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REVIEW ARTICLE

The role of hematopoietic stem cell transplantation in chronic myeloid leukemia

Alois Gratwohl · Helen Baldomero · Jakob Passweg

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Abstract Allogeneic hematopoietic stem cell transplantation (HSCT) is currently recommended as 2nd or 3rd line therapy for patients with chronic myeloid leukemia (CML) in first chronic phase or as salvage for patients with very advanced disease. As a consequence, numbers of HSCT in chronic phase have dropped significantly since the introduction of tyrosine kinase inhibitors (TKI), numbers of transplants in advanced disease to a lesser extent. These current recommendations consider primarily disease risk, defined as failure of TKI therapy; they might need to be adapted. We propose a more balanced appraisal of HSCT for individual patients which should include disease risk, transplant risk, and macroeconomic aspects. HSCT should be integrated into the treatment algorithms from diagnosis and be considered very early at first TKI failure for patients with high disease but low transplant risk. For patients with very advanced disease and high transplant risk in contrast, HSCT might only be recommended in a restricted research setting.

Keywords Chronic myeloid leukemia · Hematopoietic stem cell transplantation · Allogeneic · Autologous · Risk assessment

Introduction

Chronic myeloid leukemia (CML) has seen unprecedented changes over the last decade. The introduction of tyrosine kinase inhibitors (TKI) has changed the outlook for patients with this previously uniformly fatal disease. The ease of application, the rapid response, and the mostly excellent tolerability by the patients has focused interest on targeted drug therapy [1–7]. Hematopoietic stem cell transplantation (HSCT) has lost its former importance as the "only curative therapy" [8–12]. This is reflected by the numbers of publications in medical journals or by the numbers of presentation on the topic at scientific or promotional meetings. If any, it is considered by many as tool of last resort when everything else has failed. This phenomenon is not restricted to CML. Ease of application and improved response to modern drug therapy has almost halted HSCT for multiple myeloma and limited HSCT to selected patients [13, 14]. Still, HSCT is the most powerful intervention; it holds the potential for "cure" and outcome has dramatically improved over the last years [15, 16]. It might be good to look at the past and to reconsider the current status and the potential role of HSCT in the treatment algorithm of CML today.

A. Gratwohl (✉) · H. Baldomero · J. Passweg
Hematology, University Hospital, Dittingerstrasse 4,
4053 Basel, Switzerland
e-mail: alois.gratwohl@unibas.ch

Evolution of HSCT for CML

Historical perspective: the role model of CML for HSCT

The first report of a successful HSCT from a syngeneic donor to a patient with CML dramatically changed the concept on how to look at CML. For the first time, it became possible to achieve a Ph state, to eradicate the malignant BCR/ABL clone, and to reverse the previously inexorable course of the disease [17]. The concept was rapidly taken up and extended to HSCT from an HLA-identical sibling donor. It did coincide with the introduction of cyclosporine A as novel and most powerful tool for the prevention of graft-versus-host disease (GvHD) and the concept of HSCT in first complete remission of acute leukemia; hence, it was introduced in patients with CML early in their disease, in first chronic phase [8–10, 18].

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). The concept proved to be right and CML became soon the most frequent indication for an allogeneic HSCT in Europe and worldwide (Fig. 1) [11, 19]. Of note, as of June 2014, 3 of these 12 patients were reported to be alive at plus 35 years, one as lost to follow-up.

CML played a role model for HSCT in general in many aspects. CML did provide the first example for risk assessment with the EBMT risk score (see below)

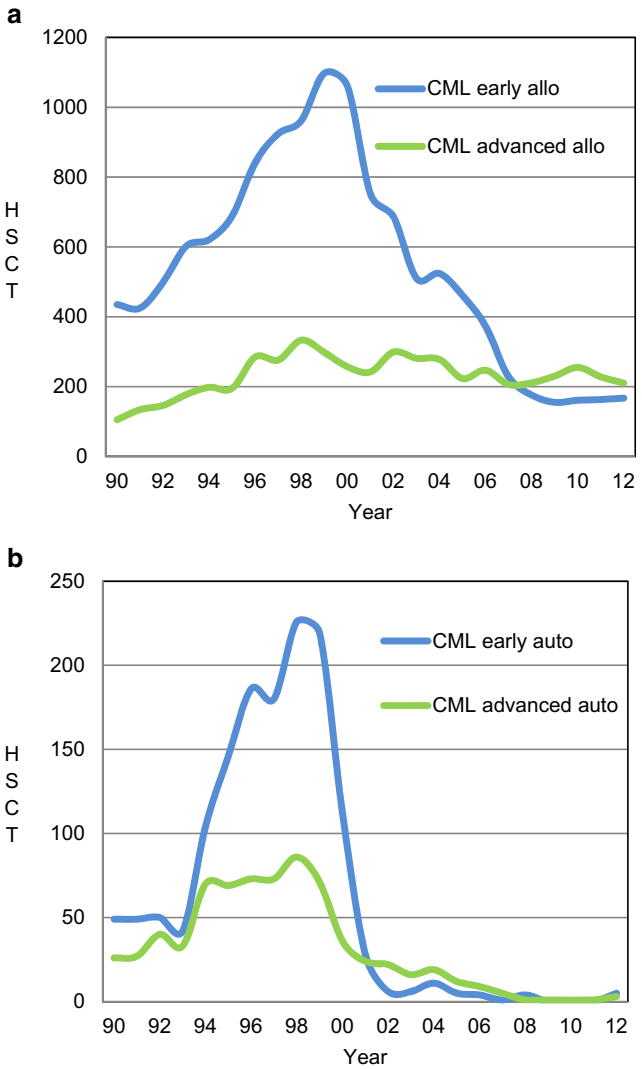

Fig. 1 Evolution of HSCT in Europe from 1990 to 2012. The graph illustrates increase and decrease of absolute numbers of allogeneic (Fig. 1a) and autologous (Fig. 1b) HSCT in Europe over time. In blue early disease (first chronic phase), in green advanced disease stage at time of HSCT (accelerated phase or blast crisis). **a** Evolution of allogeneic HSCT. **b** Evolution of autologous HSCT

[20–22]. It became clear that disease stage was more important than bulk of the disease. Splenectomy, considered initially as essential showed no advantage, nor did splenic irradiation [23]. CML was the first disease to demonstrate a consistent graft-versus-leukemia effect. Relapse risk was highest after T cell depletion in CML compared to other diseases, in contrast, donor lymphocyte infusion (DLI) proved to be the most powerful tool in CML. CML paved the way for reduced intensity conditioning, specifically with the additional role of preemptive DLI [24–26]. 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. They remained at a stable level in middle and low income countries where costs of drug therapy became higher than costs for a transplant [11, 19, 27–30].

CML showed as well a role model for autologous HSCT. It was introduced in Europe early on, almost simultaneously with allogeneic HSCT. The first patient was reported to the EBMT database in 1979 from France, to be followed by 4 patients in 1980, from France as well. None of them stayed alive. The concept was clear, restore chronic phase in patients with advanced disease through stem cells obtained in early phase. Pilot studies proved to be promising and led to the design of several multicenter prospective randomized trials in Europe [31, 32]. None was completed; the introduction of the TKI ended these trials prematurely and the answer about the potential role of autologous HSCT remains open. At least, a retrospective meta-analysis of six multicentre trials in Europe and the US showed no advantage of such a procedure compared to concurrent drug treatment [33]. Numbers of autologous HSCT almost vanished away since 2006 [11] (Fig. 1).

Current status in 2014

Data from the EBMT activity survey report a total of 377 allogeneic HSCT for CML in 2012, 167 in early phase of the disease, 210 in advanced phase from 35 countries, and 8 autologous HSCT, 5 in early disease, 3 in advanced phase. Their distribution over disease stage, donor type, and stem cell source is illustrated in Table 1. Compared to previous years, total numbers remained stable.

Allogeneic HSCT were performed in 35 countries. There were significant differences in transplant rates (numbers of HSCT per 10 million inhabitants) between reporting countries (Fig. 2). They ranged from none to more than 10 in Belgium, Estonia, Finland, Sweden, and Switzerland.

Table 1 HSCT for CML in Europe 2013 (preliminary data)

	Allogeneic HSCT							Autologous HSCT	Total
	Donor type			Stem cell source			Total	Total	
	Syngeneic	Family	Unrelated	BM	PB	CB			
cP	0	60	80	34	102	4	140	0	140
Not cP	0	78	117	32	157	6	195	3	198
Total	0	138	197	66	259	10	335	3	338

Outcome of HSCT for CML

Factors associated with outcome

HSCT has been and still is associated with significant early and late transplant-related mortality. In the early days, mortality appeared erratic, with some young patients dying, others surviving. In the mid-eighties of last century, it became apparent that outcome was related to specific pretransplant criteria, independent of transplant technology. This was especially important for patients with CML who faced the difficult decision to make, an early transplant with the significant risk for immediate mortality versus the risk of blastic transformation with minimal chances for rescue with HSCT. The EBMT risk score, based on five pretransplant factors did permit a rapid assessment on a scale from 0–VII at the physician's desk and gained rapid acceptance (Table 2). The risk score was validated in several independent cohorts and proved to be valid, with some minor modifications, for all acquired hematological disorders and for autologous HSCT as well [20–22].

The difficulty in risk assessment lies in the fact that some factors such as disease stage have congruent impact on the two key endpoints, transplant-related mortality and relapse, hence affect overall survival uniformly in the same direction; others have discordant effects. The net result might then depend 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 disease compared to those transplanted in advanced disease stage. Reduced intensity might be of benefit in an older patient with comorbidities but early disease; it might be of no benefit in the same patient with no comorbidities but advanced disease (Table 3) [20–22].

As a general concept, risk factors act additively but not in a symmetrical way. A negative CMV serostatus might further improve 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 the 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 %. As we will see below, integration of all elements, including macroeconomic factors of patient's location, should impact on choice of transplant technique and the final decision to proceed with HSCT or to abstain from it [34–39].

Impact of pretransplant treatment

Most patients will have pretreatment for their CML before HSCT. Earlier studies indicated a higher transplant-related mortality in patients pretreated with busulfan compared to hydroxyurea and in patients given interferon alpha up to the day of the transplant. Today, all patients will have had TKI before their transplant. There are clear indications that no type of TKI given before or after the transplant has a deleterious effect on outcome after HSCT; in one study, results appeared even better for patients with TKI prior to HSCT. In contrast, type of response to TKI therapy will impact on post transplant outcome with a good outcome for patients intolerant to TKI but with a higher likelihood of worse outcome for those who failed TKI therapy before HSCT [34, 40–45].

Impact of HSCT methodology

Despite now 30 years of experience, the best conditioning regimen and the best graft-versus-host disease prevention method remains to be defined. No other conditioning has been documented to arrive at better long term overall survival than cyclophosphamide and total body irradiation or the combination of busulfan and cyclophosphamide, no other graft-versus-host disease prevention method than the combination of cyclosporine and short methotrexate [8]. Reduced intensity conditioning has extended application of HSCT to elderly patients or to those with comorbidities [26]. In a large observational retrospective study by the CIBMTR, it showed a better overall survival in elderly patients compared to non-myeloablative conditioning; no comparison was made

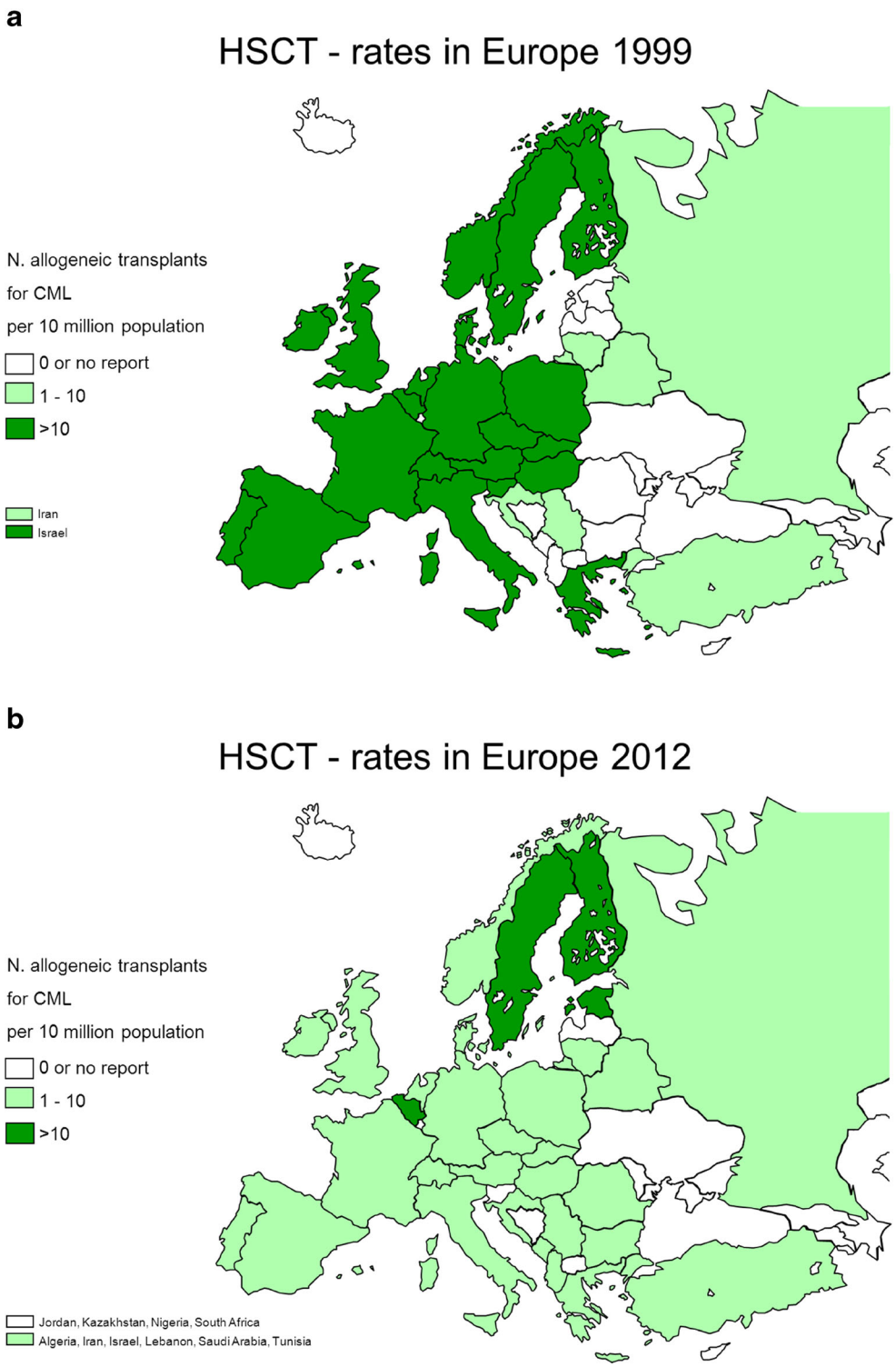

Fig. 2 Transplant rates in Europe 1999 and 2012. The figure depicts number of HSCT per 10 million inhabitants and illustrates the decrease in transplant rates for CML over time, in contrast to the transplant rates for all indications in general. It depicts as well the vast heterogeneity between countries. **a** Transplant rates for CML in 1999. **b** Transplant rates for CML in 2012. **a** Transplant rates for all allogeneic indications in 1999. **a** Transplant rates for all allogeneic indications in 2012

with standard conditioning [42]. Bone marrow as stem cell source appears to be of advantage in early low-risk disease, peripheral blood in advanced disease [46, 47]. Of general importance to note, there are no indications that impact of transplant technology in CML differs from that in any other disease treated with HSCT [8, 15, 48].

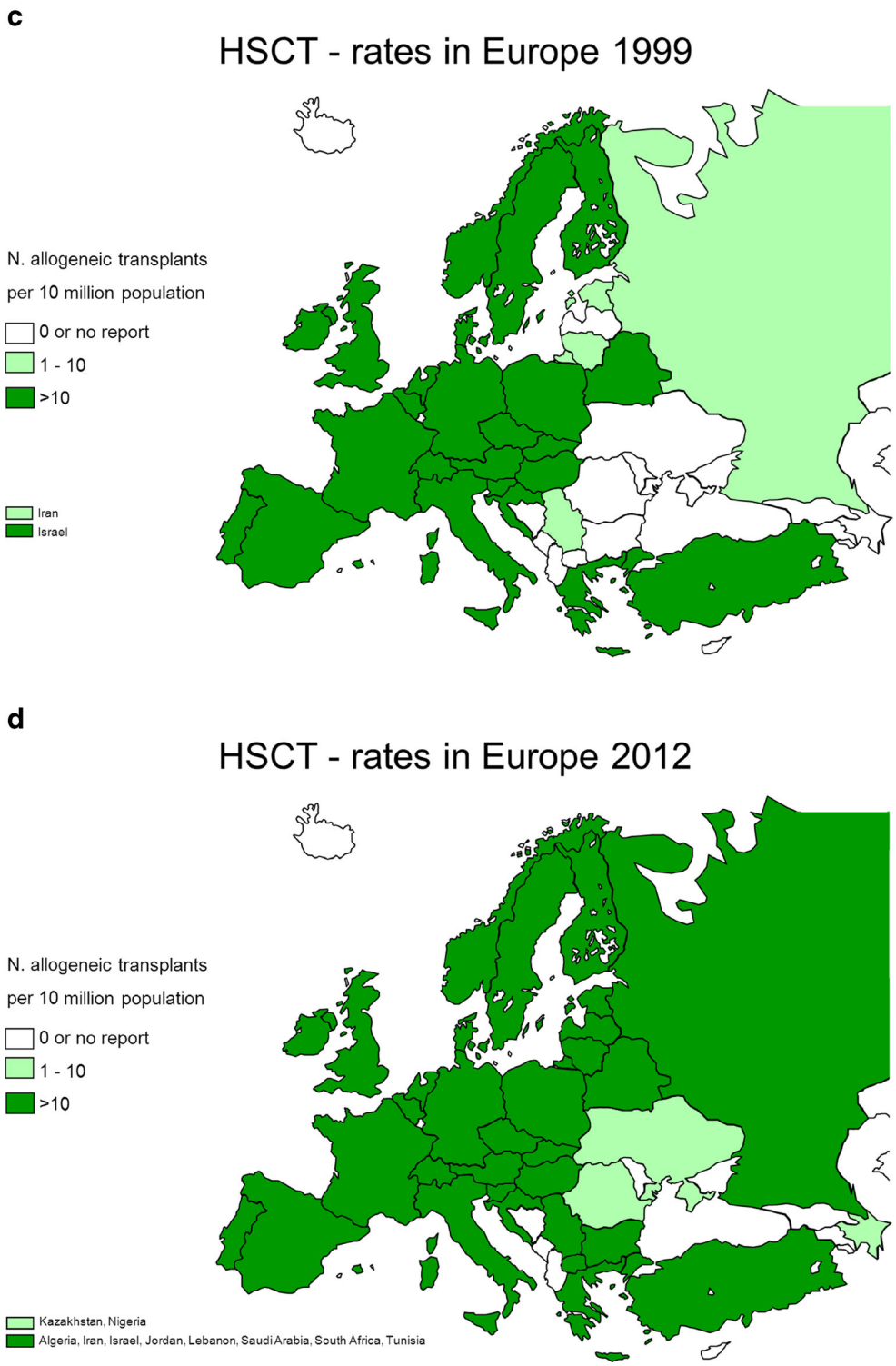

Fig. 2 (continued)

Graft-versus-host–graft-versus-leukemia effects

There is no doubt about the astonishing graft-versus-leukemia effects observed in CML as documented by the powerful effects of DLI [25, 43]. Complete and lasting molecular remissions can be obtained with even one infusion of cells, some without any signs of graft-versus-host disease. Many attempts have been made to exploit this effect better; so far, no study has proven to separate graft-versus-host from graft-versus-leukemia

Table 2 EBMT risk score

	Score points		
Risk factor	0	1	2
Age	<20 years	20–40 years	>40 years
Disease stage	Chronic phase	Other	Blast crisis
Time interval diagnosis–transplant	<12 months	>12 months	–
Donor type	HLA-identical sibling	Other	–
Gender combination	Other	Female donor for male recipient	–

effects in advance. The net detrimental effects of graft-versus-host reactions still outweigh the benefits [8].

Table 3 Risk factors in HSCT

Risk factor	Transplant-related mortality	Relapse	Overall survival
Disease			
Disease stage, advanced	↑	↑	↓
Pretreatment	↕	↕	↕
Time interval Dx-Tx			
<12 months	↓	↓	↑
Patient			
Age, higher	↑	↑	↓
Gender, female	↓	↔	↑
Karnofsky score<90	↑	↔	↓
Comorbidity present	↑	↔	↓
CMV status	↑	↓	↓
Cytokine polymorphisms	↕	↕	↕
Donor			
Syngeneic	↓	↑	↑
HLA identical sibling	↔	↔	↔
Matched unrelated	↑	↓	↔
Mismatched	↑	↓	↓
Gender FDMR	↑	↓	↓
Stem cell source			
BM, early disease	↓	↔	↔
PB, late disease	↓	↓	↑
Cord blood	↑	↑	↓
Conditioning			
Reduced	↓	↑	↕
GvHD prevention			
T cell depletion	↕	↑	↓
Macroeconomic factors			
Team accreditation status +	↓	↓	↑
Center experience greater	↓	↓	↑
GNI/capita country high	↓	↓	↑
Pretreatment in experienced center	↓	↓	↑

HSCT versus non-transplant therapy studies

No study has ever compared in a randomized way outcome after a transplant or a non-transplant strategy for patients with CML and an identified donor. Most likely, such a study will never be done. Hence, all recommendations depend on interpretation of comparative outcome data. The question appeared clear in the early days of allogeneic HSCT when no drug therapy was available to induce a BCR/ABL negative state. The question about long-term outcome arose first time with the introduction of interferon alpha [49]. HSCT was still considered treatment of choice. The hypothesis prevailed that HSCT would be associated with early mortality but a subsequent survival benefit which could compensate for the "early years of life lost". The German CML study group did test this hypothesis in a prospective study, 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 after a median observation time of 8 years in patients on drug treatment. The conclusions arrived at already in times of TKI therapy were clear: "The general recommendation of HSCT as first-line treatment option in chronic phase CML can no longer be maintained" [50].

These result formed the basis for the subsequent European leukemiaNet (ELN) guidelines on the use of HSCT in TKI-treated patients (see below) [50]. It became neglected that the CML III study was followed by the CML IIIa trial which did integrate the then known EBMT risk score factors. Teams were urged to proceed to transplant within the first year and to abstain from interferon use in the 3 months preceding the transplant. A recent comparison between the CML III and IIIA study clearly indicated a major improvement in outcome in the latter [51]. It will be important to see the survival data from that study at 10 years observation time. No study so far compared HSCT systematically with TKI treatment, but the CML IV study did permit early HSCT in this TKI-based study. Overall survival of 84 patients (median age, 37 years) with HSCT either first line (19 patients) or after imatinib failure (37 patients in CP, 28 patients in AP) was 88, 94, and 59 %; transplant-related mortality was 8 %; chronic graft-versus-host disease occurred in 46 %. Of note, overall survival of the patients transplanted in CP was not different from that

of the concomitantly imatinib treated patient cohort. No early excess mortality was noted [45]. Several other retrospective studies have compared single center or national study populations treated concomitantly with TKI or allogeneic HSCT. There were some conflicting results. Most comparisons relate to patients in initially early phase CML. Few studies compared outcome after BC in a comparative way. The general consensus appears that allogeneic HSCT offers a reasonable outcome even in accelerated phase or blast crisis [52–57].

Several studies did initiate in the nineties a prospective randomized comparison of autologous HSCT with drug treatment. None of the studies was completed; they were aborted prematurely at the time of imatinib introduction. A retrospective meta-analysis of six studies showed no advantage for the patients with autologous HSCT; hence, autologous HSCT has been largely abandoned as treatment for patients with CML [33].

Current recommendations

European leukemiaNet

The current ELN recommendations consider allogeneic HSCT, define when a donor search should be undertaken, and recommend at given states allogeneic HSCT [50]. The key elements include the following statements: "Allo SCT will continue to be an important treatment of patients who fail to respond durably to TKIs." "It seems reasonable that for patients in CP, transplant should be reserved for those who are resistant or intolerant to at least one second generation TKI." "Allo SCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response." "AP and BP as a progression from CP in TKI pretreated patients: allo SCT in all patients."

Other recommendations

The NCI recommendations (www.cancer.gov/cancertopics/pdq/treatment/CML/Patient/page4) remain open. They list HSCT among six types of standard treatment, targeted therapy, chemotherapy, biologic therapy, high-dose chemotherapy with stem cell transplant, donor lymphocyte infusion (DLI), and surgery, without specifications.

The German Onkopedia (www.dgho-onkopedia.de/de/onkopedia/leitlinien/cml/index_html?searchterm=cml) webpage is very detailed and follows in principle the ELN recommendations but relate more on disease risk aspects than transplant risks.

The UK recommendations (www.patient.co.uk/doctor/chronic-myeloid-leukaemia-pro) are vaguer about the timing of allogeneic HSCT but integrate transplant risk: AlloSCT should ideally be undertaken in the chronic phase of CML when it is associated with 3- to 5-year survival rates of 40–80 % and 10-year survival rates of 30–60 %. The optimal time of transplantation is controversial but thought to be up to 24 months following diagnosis. Transplantation-related mortality ranges from 5 to 50 % depending on factors including the patient's age, donor origin (related versus unrelated), degree of HLA matching, host cytomegalovirus status, use of conditioning regimens, and institutional expertise.

Critical appraisal

Listed are just four of manifold international recommendations for treatment of CML and integration of HSCT. They all mention allogeneic HSCT, none autologous HSCT. They all agree on the major role of allogeneic HSCT in blast crisis; they differ slightly in their view on the place of allogeneic HSCT in early disease and in accelerated phase. They are in line with several other published expert reviews [2, 6, 58–61]. But most focus with few exceptions primarily on disease risk. They consider primarily a failed response to first and second generation TKI or a mutation with primary resistance such as the T3 151 mutation as indication. Several separate as well donor search into search for a family donor first, for an unrelated donor at a later stage. Transplant risk, with the exception of the UK recommendation is vaguely specified.

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, 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. The ease of drug administration has as well shifted the patient community from major University centers towards decentralized medical practice. In parallel, interest in the HSCT community has shifted to questions of novel transplant technologies, much less on comparisons with non-HSCT approaches. As a consequence, no single study is currently listed which compares HSCT with non-HSCT treatment at any stage of the disease (https://clinicaltrials.gov/ct2/home; last assessed July 2nd 2014). It is unlikely that such comparative trials will soon follow. Hence, all recommendations are based on individual interpretation of past results. This will admittedly be influenced by the expectations of the expert.

Outcome of HSCT has substantially improved over the last decade, numbers of HLA typed unrelated donors has increased to more than 22 million worldwide and assessment of the likelihood to find a well-matched donor can be done today in a very short time. Improvement was greater for patients with early disease; it was substantially greater for

patients transplanted in a JACIE accredited center in Europe [62]. Survival of patients under drug treatment with advanced disease in parallel was substantially better for those treated in a University affiliated center compared to those in a community practice [63]. And, there are no hints that quality of life is worse after HSCT for long term survivors [64, 65]. Some consequences could be drawn.

Current recommendations of professional organizations such as the ELN should consider integration of a quality management system into the treatment algorithm. HSCT should be integrated at diagnosis, with HLA typing, evaluation of the likelihood to find a donor and transplant risk assessment. In case of early failure, HSCT could be considered rapidly for those with minimal transplant risks; drug treatment changed for those without this option. The same will apply for those roughly five percent of patients with rapid transformation at any time and for those with failure to respond to second or third line therapy. The same applies for patients with blast crisis. Disease, transplant, and economic risks need to be assessed [21, 35, 37, 38, 66–68]. Patients with high transplant risks should not be entered into long-lasting unsuccessful donor searches to end with HSCT in desperation without any reasonable likelihood for success. Continued drug therapy, experimental approaches, or palliation might be the wiser option. A similar approach has been advised for acute myeloid leukemia [69]. In order to arrive at such a policy, patients and patient's advocacy groups need to be informed, cooperation has to be established between the local medical community and the transplant centers, professional organizations have to adapt recommendations within a quality management system and to collect and analyze the appropriate data. More patients will profit from a safe transplant; fewer patients will undergo a futile transplant procedure.

Conflict of interest The manuscript is solely written by the authors. A.G. declares no conflicts of interest; H.B. declares no conflicts of interest; J.P. declares no conflicts of interest.

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