HSCT is a complex task. The composite end points, overall survival, and relapse-free survival are influenced by two other independent keys: transplant-related mortality and relapse incidence. Some risk factors have congruent effects on transplant-related mortality and relapse incidence, hence affecting overall survival uniformly in the same direction. Disease stage is one such example. Other risk factors have discordant effects and the result then depends on the sum of all other risk factors. T-cell depletion reduces the risk of graft versus host disease but increases the risk of relapse. The net benefit on overall survival will differ between patients transplanted in early stages compared to those transplanted for advanced phase disease. Reduced intensity conditioning might be of benefit in an older patient with comorbidities and transplanted for early disease, but in contrast might be of no benefit in the same patient with no comorbidities and a transplant in advanced disease [51, 52]. As a general concept, risk factors act additively but not in a symmetrical way. A negative CMV serostatus might further improve

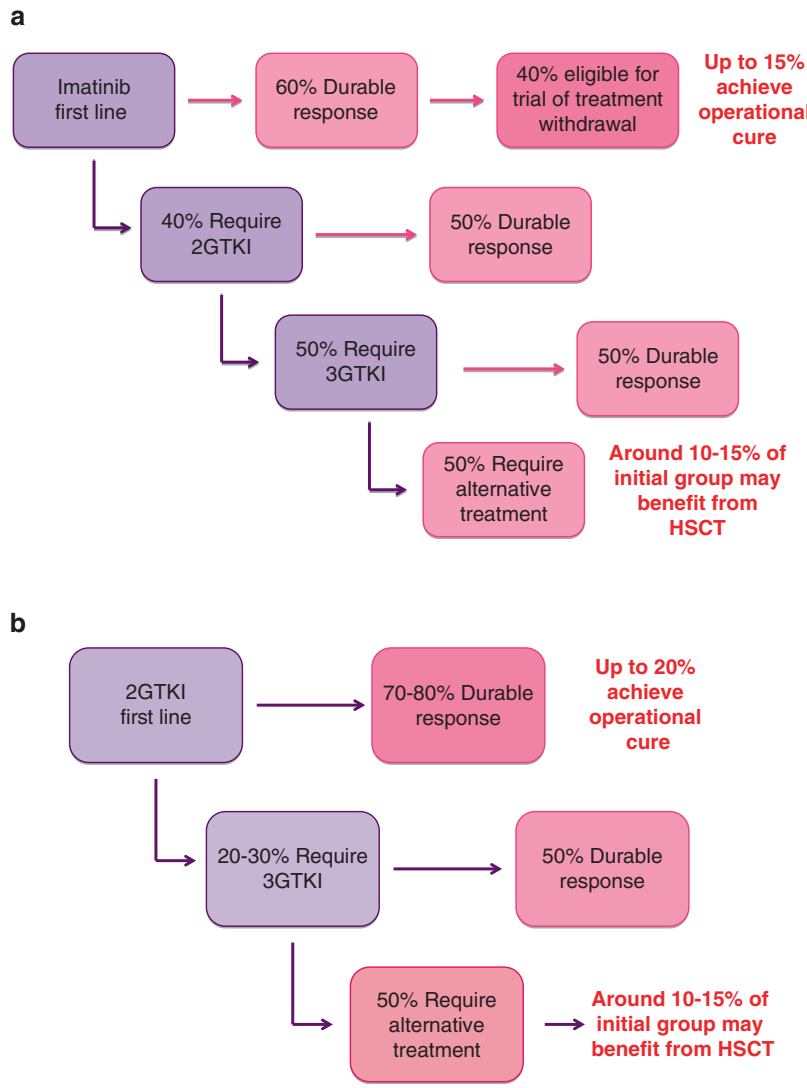

Fig. 11.3 (**a**) Predicted outcome of patients treated with first-line imatinib. (**b**) Predicted outcome of patients treated with first-line second-generation TKI

outlook for a low-risk patient but will have no additional beneficial effect in a high-risk patient; in contrast, a reduced Karnofsky score might be of minimal impact in a low-risk patient but deleterious in a high-risk patient. Hence, the general statement that probability of survival after an allogeneic HSCT for CML at 5 years is 60% is of limited value; it might range from more than 90% to less than 5%.

Assessing risk and predicting outcome for HSCT in CML in the TKI era has some additional complications. Because the numbers of transplants have fallen so dramatically, most publications in the past 15 years have been unable to identify a homogenous group of patients where the results might be of value to individual patient discussions. Studies have attempted to address important questions, for example, the impact of TKI therapy pre- or post-transplant, the role of reduced intensity versus myeloablative conditioning regimens, the stem cell source, etc. However, in order to achieve the numbers necessary for statistical analysis, they tend to use all the patients within their dataset merging risk factors other than that under study, that have a profound impact on outcome, such as disease phase, donor type, GvHD prophylaxis, conditioning regimens, stem cell source, etc. Larger numbers of patients

are available in the international transplant registries but they often lack important information, such as co-morbidities, the nature of therapy pre-transplant, the indication for transplant, the use of TKI post-transplant, and the reason for choosing reduced intensity over myeloablative preparative regimens. As a result there remain many unanswered questions regarding the optimal approach in individual patients.

11.3.2 Impact of Pre-Transplant Treatment

Most patients will have pre-treatment with a TKI for their CML before HSCT. To date there is no suggestion that a TKI given before the transplant has a deleterious effect on outcome after HSCT [63, 64]. More recently Turkish colleagues described 65 patients transplanted in the post-TKI era, defined as after 2002: 48 (73%) had received a TKI prior to the procedure and they were unable to identify any adverse impact [65].

An interesting study was reported from China where the use of a TKI prior to transplant was often a financial rather than a medical decision. They described 106 patients, of whom 36 had received imatinib before HSCT and 83 were in first chronic phase at transplant The estimated 10-year LFS and overall survivals (OS) were not statistically significant between the imatinib-treated and the imatinib-naive groups (79.6% vs. 62.4% P = 0.432, 68.9% vs. 55.5% P = 0.086, respectively). There was a suggestion of higher early non-relapse mortality in the imatinib-treated group but this did not affect long-term outcome. Interestingly the imatinib-exposed cohort contained higher proportions of patients with advanced-phase disease, and a longer duration from diagnosis to HSCT resulting in higher EBMT scores. This, in turn, influenced the choice of conditioning regimen [66].

Early papers addressing the potential impact of TKI therapy prior to transplant invariably contained patients who had been treated only with imatinib. Now patients come to HSCT often having received three or more TKI, and it becomes difficult to distinguish a possible negative effect of TKI from the poor biology of a patient who has failed successive TKIs. A study of 28 patients in different disease phases who had all received at least two TKIs was unable to show an adverse impact on outcome compared to historical controls [67]. In contrast a Japanese group reported 237 patients of whom 153, 49, and 35 had received one, two, or three TKIs prior to HSCT. Ninety-seven, 57, 32, and 51 patients were in the first chronic phase, second, or subsequent chronic accelerated phase and blast crisis, respectively, at the time of transplant; the overall and leukemia-free-survivals were 67% and 54% in patients exposed to fewer than three TKIs and 61% and 54% in patients who had received at least three TKIs. The relapse incidence in patients treated with three TKIs was twice (34%) that of patients exposed to fewer TKIs (17%). This is unlikely to be explained by TKI exposure per se and more likely reflects more resistant disease [68].

11.3.3 Impact of HSCT Methodology

Despite more than 40 years' experience, the best conditioning regimen and the best GvHD prophylaxis for HSCT in CML are still undefined. No other conditioning regimens produce a better long-term overall survival than cyclophosphamide and total body irradiation or busulfan and cyclophosphamide; no other GVHD prophylaxis has been shown to be superior to cyclosporine and methotrexate. In a large observational retrospective study by the CIBMTR, RIC gave a better overall survival in elderly patients compared to non-myeloablative conditioning; no comparison was made with standard conditioning [69].

Peripheral blood-derived stem cells (PBSC) have largely replaced bone marrow as the stem cell source for sibling, unrelated, and haploidentical transplants in adults. Initial studies showed a clear early advantage of peripheral blood with more rapid engraftment, and a slightly higher incidence of graft versus host disease but overall similar survival. Today, several studies have demonstrated an advantage of bone marrow as stem cell source in early disease, and of peripheral blood in advanced disease [70, 71]. In a

large CIBMTR study of unrelated donor HSCT, patients transplanted in the first chronic phase had 5-year rates of survival of 35% with PBSC compared to 56% with bone marrow. Relapse rates were low with both graft types suggesting that there was no advantage in higher rates of chronic GVHD after PBSC transplant. In contrast, for patients with CML transplanted in the second chronic, accelerated, or blast phase, there were no significant differences in rates of overall survival, non-relapse mortality, or relapse, which differs from HLA-matched sibling transplantation where mortality is lower using PBSCT in those with advanced CML [72]. Despite these differences, use of stem cell source still appears erratic, with major differences between European countries.

11.3.4 Impact of Maintenance TKI Post-Transplant

The value of using a TKI post-transplant is unclear and is further compounded by the current availability of at least five TKIs for use prior to transplant referral. In 2021 most patients in the first chronic phase will come to transplant having failed both second- and third-generation TKIs (2G-TKI, 3G-TKI), and the rationale for continuing treatment post-transplant with a drug to which the patient was resistant or intolerant is unclear. The situation might be different in patients transplanted for advanced-phase disease where exposure may be limited to none or just one TKI, with the patient being restored to a second chronic phase using AML-like chemotherapy, or where the patient was transplanted after the detection of a T315I mutation and who has been restored to varying levels of remission with ponatinib.

Furthermore the administration of TKI post-transplant may not be straightforward. A phase I/II study investigating the use of nilotinib after HSCT for high-risk Ph-positive leukemias reported 2-year overall and leukemia-free survivals of 69% and 56%, respectively. In this small study of 16 patients, 38% discontinued therapy, mainly because of gastrointestinal and/or hepatic toxicities [73]. In a separate phase I/II study, only a third of patients eligible for nilotinib maintenance completed the year of intended therapy [74].

A recent CIBMTR study compared 89 patients who received a TKI post-transplant with 301 who had no maintenance therapy. All patients received TKI therapy before HCT. In this landmark analysis from Day +100 the adjusted estimates for 5-year relapse (maintenance, 35% vs. no maintenance, 26%; $P = 0.11$), LFS (maintenance, 42% vs. no maintenance, 44%; $P = 0.65$), or overall survival (maintenance, 61% vs. no maintenance, 57%; $P = 0.61$) did not differ significantly between patients receiving TKI maintenance or not. These results were not affected by disease status at transplant [75]. However the results are difficult to interpret because the two groups were not comparable: for instance there was a higher percentage of patients in second or subsequent chronic phase in the maintenance group ($P < 0.001$) and there was no information regarding prior response to individual TKI or the indication for giving post-transplant maintenance.

11.3.5 Management of Relapse Post-Transplant

The most appropriate management of relapse post-transplant is also contentious. DLI have been used for 30 years to restore remission in patients who have relapsed in chronic phase after transplant in chronic phase and are most effective when given at a time of low disease burden, i.e., cytogenetic or molecular evidence of residual disease [44, 45]. DLI are not without complications having the capacity to cause pancytopenia and to induce potentially fatal GvHD, the latter being more frequent if the DLI are given within the first 12 months of transplant. In contrast TKI are relatively easy to give, and side effects should they occur are reversible on discontinuation. This has encouraged many investigators to give TKI for relapse which in the early years showed good results, apart from the dilemma of when they should be stopped. Giving a TKI for relapse in a patient who required their transplant for resistance to multiple TKIs is more problematic.

A study from the EBMT retrospectively analyzed 500 patients who received DLI for relapse (16% molecular, 30% cytogenetic, and 54% hematological) after HSCT for CML. Complete cytogenetic remission was achieved in 341 patients (71%) at a median of 7.5 months. A total of 222 (44%) patients developed secondary GVHD at a median of 3 months from first DLI with 61, 70, 40, and 20 patients being diagnosed with secondary acute GVHD grades 1, 2, 3, and 4, respectively. Secondary chronic GVHD occurred in 87 (17%) patients. The estimated probabilities of survival at 5 and 10 years from DLI were 64% and 59%, respectively. However the estimated probabilities of failure-free and GvHD free survival (FGFS) at 5 and 10 years were considerably less at 29% and 27%, respectively. The probability of survival in remission without secondary GVHD was highest (>50% at 5 years) when DLI were given beyond 1 year from HSCT for molecular and/or cytogenetic relapse that was not preceded by cGvHD [76]. Such information can help guide the choice of DLI or TKI in individual patients, particularly in those with prior and/or current GvHD and relapsing soon after transplant.

11.4 Outcome of HSCT in CML in the TKI Era

11.4.1 Chronic Phase Disease

Early after the introduction of TKI into clinical practice many patients continued to be transplanted. The reasons were varied and included lack of access to TKI, patient and physician choice, a lack of long-term follow-up from TKI treatment, a favorable EBMT risk score with or without a high Sokal/Euro score, resistance and/or intolerance to the only available TKI, imatinib, and concern regarding the long-term costs of life-long TKI. This situation enabled a number of comparisons of transplant versus TKI in retrospective cohorts. In 2021 these are of limited value as TKIs are the treatment of choice for newly diagnosed patients in the chronic phase, and most patients will be given multiple TKIs before transplant referral.

Just before the widespread availability of TKIs, the German CML study group tested the hypothesis that HSCT would be associated with early mortality but a subsequent survival benefit might compensate for the "early years of life lost" in the CML III trial. Availability of a matched family donor was used as "genetic randomization." In this study with 349 patients, survival was significantly better in patients on drug treatment after a median observation time of 8 years, in no small part because patients were able to access TKI therapy later in their disease course. The conclusion was clear: "the general recommendation of HSCT as first-line treatment option in chronic phase CML can no longer be maintained" [77]. These results formed the basis for the subsequent ELN guidelines on the use of HSCT in TKI-treated patients, currently in their fourth iteration [78]. Allogeneic HSCT is considered a third- or subsequent-line therapy for chronic phase disease and the preferred option for patients with advanced phase.

The German Swiss CML IV study permitted early HSCT in their first TKI-based study [79]. A total of 84 patients (median age, 37 years) received HSCT, either first line (19 patients) or after imatinib failure (37 and 28 patients in chronic and accelerated phases, respectively). Overall survival of this cohort was 88% for all, 94% when treated in the chronic phase, and 59% for those transplanted in the accelerated phase. Transplant-related mortality was 8%; chronic graft versus host disease occurred in 46%. Of note, overall survival of the patients transplanted in CP was no different from that of the concomitantly imatinib-treated patient cohort. This study serves as a reminder of the excellent outcome of HSCT in selected patients.

More recently a Chinese group reported the outcomes of imatinib treatment (n = 292) versus HSCT (n = 141) for CML, in a situation where the choice of HSCT over imatinib may have been driven by financial constraints rather than medical advice. In CP1, patients treated with imatinib (n = 278) had superior event-free and overall survivals at 5 years at 84% and 92% compared to transplanted patients at 75% and 79% ($P < 0.05$), respectively. In contrast they were unable to

demonstrate differences in outcome for patients treated in the accelerated phase or blast crisis [80].

11.4.2 Advanced-Phase Disease

Patients presenting in or progressing to the accelerated phase are heterogeneous in terms of disease biology and response to treatment, leaving some to question whether acceleration is a separate entity that can be clearly defined or is simply part of the spectrum of chronic phase with features (such as the blast cell count) that might identify the patient as high risk in the same way as a diagnostic risk score such as Sokal. There are limited data available for HSCT in acceleration. A study form Beijing compared HSCT versus imatinib in 132 patients, of whom 87 received imatinib and 45 allogeneic HSCT. Multivariate analysis found a CML duration ≥12 months, hemoglobin <100 g/L, and peripheral blood blasts ≥5% to be independent adverse prognostic factors for overall and progression-free survival. They developed low (no adverse factors), intermediate (anyone factor), and high (two or more factors) scores and showed that HSCT provided significant overall and/or progression-free survival advantages for high- and intermediate-risk patients: the outcome for low-risk accelerated phase was excellent and similar for imatinib and HSCT [81].

A study from the same group comprising 83 patients in blast crisis, 45 who received TKI and 38 who were treated with HSCT after TKI, showed that TKI-HSCT significantly improved the 4-year overall (46.7% vs. 9.7%, $P = 0.001$) and event-free survivals (EFS) (47.1% vs. 6.7%, P = 0.001) compared to TKI alone. Hemoglobin <100 g/L, failure to return to chronic phase after TKI therapy, and TKI treatment alone were independent adverse predictors of OS and EFS. The HSCT group comprised 27 patients who presented de novo and 11 patients who progressed on TKI. All 27 received a TKI and 21 achieved a second chronic phase. Those who had progressed on TKI were treated either with an alternative TKI or with chemotherapy and 9 returned to a chronic phase, such that 30 of the 38 transplanted patients were in a second chronic phase at the time of transplant. Eighteen patients survived with 12 patients dying of non-relapse mortality and 8 of relapse. In contrast, although a similar proportion of the 45 patients treated with TKI alone achieved chronic phase, there were only four survivors. Of the 23 patients who failed to achieve a second chronic phase there were no survivors in the group that did not proceed to HSCT [82].

The EBMT have recently reported a retrospective study of 171 patients allografted for blast crisis after TKI therapy. At transplant, 95 patients were in a second or subsequent chronic phase and 75 patients had active blast crisis. In multivariable analysis, active blast crisis at transplant was the strongest factor associated with decreased overall and leukemia-free survival. For patients in second or subsequent chronic phase at transplant, age > 45 years, Karnofsky <80%, time from blast crisis to HSCT >12 months, myeloablative conditioning, and unrelated donor transplant were risk factors for inferior survival [83].

11.4.3 Patients with a T315I Mutation

Outcomes for transplant were reported in 22 patients with T315I mutations who received HSCT (mostly haploidentical) as ponatinib was unavailable. At the time of HSCT 7, 8 and 7 patients were in first chronic, accelerated/second chronic and blastic phases, respectively. The estimated 2-year LFS was 80.0%, 72.9%, and 0% in the three groups confirming the poor outcome of HSCT in blast crisis and the need to transplant patients with adverse prognostic features such as the T315I mutation before disease progression [84].

The outcome of 184 patients with T315I mutations, in which 128 received ponatinib and 56 an allogeneic HSCT showed that 2- and 4-year survivals were significantly higher in patients with chronic-phase CML who received ponatinib at 84% compared with those who underwent HSCT at 60.5%. In patients in the accelerated phase, survival rates were not significantly dif-

ferent between the groups and in those in blast crisis ponatinib was associated with a shorter survival compared with HSCT. The authors concluded that ponatinib was a valuable treatment option for patients with a T315I mutation who remained in the chronic phase but in those who had progressed to an advanced phase, HSCT was the preferred therapy [85]. It is entirely possible, however, that with additional follow-up, the durability of response to ponatinib will be inferior to that of HSCT even in the chronic phase.

11.5 Timing of HSCT in 2021

The ASBMT and EBMT are very consistent in their most recent recommendations and consider HSCT as a standard indication for patients with failed TKI response and for patients in advanced disease [86, 87]. They emphasize that additional risk factors other than stage of the disease and response to TKI have to be integrated into the final decision to proceed or to abstain from HSCT.

11.5.1 Advanced-Phase Disease

The response to TKI in patients presenting in accelerated phase is highly variable, with many achieving deep and durable molecular responses and a minority displaying early TKI resistance and acquisition of additional chromosomal abnormalities. The general consensus is to treat patients as in the chronic phase but have a low threshold for transplant referral if responses are less than optimal. The more difficult question is the necessity to try to achieve a second chronic phase prior to transplant and here there is no clear answer. In the pre-TKI era, the outcome for HSCT in the accelerated phase was similar to that of the second chronic phase. However, if the accelerated phase cohort contained then, as now, a group of patients with disease biology more similar to chronic phase, then the transplant outcome might have been overly optimistic, in which case returning a patient to a second chronic phase would be advisable. There are currently no data to support this hypothesis.

In contrast there is general agreement that presentation in, or progression to, advanced phase disease is associated with very poor outcome, whether the patient is treated with TKI or HSCT or both. Fortunately blast crisis is now a rare event. In the pre-TKI era the rates of blast transformation per annum were approximately 1-5-4% and were consistent year on year. The estimated 10-year cumulative incidence of blast crisis in the pivotal IRIS study was 7.9% but the majority of the progressions occurred in the first 4 years. The use of 2G-TKI in first-line therapy appears to further reduce this risk with progression rates at 5 years of 0.7–1.3% for nilotinib and 3.0% for dasatinib compared to 4.8–5.7% for imatinib in the randomized Enestnd and Dasision studies [10, 12].

Once blast crisis is established the only treatment to offer any possibility of long-term survival is allogeneic HSCT, ideally after a return to a second chronic phase. This can be achieved by the use of TKI alone or in combination with AML-like chemotherapy, although the consensus is that combination treatment offers the higher probability of response. Recent data obtained from a small group of patients using the third-generation TKI, ponatinib, have demonstrated the feasibility of using this in combination with FLAG-Ida and showed encouraging outcomes for patients who were able to proceed to HSCT [88]. The actual choice may depend on factors including age, co-morbidities, and performance score but these periods of stability are short lived and patients should proceed to transplant as soon as possible. The results of haploidentical HSCT have improved very considerably over recent years following the introduction of post-transplant cyclophosphamide and have the advantage that almost all patients will have a suitable donor. If a fully matched family or unrelated donor cannot be identified in a timely manner, haploidentical transplant is now a very real alternative.

The MD Anderson Cancer Center reported their experience in 477 patients presenting in or progressing to blast crisis. Treatment modalities were TKI alone (n = 149; 35%), TKI plus chemotherapy (n = 195; 46%), and non-TKI based therapies (n = 82; 19%). Patients treated with

a combination of TKI with chemotherapy had significantly higher rates of major hematological, complete cytogenetic, and major molecular remissions compared to other modalities. One hundred and four patients (22%) proceeded to HSCT and the proportion of patients who received a transplant was higher among those treated with TKI-based combinations (21%) than those treated with TKI alone or non-TKI therapy (3% and 10%, respectively). Patients who received HSCT after their initial treatment for CML-BP had a significantly longer survival than patients who did not receive transplant [89].

11.5.2 Chronic-Phase Disease

Once progression has occurred treatment strategies are limited and the focus must be on the prevention of blast transformation through identification of high-risk patients at diagnosis, currently via ELTS and Sokal scores, and the presence of additional chromosomal abnormalities but perhaps in the future by next-generation sequencing for prognostic mutations in other somatic genes, rigorous molecular monitoring, and adherence to international guidelines for triggers for changes in management.

There are rare patients who, although responsive to TKI, are unable to tolerate the drugs in the long-term. Such patients may benefit from HSCT although often the reasons that they cannot tolerate TKI are often related to comorbidities that may also preclude transplant. Younger patients with poor compliance and a real risk of disease progression form another significant minority who may come to transplant early.

A Canadian study described 51 patients with CML underwent HSCT, including 15 in advanced phase at diagnosis, 30 with TKI resistance as defined by the European LeukemiaNet guidelines, 2 with TKI intolerance, and 4 because of physician preference. At diagnosis, 33 of the 51 patients were in first chronic phase but by the time of HSCT, 16 of the 33 had progressed on imatinib. The 8-year overall and event-free survivals were 68% and 46%, respectively. Predictors for overall survival included first chronic phase at the time of HSCT, an EBMT score of 1–4, and complete molecular remission after HSCT [90].

As experience in the use of TKI increases, there is increasing evidence that resistance to a 2G-TKI, unless associated with poor compliance and/or the presence of a kinase domain mutation sensitive to an alternative agent, is a poor prognostic factor. Switching the patient to an alternative 2G-TKI is associated with a low probability of attaining the major molecular remission consistent with a prolonged survival. At this point and irrespective of whether the 2G-TKI has been used in first or second-line treatment, the patient should be switched to a third-generation drug, co-morbidities permitting, and referred to the transplant unit for donor identification and consideration of HSCT (Fig. 11.4). At the time of starting a 3G-TKI, it is difficult to pre-

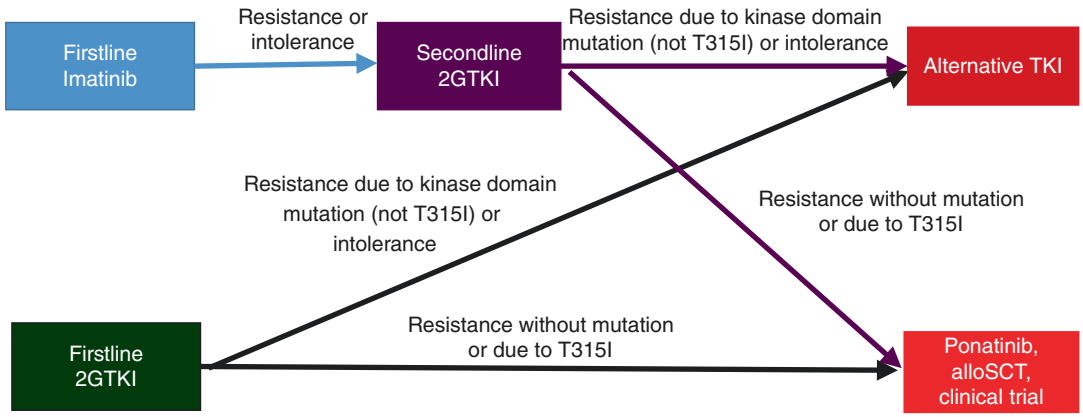

Fig. 11.4 Algorithm for management of patients with CML in 2021

dict response but the outcome of patients who discontinue ponatinib for resistance or intolerance is poor with one study demonstrating a median survival for all patients of 16.6 months after stopping ponatinib (31, 9, and 13 months for patients stopping in chronic, accelerated, and blast phases, respectively). Predictably there was a trend for better survival in patients who discontinued ponatinib for toxicity rather than resistance [91].

11.6 Concluding Remarks

The introduction of TKI as targeted therapy has eased and improved the treatment of CML in an unprecedented way. It has increased the understanding of the disease and changed attitudes but complicated decision trees. The astonishing results with TKI have interrupted many comparative trials and focused multicenter research interests on comparative trials of different drugs. In parallel, interest in the HSCT community has moved to questions of novel transplant technologies rather than comparisons with non-HSCT approaches. It is highly unlikely that there will ever be a comparative study of HSCT versus no HSCT in CML at any disease phase. As a consequence, all recommendations are based on individual interpretation of past results.

The ease of drug administration has shifted the patient community from major university centers toward decentralized medical practice, which is appropriate for the majority of patients. However there is a risk that the busy generalist can miss the signs of poor response and delay or defer changes in treatment and/or referral for HSCT. This is reflected in the better survival of patients on drug treatment for advanced disease treated in a university-affiliated center compared to those in a community practice [61].

During the TKI era, the outcome of HSCT has also substantially improved; the numbers of HLA-typed volunteer-unrelated donors has increased to more than 22 million worldwide, and improvements in haploidentical transplant mean that suitable donors can be identified promptly. The outcome of HSCT is substantially better in centers with longer disease experience and higher patient volumes. Experience in complications and disease management is essential in order to ascertain optimal survival. In the case of early TKI failure, HSCT should be considered early for those with minimal transplant risks and the drug treatment changed for those with less favorable transplant options. The same applies to patients experiencing transformation at any time and for those with failure to respond to second- or third-line therapy. In contrast patients with high transplant risks and aggressive disease should not be referred for HSCT without any reasonable likelihood for success. Continued drug therapy, experimental approaches, or palliation might be the wiser option. In order to arrive at such a policy, patients and patient advocacy groups need to be informed, cooperation should be established between the local medical community and the transplant centers, and professional organizations must continue to adapt their recommendations as appropriate. In this way, more patients will profit from a safe transplant; fewer patients will undergo a futile transplant procedure.

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