Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

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The introduction of imatinib mesylate has changed attitudes towards hematopoietic stem cell transplantation (HSCT) for chronic myeloid leukemia (CML). Information on the current use and results of HSCT is warranted. Data from 592 teams in 42 European countries described their use of HSCT for CML from 1990 to 2004. Outcomes were analyzed for 13,416 patients, with a median age of 36 years (range 1-71 years); 60% were male. The analysis considered three time cohorts, 1980 to 1990, 1991 to 1999 and 2000 to 2003. Survival, transplant-related mortality and relapse incidence were assessed at 20 years for the first cohort and compared at 2 years between the three cohorts. The numbers of HSCT for CML increased from 540 allogeneic HSCT in 1990 to 1,396 HSCT in 1999 and declined to 802 in 2004. One third of all patients and half of those with a low risk were alive at 20 years. Survival at 2 years has improved from 53% to 61% in the most recent years due to a reduction in transplant-related mortality from 41% to 30% in all patients and from 31% to 17% in low-risk patients. Stage, donor type, time interval, age and donor-recipient sex combination remain the main risk factors; patients with a risk score of 0 or 1 have a survival probability of 80% at 2 years. HSCT remains an important treatment option for patients with CML. The data describe the current status of this option and the outcome a patient can expect today. They provide an objective basis for decision making.

Key words: chronic myeloid leukemia, hematopoietic stem cell transplantation, outcome, transplant related mortality, long term results, Europe.

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The first report of a successful transplant of bone marrow from syngeneic twin donors in patients with chronic myeloid leukemia (CML) 30 years ago marked the beginning of a new era in the treatment of this disease.[1] It established the concept that CML could be eradicated by intensive chemoradiotherapy and transplantation of healthy donor cells and gave proof of principle that successful immunotherapy of a hematological malignancy could become reality. The concept was rapidly followed by others with transplants from HLA-identical siblings[2-5] and was soon confirmed in a series of more than 100 patients by the International Bone Marrow Transplant Registry.[6] In the 1990s the use of allogeneic hematopoietic stem cell transplantation (HSCT) for CML expanded rapidly and CML became the most frequent indication for an allogeneic transplant worldwide.[7] Despite its inherent morbidity and mortality, allogeneic HSCT became standard care for patients with CML.[8-11] Risk factors were defined and an early transplant within the first year after diagnosis became the preferred choice for patients with a compatible donor.[12] Not needing splenectomy eased the procedure.[13] The successful introduction of donor lymphocyte infusions in cases of relapse[14-19] further enhanced the successful eradication of the Philadelphia positive clone and paved the way for the introduction of reduced intensity conditioning transplants.[20-26] HSCT became available for patients of advanced age and with associated co-morbidities. This strategy was changed in 1999 with the advent of a new, specific tyrosine kinase inhibitor, imatinib mesylate (Glivec®).[27-34] Imatinib blocks BCR/ABL expression and can induce hematologic and cytogenetic complete remissions far more frequently than could previous treatments with interferon α or other agents. Even molecular remissions, though not durable, can be achieved in some patients. These excellent short-term results are obtained with minimal side effects and with an only once daily oral medication. Although long-term results with imatinib are lacking, the big difference in early outcome has challenged the previous concept of early HSCT for patients with CML.[10] However, the numbers of transplants for CML declined even before imatinib became available. It is evident that information on the current status of HSCT for CML and up-to-date results are necessary for adequate patient counselling.

Design and Methods

Study design

This retrospective multicenter study by the EBMT Chronic Leukemia Working Party combines two elements. First it summarizes HSCT activity for CML in Europe between 1990 and 2004. This period reflects the time span of the

Table 1. Characteristics of patients transplanted for CML during the three time periods.

Total number	*1980-1990 2628*	*1991-1999 7770*	*2000-2003 3018*	*p*
Age	33	37	37	<0.01*
Median years (Range)	1-62	1-71	1-69	
Numbers				
<20 years	320	777	333	<0.01°
20-40 years	1717	4058	1457	
>40 years	590	2935	1224	
Sex				
Male	1537 (59%)	4646 (60%)	1817 (60%)	0.19°
Female	1091 (41%)	3126 (40%)	1201 (40%)	
Donor type				
HLA-identical sibling	2238 (85%)	4839 (62%)	1698 (56%)	<0.01°
Twin	40 (2%)	52 (1%)	22 (1%)	
Other family member	164 (6%)	617 (8%)	202 (7%)	
Unrelated donor	186 (7%)	2264 (29%)	1096 (36%)	
Disease stage				
First chronic phase	1828 (70%)	5611 (72%)	2081 (69%)	<0.01°
Accelerated phase	444 (17%)	1091 (14%)	327 (11%)	
Other	189 (7%)	455 (6%)	438 (14%)	
Blast crisis	167 (6%)	615 (8%)	172 (6%)	
Stem cell source				
Bone marrow	2628 (100%)	6143 (79%)	1397 (47%)	<0.01°
Peripheral blood	–	1590 (21%)	1593 (53%)	
First chronic phase				
HLA-id sibling	1621 (89%)	3706 (66%)	1274 (61%)	<0.01°
Twin	17 (9%)	41 (1%)	13 (6%)	
Other family member	79 (4%)	373 (7%)	108 (5%)	
Unrelated donor	111 (6%)	1491 (26%)	686 (33%)	
Time interval#				
<12 months	1114 (42%)	3757 (48%)	1829 (61%)	<0.01°
>12 months	1514 (58%)	4015 (52%)	1189 (39%)	
Risk score@				
0-1	594 (23%)	1466 (19%)	645 (21%)	<0.01°
2-4	1902 (72%)	5582 (72%)	2003 (67%)	
>4	132 (5%)	724 (9%)	370 (12%)	
Conditioning				
Standard	344 (99%)	3555 (94%)	2107 (83%)	<0.01°
Reduced intensity	5 (1%)	234 (6%)	436 (17%)	

**One-way ANOVA; °all tests are the trend version of the χ^2 test. Subtotals do not always add up to grand totals due to missing values. #Time from diagnosis to transplant; @EBMT risk score.[12]*

annual EBMT activity surveys. Second, it provides long-term outcome results of a large cohort of patients and gives perspectives on long term outcome beyond 20 years after HSCT. Comparison of the outcomes of three cohorts at 2 years gives an estimate of the improvements over time with regard to early outcome, e.g. survival and cumulative incidence of transplant-related mortality and relapse.

Activity survey

The activity survey of the EBMT was introduced as a quality control instrument in 1990.[35] All member teams and affiliated transplant teams annually report their transplant numbers for the preceding year, providing data on the indication for transplantation, donor type and stem cell source. This survey is estimated to cover over 90% of all allogeneic HSCT performed in Europe. In 2004, 592 teams from 42 countries participated; 342 did both allogeneic and autologous HSCT (58%), 224 restricted their activity to autologous HSCT (38%) and 6 teams to allogeneic HSCT only (1%). Twenty teams had performed no transplants in 2004 (3%).[36] The participating teams are listed in the *Online Appendix*. The focus of this report is on transplant numbers for CML. Information on CML in the survey is restricted to its phase, first chronic phase or not first chronic phase. The data on transplants are summarized in absolute numbers and calculated as transplant rates (number of HSCT per 10 million inhabitants; based on 2002 census data), as previously published for all participating European countries.[36] Numbers are expressed for all transplants combined and for CML specifically.

Outcome analysis

All patients transplanted in Europe for CML between 1980 and 2003 and reported to the EBMT were included in this analysis. Overall, 13,416 patients with sufficient baseline information were analyzed in three time cohorts as outlined in Table 1. The median age of these patients was 36 years (range 1-71 years) and 60% were male. The time periods covered were 1980 to 1990 (2,628 patients, 20%) 1991 to 1999 (58%) and 2000 to 2003 (22%). The time of the data analysis was December 31st, 2005 which allowed a minimum follow-up of 2 years for all patients. Information was obtained in paper form or by the EBMT data capture system PROMISE (*www.ebmt.org*). There were significant differences between the cohorts. The median age rose from 33 to 37 years, accompanied by an rise in maximum age from 62 to 71 years and a rise in the proportion of patients above the age of 40 years from 22% to 41% from the first to the last cohort ($p< 0.01$). The proportion of unrelated donors rose from under 10% (7%) to more than a third (36%) in the most recent cohort and there was also a shift in stage of disease towards more patients being transplanted in second chronic phase or more advanced stage ($p<0.01$). The proportions of transplants in first chronic phase or blast crisis remained comparable. This trend is reflected in a larger proportion of patients with higher EBMT risk scores, despite an increase in numbers of patients transplanted within 12 months of diagnosis ($p<0.01$).

Only five patients in the first time cohort were treated with reduced intensity conditioning, whereas about 17% of patients were given reduced intensity conditioning in the most recent cohort.

Statistical analysis

All statistical analyses were performed using SPSS version 11 with the exception of the cumulative incidence analyses which were carried out in NCSS 2001. Analyses of categorical variables were performed using χ^2 tests for association or a trend test for proportions when categories were ordered. Survival curves were estimated using the Kaplan-Meier approach for overall survival. Cumulative incidence curves were applied to estimate the competing risks, i.e. transplant related mortality and relapse incidence. The use of cumulative incidences permits a real estimate of the proportion of patients alive with or without relapse or death from transplant-related causes or relapse at any given time post-transplant. A Cox model was used to assess in multivariate analyses the relative impact of previously defined risk factors: age, stage of disease, donor type, time interval and donor recipient sex combination. Calendar period of transplantation, stem cell

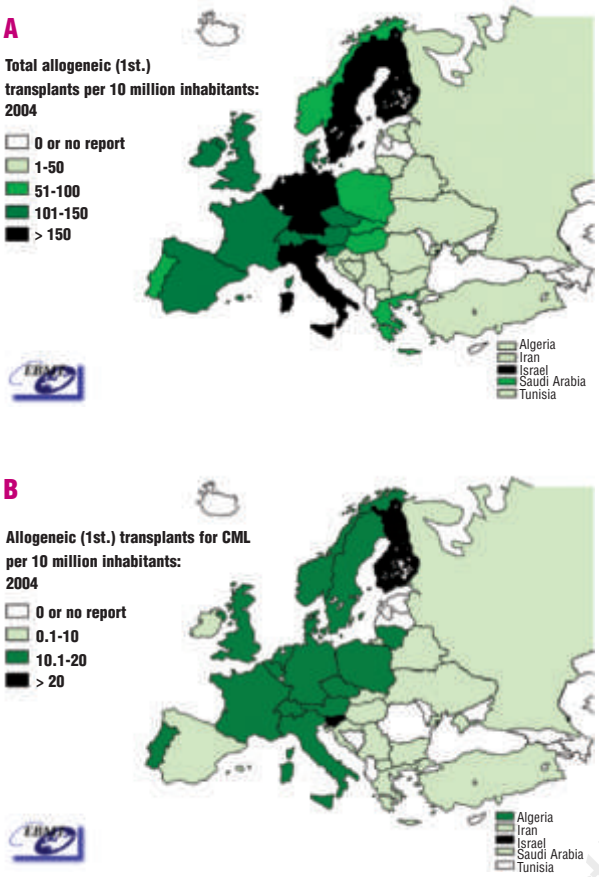

Figure 1. Transplant rates in Europe 2004 per 10 million inhabitants per country. A. All allogeneic HSCT only. B. Allogeneic HSCT for CML only.

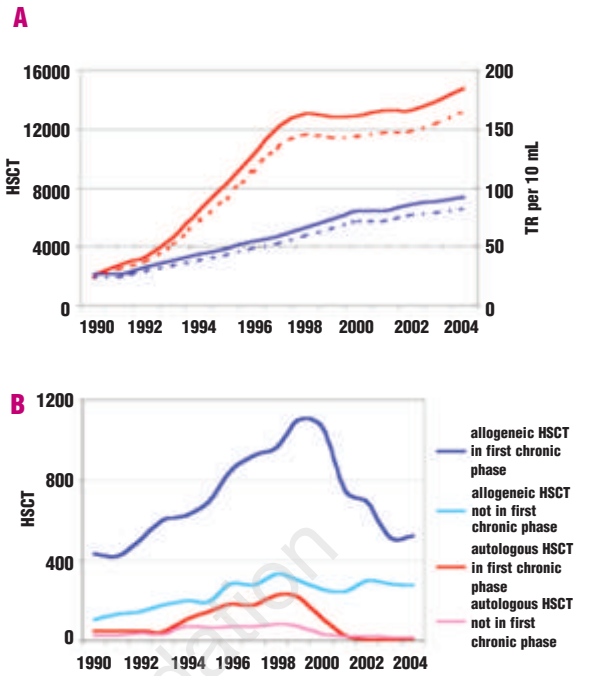

Figure 2. Development of HSCT in Europe from 1990 to 2004. A. Absolute numbers (—) of allogeneic HSCT (blue) and autologous HSCT (red) and transplant rates (TR) (- - -) per 10 million inhabitants. B. Absolute numbers of allogeneic HSCT (blue) and autologous HSCT (red) for various stages of CML.

source and type of conditioning regimen were included as additional elements. Results are expressed as relative risks in a hazards ratio. The definition of relapse of CML changed over time. For this analysis, the general crude information of whether a relapse had or had not occurred, as reported by the individual team, was used. This was intended to signify hematologic relapse but cytogenetic and molecular relapses might inadvertently have been reported as relapses. In order to test for a potential impact of calendar period on outcome after relapse a specific analysis was added. This should detect an influence of new modalities, such as the introduction of donor lymphocyte infusions in 1990[14-19] or differences in reporting. The impact of relapse on survival post-relapse was analyzed as follows. Relapse was evaluated as a time dependent covariate. Its influence on survival at 2 years post-relapse was compared to that in patients with no relapse in a Cox model integrating all EBMT risk score factors. This impact of relapse on 2-year post relapse survival status was calculated separately for all three time cohorts. No attempt was made to estimate current leukemia-free survival[37,38] since information at various time points was insufficient for too many patients.

Results

Activity survey: transplant numbers and transplant rates for CML in Europe 1990 to 2004

Overall, 22,216 HSCT were carried out in Europe in 2004, of which 7,407 were allogeneic (33%) and 14,809 were autologous (67%). As previously reported,[36] there were major differences in transplant rates between the European countries for HSCT as a whole, for autologous HSCT (*data not shown*) and for allogeneic HSCT (Figure 1A).

Of these 22,216 HSCT, 832 (3.7%) were for CML. These 832 transplants for CML included 802 allogeneic HSCT [524 performed in first chronic phase (65%) and 278 (35%) in advanced phase] and only 30 autologous HSCT [11 (37%) in first chronic phase and 19 (63%) in advanced phase]. Transplant rates differed substantially between European countries (Figure 1B). There were additional differences in transplant rates depending on disease stage. The numbers of HSCT have increased continuously during the last decade in Europe. Numbers of autologous HSCT have risen at a slower rate since 1997, whereas allogeneic HSCT continued to rise at a rate of 8 -10% per year. As illustrated in Figure 2A, the rate of traansplants in 2004 was 165 autologous and 82 allogeneic HSCT per 10 million inhabitants in Europe. The evolution was different for CML. The number of allogeneic HSCT for CML rose from 540 in 1990, of which 80% were performed in first chronic phase, to a peak of 1,396 in 1999. The overall number then declined to 791 in 2003, with a greater decrease for

Table 2. Probability of survival and cumulative incidence of transplant-related mortality and relapse in a cohort of 2628 patients undergoing allogeneic HSCT for CML between 1980-1990.

	At Tx	At 2 years				At 5 years				At 10 years				At 15 years				At 20 years			
	N	N	SURV	TRM	RI	N	SURV	TRM	RI	N	SURV	TRM	RI	N	SURV	TRM	RI	N	SURV	TRM	RI
All patients	2628	1365	50%	–	–	1154	44%	–	–	822	39%	–	–	255	34%	–	–	16	32%	–	–
Donor type																					
HLA-id sibling	2238	1228	53%	38%	14%	1035	46%	41%	21%	738	41%	42%	25%	241	36%	44%	26%	16	34%	–	–
Twin	40	28	69%	10%	46%	28	53%	10%	54%	13	44%	10%	60%	6	36%	10%	60%	–	–	–	–
Other	164	56	32%	50%	14%	47	28%	51%	20%	36	25%	53%	20%	5	25%	54%	22%	–	–	–	–
Unrelated	186	53	27%	58%	8%	50	26%	59%	8%	35	22%	60%	9%	3	16%	66%	10%	–	–	–	–
Disease stage																					
1st chronic phase	1828	1069	57%	–	–	923	51%	–	–	670	46%	–	–	219	40%	–	–	15	38%	–	–
Accelerated phase	444	175	35%	–	–	130	29%	–	–	88	23%			24	20%	–	–	1	18%	–	
Other	189	85	42%	–	–	71	37%	–	–	43	31%	–	–	5	25%	–	–	–	–	–	–
Blast crisis	167	36	21%	–	–	30	18%	–		21	16%	–	–	7	14%	–	–	–	–	–	–
First chronic phase only	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HLA-id sibling	1621	–	–	–	–	–	–	–	–	–	–	–	–	207	41%	45%	24%	–	–	–	–
Risk score*																					
0-1	541	359	65%	–	–	319	60%	–	–	239	55%	–	–	83	50%	–	–	8	49%	–	–
2-4	1080	617	55%	–	–	528	48%	–	–	369	43%	–	–	124	37%	–	–	7	35%	–	–
>4	132	41	24%	62%	15%	–	–	–	–	–	–	–	–	1	14%	67%	20%	–	–	–	–

*Tx: transplantation; SUR: survival; TRM: transplant-related mortality; RI: relapse incidence; N: number of patients at this time point; At tx: at time of transplant; cp: chronic phase; *EBMT risk score.*[12]

allogeneic HSCT in first chronic phase than in advanced phase disease. The number of allogeneic HSCT plateaued at 802 in 2004. The practice of autologous HSCT for CML has almost completely come to a halt (Figure 2B).

Outcome analysis

Long-term outcome of the first cohort

At the time of this analysis, 1,492 of the 2,628 patients in the cohort transplanted between 1980 and 1989 were alive (57%) and 1,136 had died: 253 patients were observed for a follow up period of 15 years and more, 16 for a follow up of 20 years or more. The probability of survival at 20 years was 34% with a cumulative incidence of transplant-related mortality at 20 years of 47% and of relapse of 26%. Survival was clearly influenced by disease stage at transplant (Figure 3). Survival was better for patients transplanted from an HLA-identical sibling, transplanted in first chronic phase, and for patients with a low EBMT risk score. Probability of survival at 20 years for the subgroup of patients transplanted in first chronic phase from an HLA-identical sibling was 41% with a cumulative incidence of transplant-related mortality at 20 years of 45% and of relapse of 24%, as illustrated in Table 2. Almost half of all patients transplanted with an EBMT risk score 0 or 1 were alive at 20 years post HSCT (49%). Nearly 40% of all patients transplanted in first chronic phase are expected to be alive at 20 years. The proportion of patients who died of transplant-related causes or relapse and the proportion of patients alive free from disease or with disease are illustrated in Figure 4.

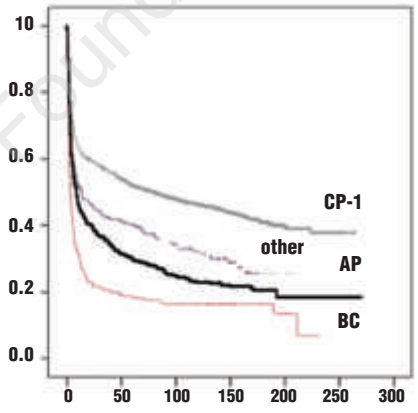

Figure 3. Survival probability of 2,628 patients transplanted between 1980 and 1990 according to disease stage at time of transplant. CP-1: first chronic phase, AP: accelerated phase, BC: blast crisis, other: all other stages.

Comparison of the outcome of the three time cohorts at 2 years

Table 3 documents the main outcomes for the three time cohorts at 2 years and illustrates the improvements over time and the main risk factors. In the cohort transplanted between 2000 and 2003, probability of survival at 2 years was 61% compared to 53% among those transplanted earlier, with a cumulative incidence of transplant-related mortality at 2 years of 30% (vs 41%) and of relapse of 22% (vs 14%). The probability of survival at 2 years for the subgroup of patients transplanted in first chronic phase from an HLA-identical sibling was 74% (vs 61%) with a cumulative incidence of transplant related mortality at 2 years of 22% (vs 37%) and of relapse of 18% (vs 11%). Improvements were observed in all subgroups of patients for survival as well as for reduction in transplant-related mortality. Survival was most markedly improved for patients with an unrelated donor (from 29% to 53%), for patients transplanted in first chronic phase (from 54% to 70%) and for patients with low EBMT risk score (from 65% to 80%). Transplant-related mortality in the same groups decreased from 41% to 30% for the whole group, from 65% to 37% for unrelated transplants, from 38% to 26% for those transplanted in first chronic phase and from 31% to 17% for patients with low EBMT risk score (0-1). In contrast, there was no improvement in risk of relapse

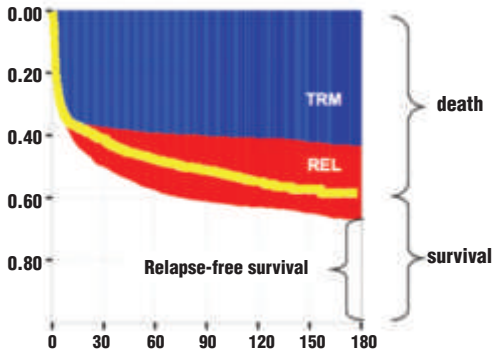

Figure 4. Survival of 1,828 patients transplanted between 1980 and 1990 in first chronic phase. The cumulative probabilities of transplant related mortality (TRM) and relapse (REL) are superimposed. The fraction above the curves illustrates the proportion of patients who died from relapse, the fraction between the curve the proportion of patients alive but after relapse.

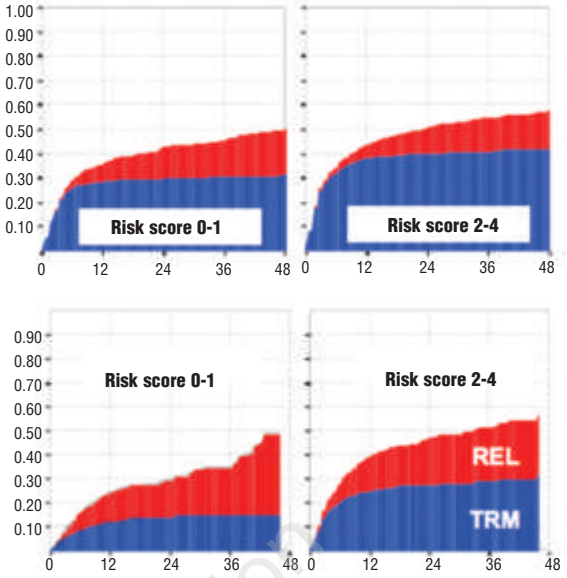

Figure 5. Cumulative impact of transplant related mortality (TRM) (blue) and relapse incidence (REL) (red) in low-risk patients transplanted between 1980 and 1990 (upper panels) or between 2000 and 2003 (lower panels).

with an increase in relapse from 14% to 22% and primarily an increased risk of relapse in patients transplanted from HLA-identical siblings and for patients transplanted in advanced stages or with high EBMT risk scores. The change in transplanted-related mortality and relapse incidence in low risk patients from the first to the last cohort is illustrated in Figure 5.

Main factors influencing outcome

The previously described main pre-transplant risk factors for outcome[12] were confirmed in this analysis. Survival was better for patients transplanted in chronic phase than for those transplanted in other stages or blast crisis due to increased transplant-related mortality and relapse among patients with more advanced disease. Survival was better for patients transplanted from an HLA-identical sibling than for those receiving grafts from another family donor or an unrelated donor. This was still valid for the most recent cohorts, even though substantial reductions in transplant-related mortality were achieved. It was true for all disease stages and for the most recent cohort and patients transplanted in first chronic phase. Survival was related to the EBMT risk score in all three cohorts. Both transplant-related mortality and deaths due to relapse rose with increasing risk score in all three time cohorts to a similar extent.

Multivariate analysis

The results of the multivariate analysis are summarized in Table 4. They confirm the constant impact of risk fac-

Table 3. Outcome of allogeneic HSCT for CML at 2 years in three cohorts: survival (SUR), transplant-related mortality (TRM) and relapse (RI).

Cohorts	*N*	*1980-1990*			*N*	*1991-1999*			*N*	*2000-2003*		
		SUR	*TRM*	*RI*		*SUR*	*TRM*	*RI*		*SUR*	*TRM*	*RI*
All patients	2628	53%	41%	14%	7771	59%	34%	17%	3018	61%	30%	22%
HLA-id sibling	2238	55%	38%	14%	4838	64%	28%	116%	1698	68%	25%	21%
Other family donor	164	35%	57%	14%	617	49%	43%	16%	202	49%	40%	23%
Unrelated donor	186	29%	65%	12%	2264	49%	42%	16%	1096	53%	37%	14%
Syngeneic twin	40	73%	10%	46%	52	80%	4%	41%	22	82%	5%	50%
First chronic phase	1818	59%	38%	11%	5611	66%	31%	14%	2081	70%	26%	18%
Accelerated phase	444	40%	49%	20%	1091	42%	44%	23%	327	47%	37%	28%
Other	189	46%	39%	20%	615	47%	36%	25%	438	46%	39%	25%
Blast crisis	167	22%	52%	29%	454	22%	48%	35%	172	16%	50%	38%
First chronic phase HLA-id sibling	1621	54%	37%	11%	3706	70%	25%	12%	1274	74%	22%	18%
First chronic phase unrelated	111	38%	59%	10%	1491	56%	38%	12%	686	63%	32%	19%
Risk score*												
0-1	594	54%	31%	13%	1466	74%	22%	13%	645	80%	17%	16%
2-4	1902	51%	42%	15%	5581	58%	35%	17%	2003	60%	32%	22%
>4	132	25%	62%	15%	724	32%	51%	24%	370	38%	41%	31%
§Standard conditioning	344	53%	41%	16%	3555	61%	32%	18%	2107	63%	29%	21%
reduced intensity	5	25%			234	55%	34%	30%	448	55%	31%	33%

*§variable introduced at the end of the cohort and not always recorded in in the Registry; *EBMT risk score.[12]*

Table 4. Multivariate analysis of factors influencing outcome at 2 years. Results are expressed as hazard ratios.

	1980-1990			1991-1999			2000-2003			All*		
	SUR	TRM	RI	SUR	TRM	RI	SUR	TRM	RI	SUR	TRM	RI
Age, years												
< 20	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
20-40	1.4	1.5	0.8	0.9	1.0	0.9	1.2	1.3	0.9	1.1	1.1	1.1
> 40	1.5	1.8	0.6	1.3	1.4	1.0	1.4	1.5	1.3	1.3	1.5	1.1
Stage												
First accelerated phase	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Accelerated phase	1.4	1.3	3.6	1.9	1.7	2.1	1.7	1.4	2.2	1.8	1.6	2.2
Other	1.7	1.2	3.3	3.7	1.5	2.2	1.5	1.3	1.6	1.8	1.4	1.9
Blast crisis	2.6	2.0	6.9	2.0	2.6	4.9	4.1	2.9	4.9	3.7	2.6	4.9
Donor type												
HLA-identical sibling	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Other family	1.3	1.4	1.3	1.7	2.0	1.2	1.6	1.5	1.2	1.8	1.7	1.3
Unrelated	2.2	2.2	1.2	1.7	1.9	1.4	1.5	1.6	1.4	1.6	1.8	1.2
Source												
Bone marrow	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Peripheral blood	n.a.	n.a.	n.a.	1.0	1.0	1.1	1.2	1.2	1.1	1.1	1.1	1.1
Time interval												
<12 months	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
>12 months	1.5	1.6	1.1	1.1	1.1	0.9	1.4	1.4	1.0	1.2	1.3	1.6
Conditioning												
Standard	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Reduced intensity	n.a.	n.a.	n.a.	0.8	0.8	1.4	1.0	0.8	1.8	0.9	0.9	1.6
Cohort												
1980-1990										1.0	1.0	1.0
1991-1999										0.7	0.6	1.0
2000-2003										0.6	0.5	1.1

**Overall analysis adjusted by cohort to avoid confounding by cohort (i.e. by differences in distribution of the other risk factors among the two cohorts. All hazard ratios are adjusted for all other factors mentioned (each column represents one Cox model). Hazard ratio > 1 implies increased risk of the (adverse) outcome (= death, transplant-related death and relapse). SUR: survival; TRM: transplant-related mortality; RI: relapse incidence.*

tors with similar risk ratios for the individual risk factors. It is noteworthy that the relative risk (RR) for unrelated transplants has decreased from 2.2 to 1.5 and that the RR for transplants in blast crisis has increased from 2.6 to 3.7. Overall survival has improved by 50% with a RR of 1.0 for the oldest cohort and a RR of 0.5 for the most recent cohort. This is due to a halving in transplant-related mortality from the earliest to the most recent cohort. Relapse as a post-transplant event had a strong impact on survival in this analysis and the risk of relapse increased the likelihood of subsequent death of any cause 4-fold (HR 4.2) compared to that of patients alive at the same time post transplant without a relapse. This risk of subsequent death in patients with relapse was not different in the three cohorts. This analysis failed to show a change in the rate of relapse death over time.

Discussion

This report reflects the past and current use and results of HSCT for CML in Europe. The numbers of transplants for CML have changed substantially. They increased rapidly up to 1999 and then began to decline despite an overall increase of allogeneic HSCT in general in 2000. This observation is intriguing, since imatinib was approved by the FDA in October 2001 and only became available in Europe in 2002. In addition, the differences in the use of HSCT between European countries are substantial. These differences are new and are evolving. Only 5 years ago, CML was the most frequent indication for an allogeneic HSCT in Europe with the lowest coefficient of variation in transplant rates.[7] There was a clear consensus for early transplantation.[9,10] This strategy changed with the introduction of imatinib.[27] For many physicians early transplant is no longer the first choice management for CML.[39] This is also reflected by an increase in transplants performed at later stages of the disease.[36] It is also interesting to note that transplant rates for CML are no longer primarily influenced by the economic strength of a country.[40] Indeed, cost considerations might favor HSCT as a once-in-a-lifetime procedure in countries with limited resources in which lifelong drug treatment with an expensive drug represents an excessive burden on resources. A recent report from South America and Mexico[41] is clearly compatible with the situation in Eastern Europe where HSCT remains the preferred choice.[40] This report also describes the expected outcome from HSCT for CML: half of the patients transplanted for early disease with an HLA-identical sibling are alive at 20 years after their transplant. The marked reduction of transplant-related mortality over time implies that patients transplanted today can expect

far better survival rates at 20 years post-HSCT than those established long-term results. It is comforting to see the confirmation of earlier reports[5,7,12,42-45] in a very large database with a substantial number of patients observed beyond 20 years. It is also comforting to see that survival has improved over time with a marked reduction in transplant related mortality. These findings fit with a recent publication of the EBMT concerning patients with early leukemia which documented a significant reduction of transplant-related mortality over time, mainly due to a reduction in infectious deaths.[45] The reduction in transplant-related mortality has been most marked in patients with unrelated donors and in those transplanted with low-risk disease. These observations are of major importance. The discussion of whether to do a transplant or not primarily concerns patients with an unrelated donor and patients with a low risk score. On the other hand, it is surprising and somewhat disappointing that the main risk factors for outcome, which were described many years ago,[12] still remain valid and remain so for both standard and reduced intensity conditioning transplants. Reduced intensity conditioning has increased the use of HSCT among older patients. The 2-year survival was not different in this analysis of CML patients nor was it in a recent analysis in patients with acute myeloid leukemia.[46,47] Stage of the disease, donor type, donor recipient sex combination and time interval from diagnosis to transplant determine the fate of the patient.[48-52]

A new and disappointing surprise was the finding that relapse had and still has a major detrimental impact on survival. Despite the introduction of both donor lymphocyte infusions and imatinib-post HSCT, the hazard ratio for a subsequent death has not changed over the whole 25 years of observation for patients with relapse. These findings indicate that treatment approaches for hematological relapse after HSCT can alter the course for some patients but not for all. Relapse remains of concern and further studies are warranted.

The data presented from this large heterogeneous group of patients and transplant teams all over Europe appear worse than those reported for single center series.[45] This is not surprising but reflects reality. At least, they represent the minimum a patient can expect from HSCT. Admittedly, there are drawbacks in this study. No detailed information is available for the large majority of the patients concerning transplant technology or, more so, pretransplant therapy. No information can be drawn concerning the impact of imatinib on transplant outcome directly. There is a debate on whether imatinib increases transplant-related mortality or not, similar to the earlier debate on the impact of busulfan or interferon α on transplant-related deaths. This information will become available with maturing data from the CML study groups, as happened for inferferon α. It is interesting to note that in a recent report of a prospective study cohort with a long follow-up, patients with complete response to interferon had the best survival after HSCT.[53]

Guidelines on the management of CML were published several years ago by an ASH committee[10] and update of these guidelines is currently being prepared. The data provided here are not guidelines and yet they do give some guidance. They provide an estimate of survival probability after HSCT. This previously shown long-term benefit[54] must be balanced against early transplant-related death and against the unknown prospect of 20-year treatment with tyrosine kinase inhibitors. The data provide an additional estimate of the increased risk to be faced when transplants are deferred and disease stage changes. The consequences of these estimates were recently debated.[39] Clearly, the general recommendation that all patients with CML and an HLA-identical donor should be transplanted within the first 12 months after diagnosis can no longer be upheld. The approach to patients with high risk disease, e.g. those with a high Hasford or Sokal risk score, and with a low-risk donor is no longer the same as for a patient with low-risk disease and a high-risk donor. Patients with high risk disease and an EBMT risk score of 0 or 1 should be considered for early transplants. In contrast, in patients with low-risk disease, e.g. those with a low Hasford or Sokal risk score, a prior trial with imatinib might be favored. An additional element must be taken into account. Different successful strategies are available today. A patient's preference might not be the same as a physician's preference. Patients might prefer a low-risk treatment despite its uncertain future or they might prefer an early risk with a late benefit. Cost needs to be considered as well. All these points must be discussed with patients at diagnosis and at defined time-points. In addition, new developments in drug treatment, e.g. new tyrosine kinase inhibitors, vaccination strategies and safer transplant procedures, will increase long-term perspectives for all patients.[55,56] As they stand, the present data give an overview of risks and benefits from HSCT for CML. They provide an objective basis for decision making for individual patients' and for health care agencies.

AG, JA, DN designed the study; CC, TR, PC, EC, AD, CG and HK coordinated data analysis and gave critical comments. RB performed the statistical analysis and all authors helped with the preparation of the manuscript. There are no conflicts of interest to declare.

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References

1. Fefer A, Cheever MA, Thomas ED, Boyd C, Ramberg R, Glucksberg H, et al. Disappearance of Ph1-positive cells in four patients with chronic granulocytic leukemia after chemotherapy, irradiation and marrow transplantation from an identical twin. N Engl J Med 1979;300:333-7.
2. Fefer A, Cheever MA, Greenberg PD, Appelbaum FR, Boyd CN, Buckner CD, et al. Treatment of chronic granulocytic leukemia with chemoradiotherapy and transplantation of marrow from identical twins. N Engl J Med 1982;306:63-8.
3. Clift RA, Buckner CD, Thomas ED, Doney K, Fefer A, Neiman PE, et al. Treatment of chronic granulocytic leukaemia in chronic phase by allogeneic marrow transplantation. Lancet 1982;2:621-3.
4. Goldman JM, Baughan AS, McCarthy DM, Worsley AM, Hows JM, Gordon-Smith EC, et al. Marrow transplantation for patients in the chronic phase of chronic granulocytic leukaemia. Lancet 1982;2:623.
5. Speck B, Gratwohl A, Nissen C, Osterwalder B, Muller M, Bannert P, et al. Allogeneic marrow transplantation for chronic granulocytic leukemia. Blut 1982;45:237-42.
6. Speck B, Bortin MM, Champlin R, Goldman JM, Herzig RH, McGlave PB, et al. Allogeneic bone-marrow transplantation for chronic myelogenous leukaemia. Lancet 1984;1:665-8.
7. Gratwohl A, Baldomero H, Horisberger B, Schmid C, Passweg J, Urbano-Ispizua Al, et al. Current trends in hematopoietic stem cell transplantation in Europe. Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Blood 2002;100: 2374-86.
8. Goldman JM, Apperley JF, Jones L, Marcus R, Goolden AW, Batchelor R, et al. Bone marrow transplantation for patients with chronic myeloid leukemia. N Engl J Med 1986;314:202-7.
9. Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. Blood 2001;98:2039-42.
10. Silver RT, Woolf SH, Hehlmann R, Appelbaum FR, Anderson J, Bennett C, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. Blood 1999; 94:1517-36.
11. Thomas ED, Clift RA, Fefer A, Appelbaum FR, Beatty P, Bensinger WI, et al. Marrow transplantation for the treatment of chronic myelogenous leukemia. Ann Intern Med 1986; 104:155-63.
12. Gratwohl A, Hermans J, Goldman JM, Arcese W, Carreras E, Devergie A, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet 1998;352:1087-92.
13. Gratwohl A, Goldman J, Gluckman E, Zwaan F. Effect of splenectomy before bone-marrow transplantation on survival in chronic granulocytic leukaemia. Lancet 1985;2:1290-1.
14. Kolb H, Mittermuller J, Clemm C, Holler E, Lederhose G, Brehm G, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 1990;76:462-5.
15. Barrett AJ, Malkovska V. Graft-versus-leukaemia: understanding and using the alloimmune response to treat haematological malignancies. Br J Haematol 1996;93:754-61.
16. Bornhauser M, Kiehl M, Siegert W, Schetelig J, Hertenstein B, Martin H, et al. Dose-reduced conditioning for allografting in 44 patients with chronic myeloid leukaemia: a retrospective analysis. Br J Haematol 2001;115:119-24.
17. Dazzi F, Szydlo R, Cross N, Craddock C, Kaeda J, Kanfer E, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukaemia. Blood 2000 96:2712-6.
18. Gilleece M, Dazzi F. Donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukaemia. Leuk Lymphoma 2003;44:23-8.
19. Guglielmi C, Arcese W, Dazzi F, Brand R, Bunjes D, Verdonck LF, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. Blood 2002;100:397-405.
20. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalle G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91:756-63.
21. Weisser M, Schleuning M, Ledderose G, Rolf B, Schnittger S, Schoch C, et al. Reduced-intensity conditioning using TBI (8 Gy), fludarabine, cyclophosphamide and ATG in elderly CML patients provides excellent results especially when performed in the early course of the disease. Bone Marrow Transplant 2004;34:1083-8.
22. Chakraverty R, Peggs K, Chopra R, Milligan DW, Kottaridis PD, Verfuerth S, et al. Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen. Blood 2002;99:1071-8.
23. Corradini P, Tarella C, Olivieri A, Gianni AM, Voena C, Zallio F, et al. Reduced-intensity conditioning followed by allografting of hematopoietic cells can produce clinical and molecular remissions in patients with poor-risk hematologic malignancies. Blood 2002;99:75-82.
24. Das M, Saikia TK, Advani SH, Pankh PM, Tawde S. Use of a reduced-intensity conditioning regimen for allogeneic transplantation in patients with chronic myeloid leukemia. Bone Marrow Transplant 2003;32:125-9.
25. Giralt S, Estey E, Albitar M, van Besien K, Rondon G, Anderlin P, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 1997; 89: 4531-6.
26. Or R, Shapira MY, Resnick I, Amer A, Ackerstein A, Samuel S, et al. Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood 2003;101:441-5.
27. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
28. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. International Randomised Study of Interferon versus STI571 (IRIS) Study Group. N Engl J Med 2003;349:1423-32.
29. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-α therapy. Ann Intern Med 1995;122:254-61.
30. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. International STI571 CML Study Group. N Engl J Med 2002;346: 645-52.
31. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348:994-1004.
32. Talpaz M, Silver RT, Druker BJ, Goldman JM, Gambacorti-Passerini C, Guilhot F, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002; 99:1928-37.
33. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002; 99:3530-9.
34. Cortes J, Kantarjian H. New targeted approaches in chronic myeloid leukemia. J Clin Oncol 2005;26:6316-24.
35. Gratwohl A. Bone marrow transplantation activity in Europe 1990. European Group for Bone Marrow Transplantation (EBMT). Bone Marrow Transplant 1991;8:197-201.
36. Gratwohl A, Baldomero H, Schmid O, Horisberger B, Bargetzi M, Urbano-Ispizua A. Special report. Change in stem cell source for hematopoietic stem cell transplantation (HSCT) in Europe. A report of the EBMT activity survey 2003. Bone Marrow Transplant 2005;36: 575-90.
37. Klein JP, Szydlo RM, Craddock C, Goldman JM. Estimation of current leukaemia-free survival following donor lymphocyte infusion therapy for patients with leukaemia who relapse after allografting: application of a multistate model. Stat Med

2000;19:3005-16.
38. Klein JP, Keiding N, Shu Y, Szydlo RM, Goldman JK. Summary curves for patients transplanted for chronic myeloid leukaemia salvaged by a donor lymphocyte infusion: the current leukaemia-free survival curve. Br J Haematol 2000;109:148-52.
39. Gratwohl A, Rosti G, Baccarani M. Does early stem-cell transplantation have a role in chronic myeloid leukemia? Lancet Oncol 2005;6: 721-3.
40. Gratwohl A, Baldomero H, Labar B, Apperley J, Urbano-Ispizua A. Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Evolution of hematopoietic stem cell transplantation in Eastern and Western Europe from 1990 to 2003. A report from the EBMT activity survey. Croat Med J 2004;45:689-94.
41. Ruiz-Arguelles GJ, Gomez-Almaguer D, Morales Torquero A, Gutierrez Aguirre CH. Vela-Ojeda J, Garcia-Ruiz-Esparza MA, et al. The early referral for reduced intensity stem cell transplantation in patients with ph+ chronic myelogenous leukemia in chronic phase in the imatinib era: results of the Latin American Cooperative Oncohematology Group (LACOHG) prospective multicenter study. Bone Marrow Transplant 2005; 36:1043-7.
42. Couban S, Simpson D, Barnett M, Bredeson C, Hubesch L, Howson-Jan K, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Canadian Bone Marrow Transplant Group. Blood 2002;100:1525-31.
43. Niederwieser D, Maris M, Shizuru JA, Petersdorf E, Hegenbart U, Sandmaier BM, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and post-grafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. Blood 2003;101:1620-9.
44. Robin M, Guardiola P, Devergie A, Yeshurun M, Shapiro S, Esperou H, et al. A 10-year median follow-up study after allogeneic stem cell transplantation for chronic myeloid leukemia in chronic phase from HLA-identical sibling donors. Leukemia 2005;19:1613-20.
45. Gratwohl A, Brand R, Frassoni F, Rocha V, Niederwieser D, Reusser P, et al. Cause of death after allogeneic hematopoietic stem cell transplantation (HSCT) in early leukemias: An EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Transplant 2005;36:757-69.
46. Crawley C, Szydlo R, Lalancette M, Bacigalupo A, Lange A, Brune M, et al. Chronic Leukemia Working Party of the EBMT. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood 2005;106:2969-76.
47. Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, et al. Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). Leukemia 2005;19:2304-12.
48. De Souza CA, Vigorito AC, Ruiz MA, Nucci M, Dulley FL, Funcke V, et al. Validation of the EBMT risk score in chronic myeloid leukemia in Brazil and allogeneic transplant outcome. Haematologica 2005;90:232-7.
49. Gratwohl A. Risk assessment for patients with chronic myeloid leukemia before allogeneic blood or marrow transplantation. Haematologica 2005; 90:151.
50. Passweg JR, Walker I, Sobocinski KA, Klein JP, Horowitz MM, Giralt SA. Validation and extension of the EBMT Risk Score for patients with chronic myeloid leukaemia (CML) receiving allogeneic haematopoietic stem cell transplants. The Chronic Leukemia Study Writing Committee of the International Bone Marrow Transplant Registry. Br J Haematol 2004;125:613-20.
51. Qazilbash MH, Devetten MP, Abraham J, Lynch JP, Beall CL, Weisenborn R, et al. Utility of a prognostic scoring system for allogeneic stem cell transplantation in patients with chronic myeloid leukemia. Acta Haematol 2003;109:119-23.
52. Savani BN, Rezvani K, Mielke S, Montero A, Kurlander R, Carter CS, et al. Factors associated with early molecular remission following T cell depleted allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood 2005;[Epub ahead of print].
53. Maywald O, Pfirrmann M, Berger U, Breitscheidel L, Gratwohl A, Kolb HJ, et al. Cytogenetic response to prior treatment with interferon-α is predictive for survival after allogeneic hematopoietic stem cell transplantation in chronic myeloid leukemia 2006; Leukemia (in press)
54. Gale RP, Hehlmann R, Zhang MJ, Hasford J, Goldman JM, Heimpel H, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. The German CML Study Group. Blood 1995;91:1810-9.
55. Martinelli G, Soverini S, Rosti G, Cilloni D, Baccarani M. New tyrosine kinase inhibitors in chronic myeloid leukemia. Haematologica 2005; 90: 534-41.
56. Lowsky R, Takahashi T, Liu YP, Dejbakhsh-Jones S, Grumet FC, Shizuru JA, et al. Protective conditioning for acute graft-versus-host disease. N Engl J Med 2005;353:1321-31.