

Special report

Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time

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Summary:

We analysed a large homogeneous group of 14403 patients transplanted for early leukaemia from an HLA-identical sibling and reported to the EBMT in four time cohorts: 1980–1989 (24%), 1990–1994 (26%), 1995–1998 (30%) and 1999–2001 (20%). We focused on death from infection. End points were survival, death from relapse and transplant-related mortality (TRM), which was subdivided into death from graft-versus-host disease (GvHD) (1315 patients; 25% of deaths), infection (597 patients; 11% of deaths) or 'other' causes (1875 patients; 34% of deaths). Survival increased from 52% at 5 years in the first to 62% in the third cohort ($P < 0.05$) and TRM decreased from 36 to 26% ($P < 0.05$) due to a reduction in death from infection ($P < 0.001$). GvHD, 'other' causes and relapse did not improve. The relative proportions of bacteria (217 patients; 36%), viruses (183 patients; 31%), fungi (166 patients; 28%) or parasites (32 patients; 5%) as cause of infectious death (cumulative incidence of death at 5 years 1.8, 1.6, 1.4 and $\geq 0.3\%$, respectively) and median time to death from infections (3 months (range 0–158 months)) did not change. Death from infections has been reduced significantly, but it still represents an ongoing risk after HSCT and draws attention to the time beyond the initial period of neutropenia.

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Since its introduction over 30 years ago, haematopoietic stem cell transplantation (HSCT) has become an established therapy for many severe congenital and acquired disorders of the haematopoietic system and chemo-radio-sensitive or immuno-sensitive malignancies. HSCT has seen rapid expansion over the last decade and is integrated in the therapeutic plan in many disease categories.^{1–6} However, it is hampered by significant morbidity and mortality. Early mortality is considered the main impediment to broader application of allogeneic HSCT. Toxicity associated with the conditioning regimen, infections, graft-versus-host disease (GvHD) and relapse of the basic disease are the main causes of failure. Depending on patient selection and risk constellation, 10 to >50% of the patients die within 1 year of procedure.^{1,7–10} Major progress has been made in supportive care, immunosuppression and infection management, thereby improving the situation over the last two decades and reducing the risk of lethal complications.^{11–15}

Infections were recognised very early as a significant contribution to morbidity and mortality during the period of pancytopenia.^{1,10,16–18} With focus on neutropenia, strict isolation in sterile units or laminar airflow compartments has been standard care practice for many years.^{19–21} Improvement in diagnosing infections, availability of better broad spectrum antibiotics, novel antifungal and antiviral agents, introduction of intravenous immunoglobulins and vaccination strategies have changed attitudes. Infections are considered as treatable conditions. Strict isolation or sterile nursing has been debated by many institutions and is no longer considered essential in international guidelines.^{19,22–24}

Furthermore, reduced-intensity conditioning (RIC) transplants have been introduced in recent years.^{25–28} With a focus on immunosuppression rather than myelosuppression, RIC HSCT reduce duration and severity of pancytopenia, induce less mucositis and less organ toxicity. These patients are less vulnerable to early infectious complications. RIC HSCT has triggered expansion of HSCT to patients with severe comorbidities or at increased age.

Attitudes have created a sense of security concerning infectious complications.

Little information, however, exists concerning the impact of these strategies on outcome. Sensitised by reports of epidemics in HSCT institutions,^{29–31} we were interested to find out whether incidence and cause of infectious deaths and time of death from infections has changed over the years.

Patients and methods

Study design

This is a retrospective cohort analysis focusing on data reported to the Acute or Chronic Leukemia Working Party of the EBMT. Selection criteria were early leukaemia (acute myeloid or acute lymphoid leukaemia in first complete remission or chronic myeloid leukaemia in first chronic phase) and allogeneic transplantation from an HLA identical sibling donor between 1980 and 2001. This restriction provides a large homogeneous patient population and sufficient time for follow-up.

The population was subdivided into four time cohorts (Table 1) to study calendar time effects on the cumulative

incidence of the various causes of death. The cohorts were chosen to have roughly equal numbers while maintaining logical boundaries at the times of introduction of peripheral blood as stem cell source and RIC HSCT. As patients transplanted in the most recent cohort have a maximum follow-up of 4 years, two separate analyses were performed. All four cohorts were used for the 12-month analysis, including a comparison of RIC and standard conditioning. Long-term analysis was restricted to the first three cohorts. This provides sufficient follow-up for all patients in the two analyses and avoids possible bias induced by RIC transplants after 1999. Follow-up was closed as of 31 December 2003.

Patient population

The analysis includes 14 403 patients with a median age of 33 years (range 1–82). Details are summarised in Table 1. There were slightly more male patients (56.7%); AML and CML contributed 40% each, 20% of patients had ALL. The female-donor, male-recipient combinations were equal in all cohorts (25%). A quarter of the recipients (25%) received T-cell depleted grafts. Bone marrow was the preferred graft product (81%) in this long-term analysis.

Table 1 Patients characteristics

Time cohort	1980–1989		1990–1994		1995–1998		1999–2001		Total	
	28 (1–57)		32 (1–59)		35 (1–62)		36 (1–82)		33 (1–82)	
Age** (years (median/range))	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<i>Age classes at transplant</i>										
<20 years	872	25.8	804	21.5	750	17.2	441	15.1	2867	19.9
20–40 years	2076	61.5	2031	54.2	2079	47.7	1335	45.8	7521	52.3
>40 years	428	12.7	909	24.3	1526	35.0	1141	39.1	4004	27.8
<i>Disease classification*</i>										
AML	1362	40.3	1498	40.0	1703	39.1	1169	40.0	5732	39.8
ALL	735	21.8	766	20.5	864	19.8	566	19.4	2931	20.3
CML	1280	37.9	1481	39.5	1793	41.1	1186	40.6	5740	39.9
<i>Stem cell used**</i>										
BM	3376	100.0	3714	99.3	3140	72.3	1404	49.0	11634	81.2
PB			27	7	1205	27.7	1464	51.0	2696	18.8
<i>T-cell depletion**</i>										
No	1230	55.2	1749	71.7	2691	84.8	2146	84.2	7816	75.2
Yes	997	44.8	692	28.3	483	15.2	402	15.8	2574	24.8
<i>Recipient male–donor female</i>										
Other combinations	2542	75.3	2829	75.5	3264	74.9	2239	76.7	10874	75.5
m–f	835	24.7	916	24.5	1096	25.1	682	23.3	3529	24.5
<i>Conditioning intensity**</i>										
Normal	554	99.5	956	99.4	1835	98.1	1851	89.9	5196	95.3
Reduced	3	0.5	6	0.6	36	1.9	209	10.1	254	4.7
<i>Patient sex*</i>										
Male	1938	57.4	2173	58.0	2417	55.4	1641	56.2	8169	56.7
Female	1439	42.6	1572	42.0	1943	44.6	1280	43.8	6234	43.3
Total	3377		3745		4360		2921		14403	

*0.05 < P < 0.10; **P < 0.05; χ^2 test on trend in the 4* table.

AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; CML = chronic myeloid leukaemia; BM = bone marrow; PB = peripheral blood; m–f = female donor for male recipient.

Changes over time

There were distinct changes over time (Table 1). There was a substantial increase in median age at transplant over time from 28 years in 1980 to 36 years in 2001. As a consequence, the proportion of patients above the age of 40 years has risen from 5% in 1980 to 39% in 1999–2001 and the maximum age has risen from 57 to 82 years. Peripheral blood as stem cell source has increased from 1% in the 1990–1994 cohort to 51% in the 1999–2001 cohort. T-cell depletion as a method of GvHD prevention reached its peak in 1980–1989 with 45%; it was applied during the most recent cohort in 16% of patients only. RIC HSCT were very rare before the year 1999 but were reported in 10% of the HSCT in the cohort from 1999 to 2001. Only those transplants marked by the participating team as RIC HSCT were considered as such in the analysis.

Definitions of study end points

For this analysis we concentrated on cause of death and cause of infectious death, and an arbitrary but logical hierarchy was created based on the initial definition of outcome reporting for HSCT.³² Cause of death was first categorised into relapse or transplant-related mortality (TRM). Patients who never achieved remission or died with relapse at any time after HSCT were classified as relapse death. Patients who died without relapse were classified as TRM. They were further subdivided into death from GvHD, death from infection or death from 'other causes' according to the coding on the reporting forms as primary cause of death. This form allows coding for GvHD, infection or 'other causes'. The information on the reporting forms was taken as it was, independent of additional remarks. Patients who died of TRM without coding for primary cause of death were classified as 'other causes'; this corresponds to 397 or 2.7% of all patients.

The same procedure was chosen for the analysis of cause of infectious death. The reporting forms over the whole 20-year period were consistent for reporting bacterial, viral, fungal or parasitic infectious death. No details on specific cause of infectious death were available on the minimal essential data reporting forms.

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.

Causes of death and the subdivision of infectious death in relation to time after transplant were analysed in two different ways. Cause of death was assessed with cumulative incidence curves and stacked cumulative incidence plots, which take into account the various causes of death as competing risks.³³ In a second approach, the relative contribution of the competing risks were assessed for the

three first calendar time cohorts by a landmark analysis, beginning at 1 year (data now shown) or 4 years post transplant. The calendar time effect on cause specific death was tested using a Cox model.

Results

Survival and main cause of death

At the time of analysis, 9026 patients were alive (63%), 8197 without, 829 with relapse; 5377 patients had died (37%), 1590 from relapse (30%) and 3787 from TRM (70%). Survival was different for the four cohorts and increased continuously over time from 52% at 5 years in 1980–89 to 62% at 5 years in 1995–99 (Figure 1) ($P < 0.05$). Early survival was similar for the last two cohorts despite a further increase in patient age, but follow-up was short in the last cohort (1999–2001).

Main causes of death are listed in Table 2 and illustrated in Figure 2. Cause of death was reported as relapse in 1590 patients (30%), as GvHD in 1315 patients (25%), as infection in 597 patients (10%) or as other cause in 1875 patients (35%). The cumulative incidences of relapse, GvHD, infections and other causes of mortality varied at different time points after HSCT (Figure 2, Table 2). All causes except relapse had a steep initial increase; GvHD and infections levelled off at approx. 10 and 5%, respectively. Relapse as cause of death began later and showed no levelling off. Figure 3 shows the relative contribution of each of these main causes among all deaths, exemplified by the cohort from 1980 till 1989. This figure illustrates that other causes, hence toxicity, did contribute to nearly 75% of deaths within the first month, when relapse was still negligible. Owing to these changing relative contributions and the different follow-up time, distributions in the four cohorts and cumulative incidences are comparable only at a fixed time point common to all cohorts. For example, cumulative incidences at 1 year were compared for all four cohorts, cumulative incidence at 5 years for the first three cohorts and cumulative incidence at 10 years for the first two cohorts only.

The landmark analysis (Figure 4) visualises new incidences of deaths and the persisting contribution of all causes including infections, which remain a contributing factor in about 2%, even among patients alive at 4 years. These low numbers are not recognisable in the cumulative incidence tables (Table 2).

Improvement over calendar time

Survival did improve over time due to decreasing cumulative incidence of TRM with a nonproportional reduction of the three causes of TRM. Cumulative mortality at 1 year in the first cohort changed from 10 to 7% in the last cohort for GvHD (NS), from 6 to 1% for infections ($P < 0.001$) and from 15 to 13% for other causes (NS). Relapse as cause of death at 1 year increased from 6% in the first to 11% in the last cohort ($P < 0.001$) (Figure 2a). Improvement was most marked for infectious death during the first 12 months (Figure 2b) with a hazard ratio of 1 in the first cohort to

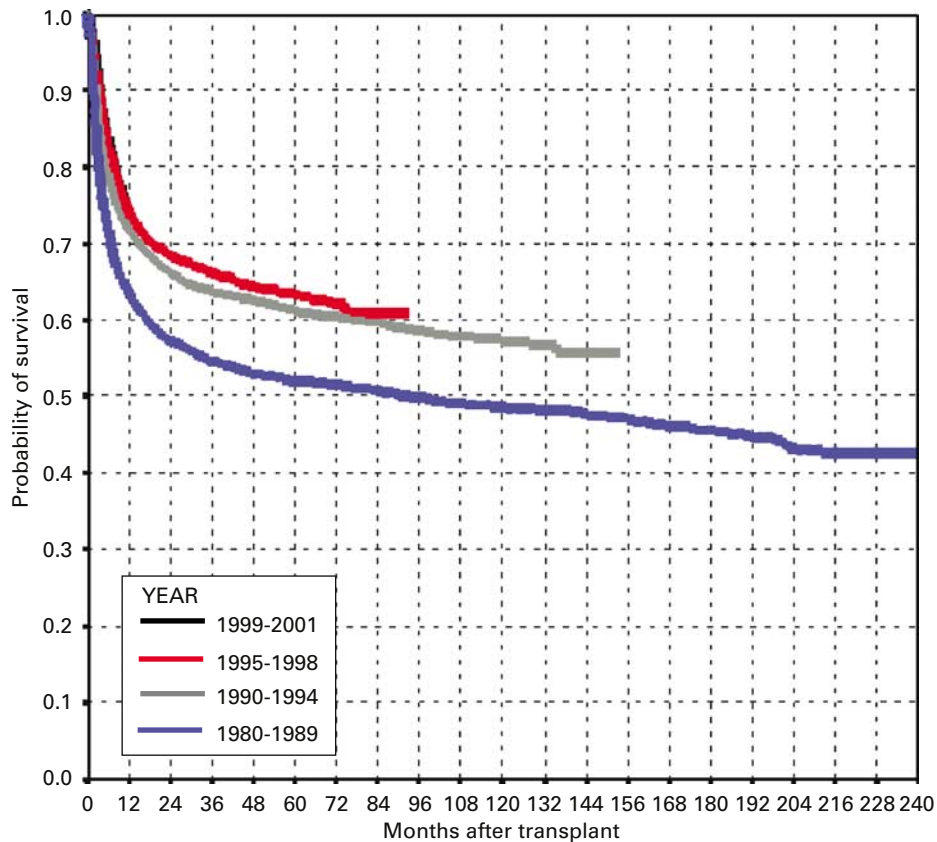


Figure 1 Probability of survival of 14 403 patients with early leukaemia and an HLA identical sibling HSCT from 1980 to 2001. Four time cohorts. Time in months post HSCT. For numbers of patients refer to Table 1.

Table 2 Cumulative incidence of main cause of death and cause of infectious death in 14 403 patients with HSCT for early leukaemia in four calendar time cohorts

Time cohort:	1980–1989				1990–1994				1995–1998				1989–2001				All cohorts			
	3 mo	1 y	5 y	10 y	3 mo	1 y	5 y	10 y	3 mo	1 y	5 y	10 y	3 mo	1 y	5 y	10 y	3 mo	1 y	5 y	10 y
<i>Main cause of death</i>																				
Relapse	0.01	0.06	0.13	0.14	0.01	0.06	0.13	0.15	0.01	0.06	0.11	—	0.01	0.11	—	—	0.06	0.07	0.12	0.14
GvHD	0.06	0.10	0.12	0.12	0.04	0.08	0.10	0.10	0.03	0.08	0.10	—	0.03	0.07	—	—	0.04	0.09	0.10	0.11
Infection	0.03	0.06	0.07	0.07	0.02	0.04	0.05	0.05	0.01	0.03	0.04	—	0.01	0.01	—	—	0.02	0.04	0.05	0.05
Other causes	0.09	0.15	0.17	0.18	0.05	0.10	0.12	0.13	0.05	0.09	0.12	—	0.06	0.13	—	—	0.06	0.11	0.13	0.15
<i>Cause of infectious death</i>																				
Bacterial	0.01	0.02	0.02	0.03	0.01	0.01	0.02	0.02	0.00	0.01	0.01	—	0.00	0.01	—	—	0.007	0.015	0.018	0.019
Viral	0.01	0.02	0.03	0.03	0.01	0.01	0.02	0.02	0.00	0.01	0.01	—	0.00	0.00	—	—	0.007	0.014	0.016	0.016
Fungal	0.01	0.02	0.02	0.02	0.00	0.01	0.01	0.01	0.00	0.01	0.01	—	0.00	0.00	—	—	0.001	0.013	0.014	0.014
Parasitic	NA				NA				NA				NA				0.001	0.003	0.003	0.003

NA = not applicable, too small numbers; mo = months; y = years.

0.65 (0.53–0.80, 95% CI) in the second, 0.47 (0.38–0.58, 45% CI) in the third and 0.20 (0.14–0.29, 95% CI) in the most recent cohort.

Causes of infectious death

Of the 597 deaths with infection as the primary cause of death, according to the reporting team 217 (36%), were

attributed to bacteria, 183 (31%) to viruses, 166 (28%) to fungi and 31 (5%) to parasites. The cumulative incidence of deaths with infection at 5 years was 5% with a cumulative incidence of 1.8% attributed to bacteria, 1.6% to viruses, 1.4% to fungi and 0.3% to parasites (Table 2). The cumulative incidence of all causes decreased over calendar time while their relative contributions remained stable (Figure 2, Table 2). In order to assess in detail the

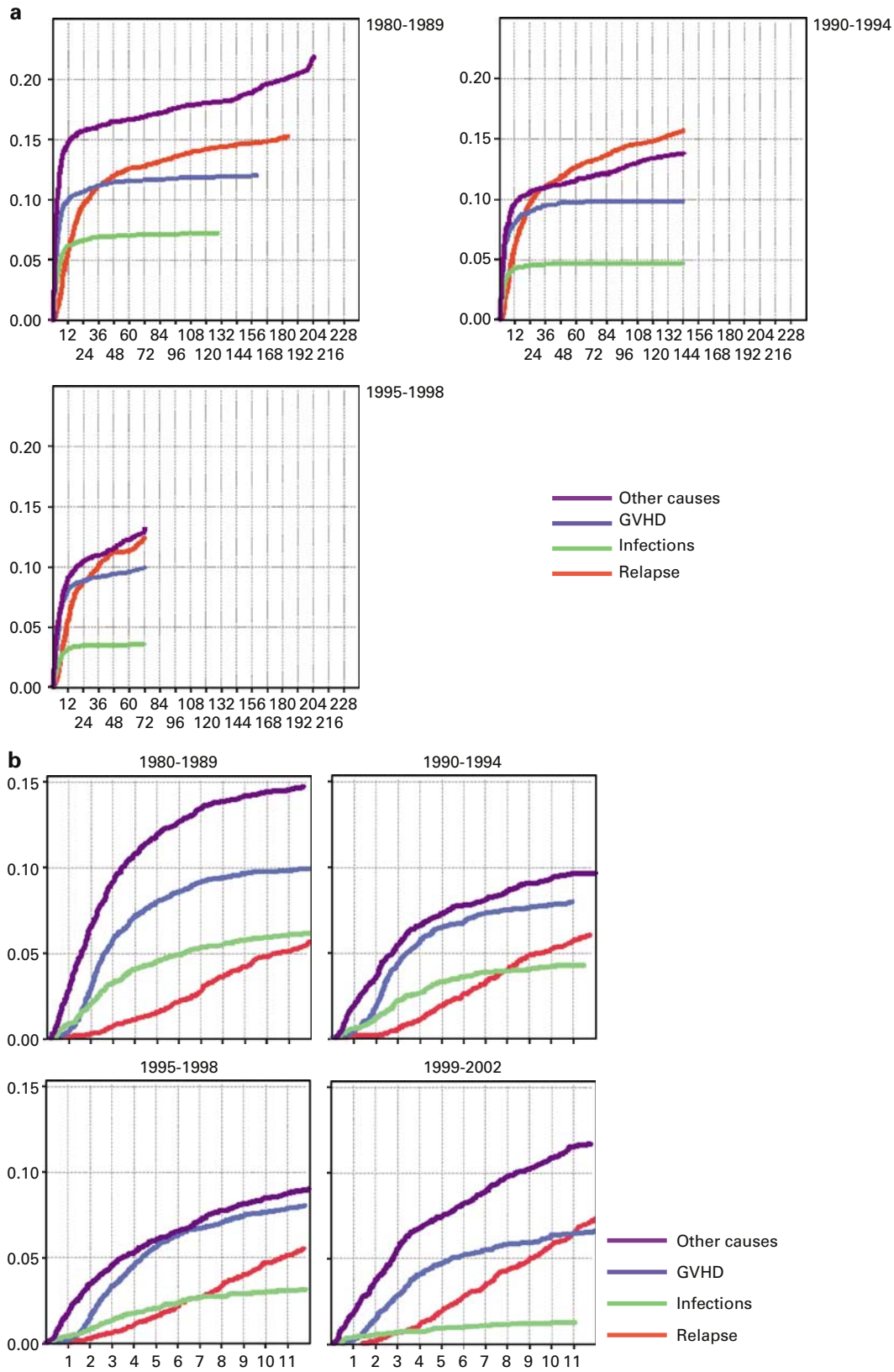


Figure 2 Main causes of death in 14403 patients with early leukaemia and HLA identical sibling HSCT. Separate cumulative incidences of death by relapse, GvHD, infection and other causes are presented in four calendar time cohorts. Time in months post HSCT. Time scale over whole follow-up time, first three cohorts only (a). First 12 months only, all cohorts (b).

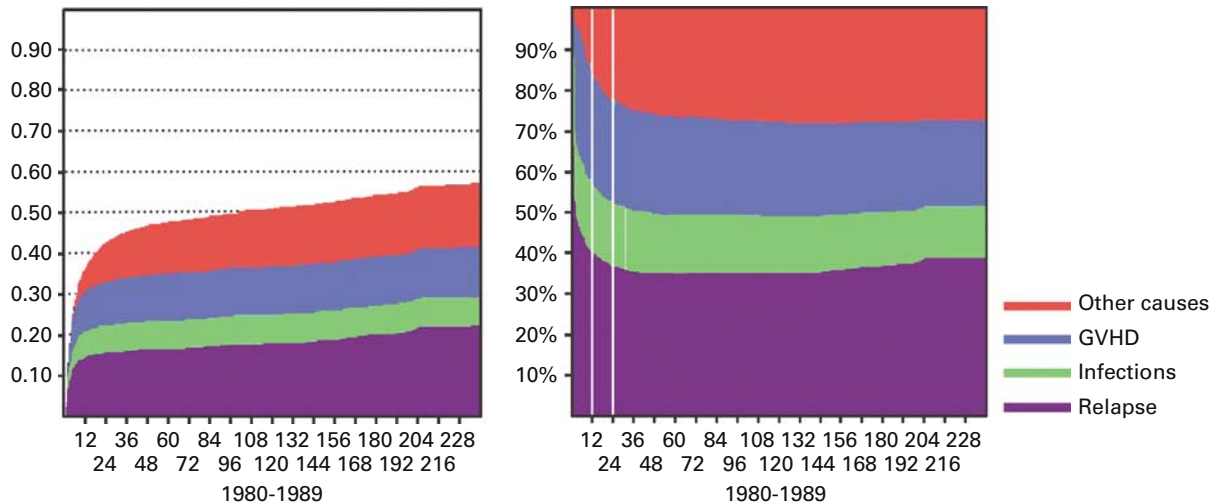


Figure 3 Stacked cumulative incidences of death by relapse, GvHD, infection and other causes exemplified by the time cohort 1980–1989. Time in months post HSCT (left panel) and relative contribution of relapse, GvHD, infection and other causes to the cumulative death incidence (all deaths = 100%) (right panel).



Figure 4 Landmark analysis of the relative contribution of relapse, GvHD, infection and other causes to the cumulative incidence of death for patients alive at 4 years post HSCT. The analysis is restricted to the first three cohorts. Time in months post HSCT.

development of the various causes of infectious death, we combined all four cohorts and calculated the cumulative incidences of all infectious causes of death. The four cohorts were combined without introducing a bias, as the proportional cumulative incidence of infections did not differ among them, nor did it differ between the RIC and standard HSCT subgroups in the fourth cohort. Deaths from all infectious causes showed a difference during the first 3 months, where the relative contribution of deaths from bacterial infections was slightly higher. Beyond 3

months, the proportion remained the same for the whole follow-up time (Figure 5).

Time of death after HSCT

Time of death depended primarily on the main cause of death. Deaths from GvHD, infections and other causes occurred all at a median of 3 months (range 0 to about 200 months; 2 to 7, respectively 9, months; 25 to 75 percentiles) (Table 3). Percentiles for time to

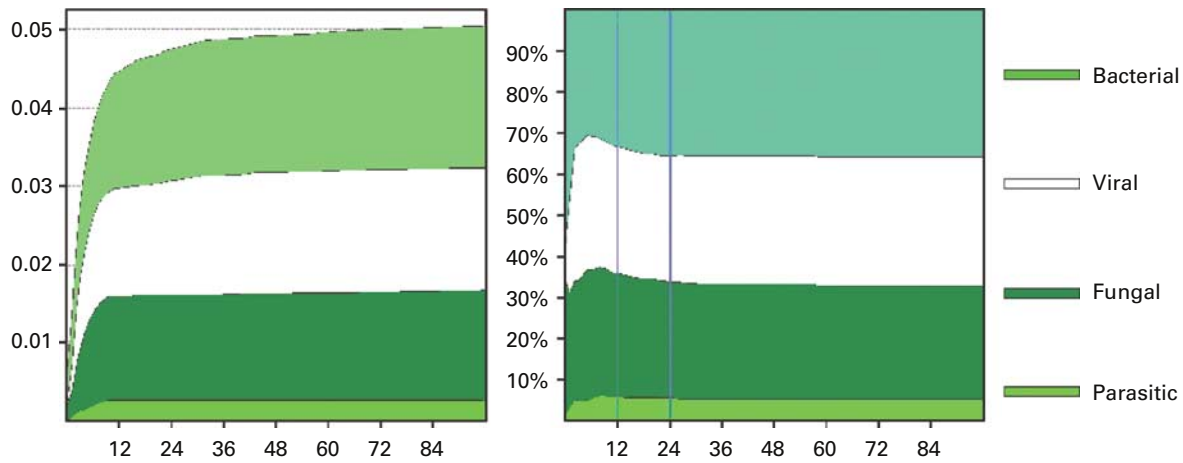


Figure 5 Stacked cumulative incidences (left panel) and relative contribution (right panel) of bacterial, viral, fungal or parasitic infections to infectious death over follow-up time. All four cohorts combined. Time in months post HSCT.

Table 3 Time to death (in months) by main cause of death and cause of infectious death in four calendar time cohorts

	1980–1989	1990–1994	1995–1998	1999–2001	All
<i>Main cause of death</i>					
Relapse ^a				^b	
GvHD	3 (2–7)	3 (2–7)	4 (2–7)	^b	3 (2–7)
Infection	3 (2–8)	3 (2–6)	4 (2–7)	^b	3 (2–7)
Others	3 (1–9)	3 (2–9)	4 (2–10)	^b	3 (2–9)
<i>Cause of infectious death</i>					
Bacterial	6 (2–12)	3 (1–5)	4 (1–8)	^b	
Viral	3 (2–6)	3 (2–6)	3 (2–7)	^b	
Fungal	2 (1–5)	4 (2–6)	4 (2–6)	^b	
Parasitic	3 (2–7)	3 (2–7)	5 (5–8)	^b	

Numbers reflect median and 25th and 75th percentiles of all intervals between transplant and death.

^aRelapse has been omitted since percentiles are biased due to the restricted follow-up time in more recent cohorts.

^bPercentiles are omitted in the most recent cohort. They can be misleading due to the restriction to 12 months' follow-up.

death were not estimated for relapse deaths, being biased by the actual amount of follow-up time that differs in the four cohorts.

Median time to death from infection was 3 months, 50% of all infections occurred before and 50% after 3 months (Table 4). In total, 25% of infectious deaths took place within the first 2 months post HSCT, 25% after 7 months, 10% beyond 1 year. Time of death differed for the different infectious causes with median time of death of 3 months for viral and fungal infections, 4 months for bacterial infections and 5 months for parasitic infections. Late events beyond 100 months were limited to bacterial and fungal infections. There was no significant change in time to infectious death among those who died from it in the four time cohorts.

Infectious deaths within the first 12 months were analysed separately for all cohorts and all four infectious causes. Time to infectious death was similar for all four infectious causes except for an early predominance of bacterial infectious deaths within the first 2 months. That

Table 4 Impact of risk factors on incidence of infectious deaths

<i>Risk factor</i>	<i>HR any infection</i>	<i>HR bacterial</i>	<i>HR viral</i>	<i>HR fungal</i>	<i>HR parasitic</i>
<i>Age class</i>					
≤20	(1)	(1)	(1)	(1)	(1)
20–40	1.9	2.2	1.5	2.5	1.1
≥40	2.4	2.1	2.4	3.1	1.9
<i>Disease</i>					
AML	(1)	(1)	(1)	(1)	(1)
ALL	1.0	1.2	0.8	0.9	0.9
CML	1.0	0.8	1.0	1.1	1.4
<i>T-cell depletion</i>					
No	(1)	(1)	(1)	(1)	(1)
Yes	1.8	2.1	1.6	1.8	1.4
<i>Gender mismatch</i>					
No	(1)	(1)	(1)	(1)	(1)
Yes	1.0	1.0	1.0	1.2	0.9
<i>Patient sex</i>					
Male	(1)	(1)	(1)	(1)	(1)
Female	1.2	1.0	1.4	1.1	1.6
<i>Reduced intensity</i>					
No	(1)	(1)	(1)	(1)	(1)
Yes	0.9	NA	1.2	1.0	2.5
<i>Source of stem cells</i>					
BM	(1)	(1)	(1)	(1)	(1)
PB	0.5	0.7	0.3	0.5	0.5

HR = Hazard ratio's in bold are significant ($P < 0.05$); NA = not applicable, model did not converge; AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; CML = chronic myeloid leukaemia; BM = bone marrow; PB = peripheral blood.

Univariate hazard ratios of infectious death rates obtained from a COX model in a competing risk context. For each end point (bacterial, viral, fungal, parasitic), all other competing causes (including relapse, GvHD and 'other') of death were censored.

pattern remained constant over the four time cohorts (Figure 6). The same holds true for viral, fungal and parasitic infections (figures not shown).

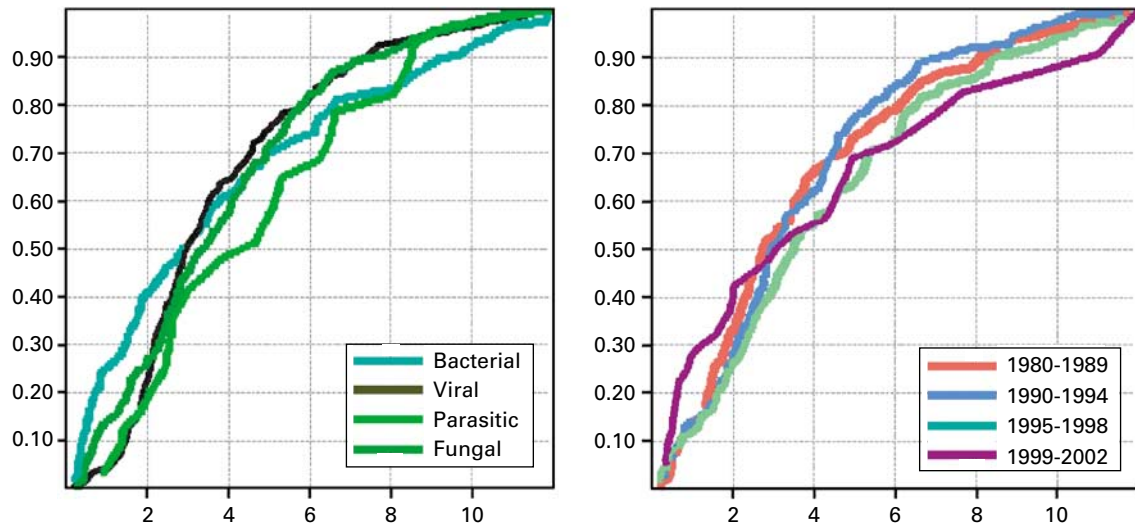


Figure 6 Time to infectious death within the first 12 months post HSCT. Proportion of patients dead at any timepoint within 12 months from bacterial, viral, fungal or parasitic infections (left panel). All four cohorts combined. The analysis is restricted to deaths within 12 months, and 100% corresponds to all patients who died from such an infection within the first 12 months. Proportion of patients dead at any timepoint within 12 months from bacterial infections (right panel) by calendar time cohort. All four cohorts combined. The analysis is restricted to deaths within 12 months, and 100% corresponds to all patients who died from such an infection within the first 12 months. Time in months post HSCT.

Factors influencing cause of infectious death

The risk factors described in Table 1 were evaluated for their impact on infectious deaths. Results are presented in Table 4. Overall, there were more infectious deaths with increasing age and T-cell depletion, and less with peripheral blood as stem cell source. Female patients had a significant, though small, increased probability of infectious deaths, mainly due to viral infections. Overall increased hazards are reflected in each of the subcategories bacterial, viral and fungal infections.

Discussion

The present data confirm and extend previous observations on infectious deaths after HSCT: infections remain of concern after allogeneic HSCT. A minimum of 10% of all deaths after HSCT were primarily due to infection^{1,10,16,18,22,23} and the cumulative incidence of infectious death at 10 years for all patients is 5%. TRM has decreased over time. This improvement was significant only for infectious deaths. All four causes of lethal infections, subdivided into bacterial, viral, fungal or parasitic infection, have improved but time to death from a given infectious agent has not changed. No improvement was seen in the proportion of death due to GvHD or other causes. Death from relapse even increased.

It is beyond the scope of this analysis to explain these changes. It is comforting to see that transplant-related complications did not increase despite an increase in age over the same time period, and that a significantly smaller proportion of patients died from infection. At the same time, it is intriguing to see that the proportion of infectious death and time to death remained unchanged. Failure to alter the pattern of infectious deaths remains unexplained.

Failure to improve on relapse might reflect the fact that patients transplanted in early leukaemia, for example, acute leukaemia in first CR, represent a group of patients with higher risk leukaemia during more recent years compared to earlier periods. Many groups no longer transplant patients with good risk leukaemia, for example, patients with translocation t8;21 or t15;17 in first complete remission. Failure to improve on death from GvHD and 'other' causes is disappointing and presents a challenge for the transplant community.

Infections remained an important cofactor with a constant proportion of about 2–3% of all causes of death up to 10 years and more post HSCT, as illustrated in the landmark analysis. Bacterial and fungal infections contributed to death beyond 10 years. Half the infectious deaths occurred beyond 3 months post transplant. Only 7% of lethal infectious complications and primarily lethal bacterial infections happened within the first month post HSCT, even less during the initial period of pancytopenia. Time of death from infection has not changed during the last 20 years. This holds true for all categories of infectious deaths: bacterial, viral, fungal and parasitic infections.

The analysis focused on infectious deaths, it did not look at incidence of infections. Our study confirms some known main pre-transplant factors associated with infectious death:^{1,10,16,34} increasing age and T-cell depletion. It also shows an advantage for peripheral blood. Unexplained and hitherto unreported remains the higher incidence of deaths from viral infections in female patients. Additional analyses will be required to see whether this represents a spurious finding or whether it reflects a higher risk of females being exposed to viruses transmitted from children, such as varicella zoster or respiratory syncytial virus. The analysis failed to show a correlation of infectious deaths with RIC, a topic of current intense debate which may be solved only by prospective comparative studies.^{35–42}

These findings have consequences. They suggest that transplant teams are, with some exceptions, proficient in handling infectious complications in patients during the period of aplasia. New teams opening up novel transplant centres need to take this experience into account. Teams have also integrated new therapeutic agents and reduced overall mortality from infections. On the other hand, there is a deficiency in combating infections during the later immunodeficiency period, whether associated or not with GvHD. Here, novel tools and novel approaches are required. Furthermore, these findings are important in view of the most recent discussions on the value of protective environments and isolation procedures for HSCT recipients.^{22,23} Most isolation methods are restricted to the period of pancytopenia during the first month, rarely later on. We had no information on methods of isolation and duration of such preventive measures for the patients in the analysis. We also had no information on white blood cell counts at the time of death.

This information is not available, was not collected for individual patients and cannot be collected reliably in retrospect for such a large number of patients. However, only a small proportion of patients, primarily with bacterial infections, did in fact die from infection as main cause of death during the early phase of transplantation. Hence, present data suggest that delayed immune reconstitution, which is known to take months to normalise, is probably a more important factor contributing to infectious deaths than pancytopenia itself.^{1,10,43–45} If methods of reverse isolation and infection prevention are discussed in general for patients undergoing HSCT, a long time interval must be considered. It will also apply to novel strategies such as home care of HSCT patients.^{46,47}

The present study is limited by several aspects. It covers a long period of time. It focused on early leukaemia and good risk patients with HLA identical sibling transplants only. The definitions for infectious deaths were selected on purpose to exclude all other potential causes. Hence, the 'real' incidence of infectious deaths is probably higher. Details on peripheral blood values at time of death or data on the degree of immune reconstitution are not captured. Late pancytopenia for any reason might have contributed significantly. Definition of cause of death might have changed over time or even within teams. Nevertheless, the study provides clear answers when infectious deaths occur. Large numbers counterbalance individual errors. The constancy of patterns, such as proportion of causes of death over time or time point of death over time, validate the results and reinforce the message.

These data clearly show that, despite improvements, infections continue to be a substantial cause of death after allogeneic HSCT. The majority of lethal infections occur beyond initial pancytopenia.

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Appendix A

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France, Clichy, J Briere, Hôpital Beaujon [662]
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France, Paris, F Dreyfus, Hôpital Cochin [280]
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France, Paris, E Gluckman, Hôpital St Louis [207]
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