Early administration of donor lymphocyte infusions upon molecular relapse after allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia: a study by the Chronic Malignancies Working Party of the EBMT

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ABSTRACT

Patients with chronic myeloid leukemia relapsing after allogeneic hematopoietic stem cell transplantation may be treated by tyrosine kinase inhibitors and/or by donor lymphocyte infusions. The best strategies and timing of administration of lymphocytes are unclear. We analyzed 155 patients who relapsed after allogeneic stem cell transplantation with disease detectable only by molecular methods and who subsequently received lymphocytes. Transplants were performed in first chronic phase (n=125) or in advanced disease (n=29) from identical siblings (n=84) or unrelated donors (n=71) between 1986 and 2003. They received lymphocytes either during molecular relapse (n=85) or upon progression to more advanced disease (1993 to 2004). The median interval from relapse to lymphocyte infusion was 210 (0-1673) days. The median follow up after it was 46 (3-135) months. Overall survival was 76±4% at five years after lymphocyte infusions (89±8% with sibling donors and 63±13% with unrelated donors (*P*=0.003)). Survival was 69±14% when lymphocytes were given within six months of the detection of molecular relapse and 81±10% (*P*=0.061) when given later; 81±11% if given at molecular relapse *versus* 71±12% (*P*=0.26) with more advanced disease. In multivariate analysis survival was worse if the donor was unrelated (HR 2.54 (95% CI: 1.15-5.53), *P*=0.021) and better with lymphocyte infusions beyond six months from molecular relapse (HR 0.4 (95%CI: 0.19-0.84), *P*=0.018). These data confirm the remarkable efficacy of lymphocyte infusions for this disease. There appears to be no advantage from administering it early upon detection of molecular relapse in patients who received allogeneic stem cell transplantation for chronic myeloid leukemia.

Introduction

Patients relapsing after allogeneic hematopoietic stem cell transplantation (HSCT) for chronic myeloid leukemia (CML) can be treated either with tyrosine kinase inhibitors (TKI) or by the administration of donor lymphocyte infusion (DLI) or both.[1] The best strategy, with respect to using either or both of DLI and TKI, and the timing of these in relation to the relapse has not yet been established.

The description of the graft-*versus*-leukemia (GvL) effect has paved the way to the development of DLI for the treatment of relapse in patients after allogeneic HSCT.[2-7] DLI is most effective in CML.[5] It can restore remission in many patients with CML relapsing after HSCT.[2-4] As responses are less frequent for advanced disease at the time of relapse, molecular/cytogenetic monitoring after transplantation and

prompt therapy with DLI prior to developing hematologic relapse may represent the optimal management of patients after transplantation.[8] The applicability of DLI in CML has been limited by morbidity and mortality associated with graft-*versus*-host disease (GvHD).[7,9-11] The practice of DLI has changed as the early bulk doses have been replaced by regimens with low starting doses followed by escalation until response or GvHD. This may reduce the severity of GvHD, while possibly preserving GvL effects.[5,12-14]

Over the past decade TKI have been available to treat patients who relapse after allogeneic HSCT. Durable responses have been reported with imatinib, nilotinib and dasatinib, and many of these patients had previously failed to respond to DLI. Modern practice has favored the use of a TKI prior to DLI because of the risk of inducing GvHD, but this is complicated by the fact that many CML patients are now only trans-

planted because of failure to several TKIs. Therefore, the question of when relapse should be treated with DLI or TKI remains important.

Methods

This study was conducted by the Chronic Malignancies Working Party (CMWP) of the EBMT (European Group for Blood and Marrow transplantation). We set out to study patients who had had their relapse first detected as molecular relapse. The initial total sample included 1045 patients from 138 EBMT centers who had received DLI as treatment of relapse at any disease stage (molecular or more advanced) between 1993 and 2004. Specific questionnaires related to DLI, including the diagnosis of molecular relapse, were circulated. Out of 1045 patients, we received completed DLI questionnaires from 344 patients from 31 centers; therefore, 701 failed to complete a questionnaire. Out of the 344 patients who did provide a completed questionnaire, 156 (45%) were excluded from the analysis as their relapse had first been detected at a more advanced stage than molecular relapse. Patients in whom the type of relapse was not known (n=33) were also not included in the study. The study, therefore, included 155 patients who had been diagnosed with molecular relapse.

Definitions

Donor lymphocyte infusion

Lymphocytes were collected from the donors by leukapheresis on one or more occasions. Infusions had to be given on multiple days at least seven days apart to be counted as separate infusions. Thirty-four (10%) patients treated with DLI had active GvHD at the time of infusion and 27 patients (8%) were still receiving some form of immunosuppressive therapy. Ten patients received concomitant imatinib therapy with DLI.

Relapse

Relapse was classified as molecular (i.e. any level of BCR-ABL transcripts detected by quantitative reverse transcription–polymerase chain reaction (RT-PCR) in 2 consecutive tests performed over a minimum of 4 weeks), cytogenetic (i.e. reappearance of one or more Philadelphia chromosome–positive (Ph[+]) metaphases at bone marrow cytogenetics), or hematologic (i.e. presence of peripheral blood leukocytosis accompanied by a hypercellular bone marrow with Ph[+] chromosome on cytogenetic analysis) in accordance with previous reports.[11,13,14] CML phase was classified in accordance with criteria proposed by Speck et al.[15]

Statistical analysis

Overall survival was calculated from the date of the first infusion of donor lymphocytes until death or last follow up. Event-free survival (EFS) was calculated from the date of the first infusion of donor cells until event or last follow-up. An event was defined as

Table 1. Outcome of patients receiving DLI for CML molecular relapse.

N.	155
Acute GvHD post-DLI	
Grade 0	88 (57%)
Grade I	19 (12%)
Grade II-	11 (7%)
Grade III-IV	12 (8%)
Unknown	25 (16%)
Chronic GvHD post-DLI	
No	89 (57%)
Yes	34 (22%)
Unknown	32 (21%)
Best response to DLI	
Molecular CR	95 (61%)
Cytogenetic CR	8 (5%)
Hematologic CR or CP	3 (2%)
No response	28 (18%)
Unknown	21 (14%)
Interval from first DLI to best response (days)	245 (9-1673)
DLI-related mortality	11 (95% CI 6-18%)
Overall survival	78 % (95% CI 72-80%)
Response to DLI from alive patients	
Yes	93 (75%)
No	16 (13%)
Unknown	15 (12%)
Complete molecular response of responders	86 (69%)

5 years OS		P
All patients	76% (95% CI: 72-80%)	
Identical siblings	89% (95% CI: 81-97%)	0.003
Unrelated donors	63% (95% CI: 50-76%)	
< 6 months after molecular relapse	69% (95% CI: 55-85%)	0.061
> 6 months after molecular relapse	81% (95% CI: 71-91%)	
DLI given for molecular relapse	81% (95% CI: 70-92%)	
DLI given for cytogenetic, hematologic or advanced phase relapse	71% (95% CI: 59-83%)	0.26

DLI: donor lymphocyte infusion; GvHD: graft-versus-host disease; CR: complete response; CP: chronic phase; OS: overall survival.

Table 2. Response to DLI by disease stage at the time DLI was given.

N.	155
DLI given in molecular relapse	N=85
Molecular CR	50 (59%)
Cytogenetic CR	5 (6%)
No or Unknown Response	14 + 16= 30 (35%)
DLI given in cytogenetic relapse	N=37
Molecular CR	27 (73%)
Cytogenetic CR	2 (5%)
Hematologic CR	1 (2.5%)
No or Unknown Response	5+2=7 (19%)
DLI given in hematologic CP	N=25
Molecular CR	16 (64%)
Cytogenetic CR	0
Hematologic CR	1 (4%)
No or Unknown Response	6+ 2=8 (32%)
DLI given in advance phase relapse (AP/BC)	N=8
Molecular CR	2 (25%)
Cytogenetic CR	1 (12.5%)
Hematologic CR or CP	1(12.5%)
No	4 (50%)

DLI: donor lymphocyte infusion; CR: complete response; CP: chronic phase; AP: accelerated phase; BC: blast crisis.

relapse after response or, in patients not responding, as progression to more advanced disease (e.g. from cytogenetic relapse to hematologic relapse or from chronic phase to accelerated phase), or death if neither relapse nor progression occurred.

Survival curves for OS and EFS were calculated using the Kaplan-Meier method.[16] The cumulative incidence of DLI-related mortality was calculated from the date of the first infusion of donor lymphocytes considering death without prior relapse or disease progression to frank hematologic relapse as failure of the event of interest and relapse or progression as competing event; patients alive relapse-free were censored at last follow up. The cumulative incidence method was used also for estimates of GvHD and response, considering death without the event of interest as competing risk.

Results

This study included 155 patients transplanted between 1986 and 2003 in 28 EBMT centers. None were treated with imatinib prior to transplant. As stated above, all patients presented first with molecular relapse and subsequently received DLI either at the same stage, i.e. in molecular relapse (n=85), or upon progression to cytogenetic (n=37), hematologic in chronic phase (n=25) or more advanced phase (n=8) disease (*Online Supplementary Table*

S1). However, 19 patients received another therapy prior to DLI: 16 patients in advanced stage and 3 in molecular relapse (9 had interferon-alpha, 6 hydroxyurea, one hydroxyurea and etoposide, one cytarabine, one imatinib, one mitoxantrone). At the time of analysis, the median follow up after DLI of surviving patients was 46 months (range 3-135 months). Patients' characteristics, type of transplant received, disease stage at time of DLI, acute and chronic GvHD post-transplantation, details of DLI, timing of DLI with respect to the date of transplant, number of DLI, T-cell dose received, interval from relapse to DLI received and reason for giving DLI (i.e. planned, for molec-

Table 3. Multivariate analysis for overall survival.

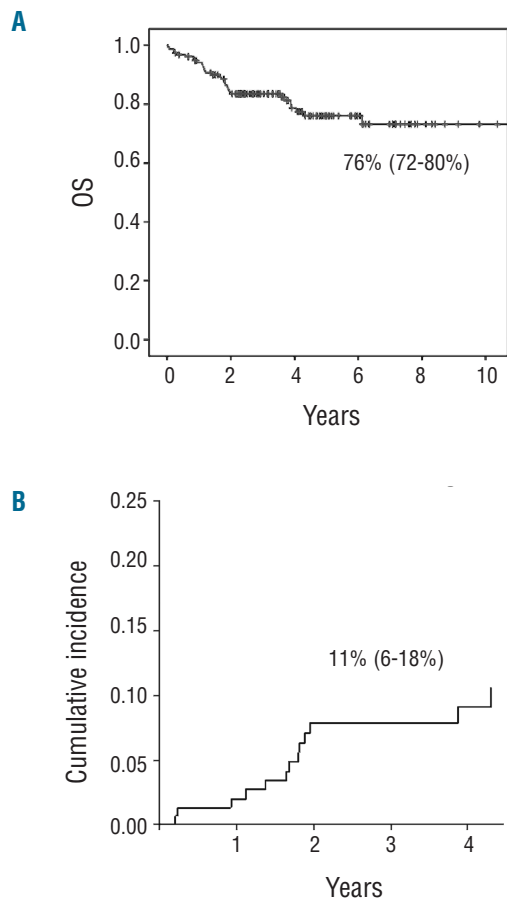| Parameters	HR	Lower 95% CI:	Higher 95% CI:	P value
Time from molecular relapse to DLI >6 months better	0.4	0.19	0.84	0.018
Type of donor Unrelated donor worse	2.54	1.15	5.63	0.021
Type of relapse	1.50	0.69	3.25	0.30

Figure 1. OS and CI of DLI-related mortality. (A) 5 years OS from first DLI of all patients of 76% (95%CI: 72-80%). (B) 5-year CI of DLI-related mortality from first DLI for all patients 11% (95%CI: 6-18%).
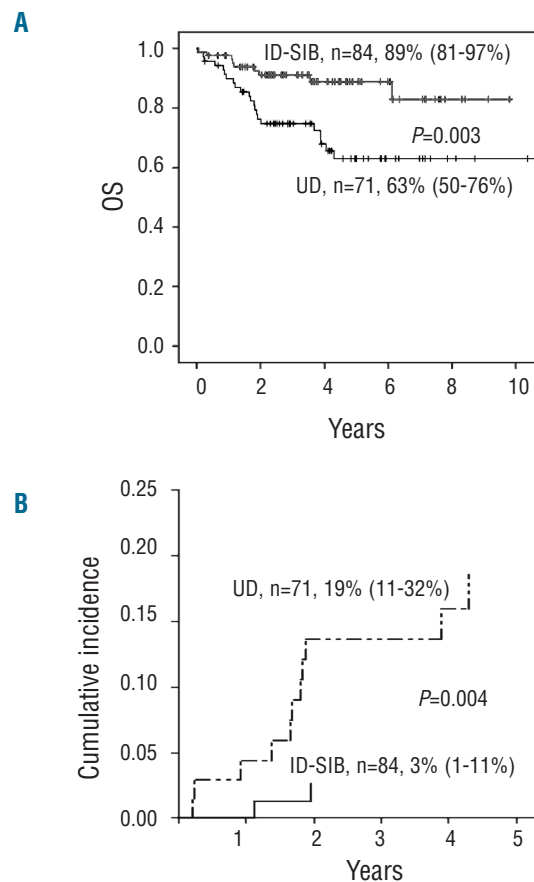

Figure 2. OS and CI of DLI-related mortality. (A) 5-year OS from first DLI from identical sibling of 89 % (95%CI: 81-97 %) *vs.* 63% (95%CI: 50-76%) from unrelated donors; *P*=0.003 (B) 5-year CI of DLI-related mortality from first DLI for identical sibling donors of 3% (95%CI: 1-11%) *vs.* 19% (95%CI: 11-32%) for unrelated donors; *P*=0.004.

ular relapse, for progressive disease) are detailed in the *Online Supplementary Table S1*.

The median time from HSCT to molecular relapse was 239 days (range 30-4274 days), from HSCT to first DLI was 580 days (range 69-4296 days), and from molecular relapse to first DLI was 210 days (range 0-1673 days). A total of 64 (41%) patients received DLI within six months of the detection of the molecular relapse. No information regarding the reasons for receiving DLI early (within 6 months) or late (after 6 months) was available. The median time to DLI administration from transplant for patients treated in molecular relapse, in cytogenetic relapse, in hematologic relapse or in advanced phase were 133 days (range 0-1154 days), 211 days (range 0-1673 days), 335 days (range 134-1526 days), and 405 days (range 180-1019 days), respectively.

Details regarding the outcome of patients who received DLI after molecular relapse are specified in Table 1. The median interval to either molecular, cytogenetic or hematologic response after DLI was 245 days (range 9-1673 days). The median initial cell dose in patients who received DLI for molecular relapse was 5×10^6 CD3$^+$ cells/kg (range 0.01-100) and 40% received only one DLI dose (median 2, range 1-14). On the other hand, for the

patients who received DLI for disease beyond molecular relapse, the median initial cell dose was higher at 10×10^6 CD3$^+$ cells/kg (range 0.5-712.5) and more patients (52%) received only one DLI dose (median 1, range 1-5). Eighty-five percent of the survivors and 68% of all patients included in the study responded to DLI, with the majority of them obtaining complete molecular remission (77% of survivors and 61% of all the patients). Table 2 shows the response rate of patients who received DLI while still in

Table 4. Multivariate analysis for DLI-related mortality.

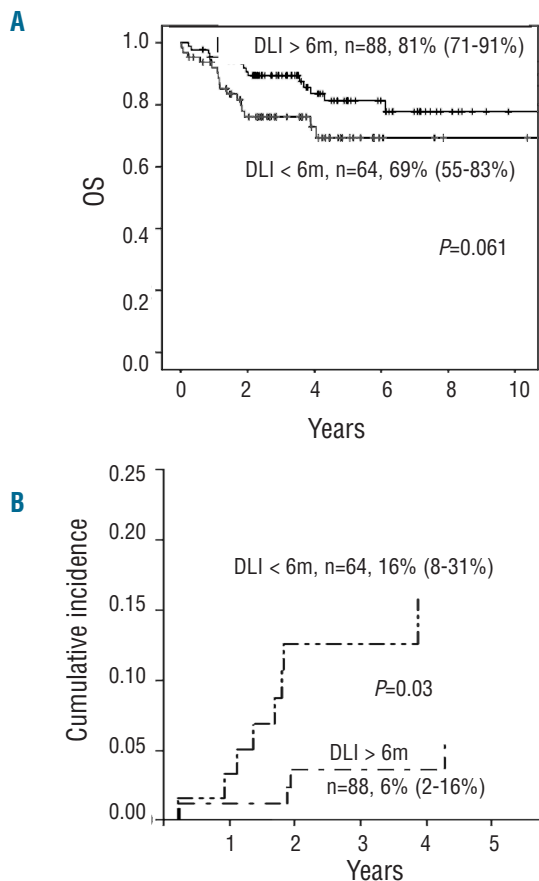| Parameters	HR	Lower 95% CI:	Higher 95% CI:	P value
Time from molecular relapse to DLI >6 months better	0.31	0.09	1.11	0.071
Type of donor Unrelated donor worse	5.78	1.26	26.64	0.024
Disease stage at DLI	0.97	0.29	3.28	0.96

A

B

Figure 3. OS and CI of DLI-related mortality. (A) 5-year OS from first DLI for patient receiving DLI before six months after molecular relapse of 69% (95%CI: 55-83%) *vs.* 81% (95%CI: 71-91%) for patients receiving it after six months; *P*=0.061. (B) 5 years CI of DLI-related mortality from first DLI for patient receiving DLI before six months after molecular relapse of 16% (95%CI: 8-31%) *vs.* 6% (95%CI: 2-16%) for patients receiving it after six months; *P*=0.03.
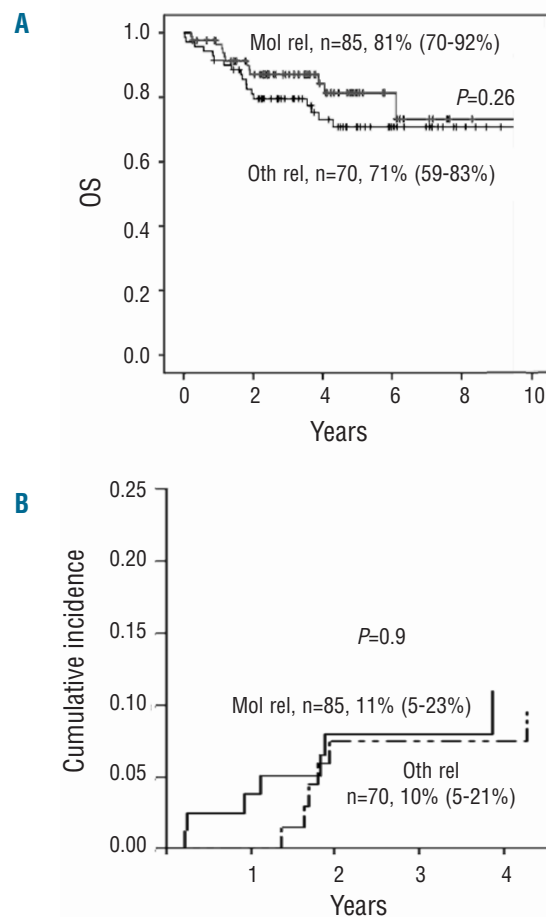
A

B

Figure 4. OS and CI of DLI-related mortality. (A) 5-year OS from first DLI for molecular relapses of 81 % (95%CI: 70-92%) *vs.* 71% (95%CI: 59-83%) for other type of relapses; *P*=0.26. (B) 5-year CI of DLI-related mortality from first DLI for molecular relapses of 11 % (95%CI: 5-23%) *vs.* 10% (95%CI: 5-21%) for other type of relapses; *P*=0.9.

molecular relapse and those receiving DLI after progressing to more advanced phases.

The cumulative incidence of GvHD (acute and chronic) after DLI at five years was 38% (95%CI: 30-48%) which was lower for identical sibling transplants at 27% (95%CI: 18-41%) compared to unrelated donor transplants at 50% (95%CI: 38-66%), (*P*=0.014), with a trend towards a higher incidence at 45% (95%CI: 32-62%) if given within six months of molecular relapse compared to 34% (95%CI: 25-47%) when given beyond six months (*P*=0.1).

The 5-year cumulative incidence of molecular, cytogenetic or hematologic response to DLI was 83% (95%CI: 77-91%), with no differences between the type of donors, 82% (95%CI: 73-91%) and 79% (95%CI: 69-90%) for identical sibling and unrelated donors, respectively, or the time when the DLI was given, 81% (95%CI: 70-92%) and 82% (95%CI: 73-92%) for before or after six months from the time of molecular relapse, respectively.

The 5-year overall survival (OS) post-DLI was 76% (95%CI: 72-80%) for all patients (Table 1 and Figure 1A). The 5-year OS was 89% (95%CI: 81-97%) for identical sibling and 63% (95%CI: 50-76%) for unrelated donors (*P*=0.003) (Table 1 and Figure 2A). There was a trend to better OS when comparing patients who received DLI after six months *versus* those who received it before six months from molecular relapse, 81% (95%CI: 71-91%) and 69% (95%CI: 55-85%) respectively (*P*=0.061) (Table 1 and Figure 3A). There was no statistically significant difference if DLI was given for molecular relapse (81%; 95%CI: 70-92%) or for other type of relapses (71%; 95%CI: 59-83%) (*P*=0.26) (Table 1 and Figure 4).

Death from DLI-related mortality was 11% at five years (95%CI: 6-18%) (Figure 1B) with 80% of the patients alive at last follow up. DLI-related mortality was associated with the type of donor with a 5-year CI of DLI-related mortality significantly worse for patients with unrelated donors (19%; 95%CI: 11-32%) compared to identical sibling donors (3%; 95%CI: 1-11%) (*P*=0.004) (Figure 2B). It was also associated with the timing of DLI, worse when DLI was given within six months of molecular relapse (16%; 95%CI: 8-31%) compared to DLI given later (6%; 95%CI: 2-16%) (*P*=0.03) (Figure 3B). Disease stage at DLI did not have any impact on DLI-related mortality: 11% (95%CI: 5-23%) for patients receiving DLI for molecular relapse and 10% (95%CI: 5-21%) for those receiving DLI for more advanced relapses (*P*=0.9) (Figure 4B).

Thirty-one patients out of 155 died: 15 from relapse, 14 from DLI-related complications (7 from infections, 5 from GvHD and 2 were unknown), and 2 from non-DLI- or CML-related causes.

In a multivariate analysis of OS, the two factors that had an impact were the type of donor (unrelated donors having a worse outcome, i.e. HR 2.54; 95%CI: 1.15-5.53; *P*=0.021) and the time from molecular relapse to first DLI, DLI given after six months being better (HR 0.4; 95%CI: 0.19-0.84; *P*=0.018) (Table 3). Starting dose, prior T-cell depletion, disease stage at DLI, donor recipient sex combination, age and prior acute or chronic GvHD were not significant and in multivariate analysis of DLI-related mortality the only factor that remained statistically significant was the type of donor, unrelated donors having again a worse outcome (HR 5.78; 95%CI: 1.26-26.64; P=0.024) (Table 4). There was a tendency for a better outcome regarding the time from molecular relapse to first DLI for patients receiving DLI after six months post molecular

relapse (HR 0.31; 95%CI: 0.09-1.1; *P*=0.071) (Table 4). Disease stage at DLI was not associated with outcome.

The event free survival post-DLI for the entire group was 63% (95% CI: 57-69%).

Discussion

This study describes the outcome of patients who received DLI after detection of isolated molecular relapse after allogeneic HSCT for CML in a period in which TKI were not widely available and, therefore, DLI was the most commonly used strategy to treat CML patients relapsing after transplantation. It compares the outcome of patients who received DLI for different types of relapses through data extracted from the EBMT registry.

This study has several limitations. It is retrospective, multicentric and spans a period of 20 years (1983-2003). However, very few patients (6%) had received TKI and, therefore, the interpretation of the data is not confounded by TKI therapy. The 155 patients studied are a sample of 1045 patients in the EBMT database treated by DLI for relapse. Again, this cohort was selected for having been diagnosed with molecular relapse after HSCT and having received DLI between 1993 and 2004. A comparison of base-line characteristics and outcome of patients included in this cohort with patients in the database not considered for this study does not show any major differences (*data not shown*). Patients received DLI at different time points, i.e. upon diagnosis of molecular relapse or later. The reasons behind the timing of DLI are not known. This cohort is subject to some potential biases, as we cannot exclude that some patients programmed to receive DLI late did not receive it because of rapid disease progression. Our major finding of less DLI-related mortality in recipients of late as compared to early DLI should not be greatly influenced by this fact. The most appropriate analysis for this type of data is a multistate model capturing all patients at the time of molecular relapse and comparing outcome with different types of intervention. It is obvious that this type of analysis cannot be conducted with the current dataset.

This study confirms previous analyses that showed that DLI is highly efficient in rescuing CML relapsing patients post allogeneic HSCT,[13,14,17,18] that unrelated donors had a worse OS, as did patients receiving DLI prior to six months after relapse,[14,17] and that this poorer outcome was mainly associated to a higher DLI-related mortality.

Unrelated donor transplant patients had a 2.5-fold higher risk of death after DLI when compared to sibling donors and patients receiving DLI more than six months after relapse a 2.5-fold lower risk of death when compared to patients receiving DLI within six months. DLI-related mortality was 5.5-fold higher for unrelated donors and 3-fold lower for patients receiving late DLI.

However, what was interesting and also quite surprising was that giving DLI early after first detection of molecular relapse had similar outcomes in terms of response to DLI, OS or DLI-related mortality as compared to DLI given in more advanced relapse types such as cytogenetic or hematologic relapses. In fact, there was an inverse correlation between timing of DLI and disease stage at DLI as more patients receiving DLI within six months of relapse received them for molecular relapse compared with more patients receiving DLI after six months of relapse who did so at a more advanced disease stage. There also was no

correlation between the time intervals from transplant to relapse and from relapse to DLI suggesting that it was not patients experiencing early relapse who received DLI earlier (*data not shown*). Obviously, we cannot exclude the possibility that patients with a more aggressive relapse (i.e. high and rapidly increasing transcript levels) were predominantly given DLI within six months of the relapse being diagnosed. Conversely, it is also possible that patients who received DLI after six months from diagnosis of relapse had low and stable levels of BCR-ABL transcripts. In addition, the availability of the donor to donate lymphocytes, the spread of the knowledge of the efficacy of DLI over the years, and other reasons may have impacted on the decision to give DLI before or after six months of the detection of the molecular relapse.

Nevertheless, in our hands, donor type and timing of DLI had a strong impact on long-term survival but disease stage at relapse had a smaller impact, and not through DLI-related mortality but through CML-related mortality. To the best of our knowledge, this is the first study that has analyzed this factor in detail. This message is rather counterintuitive as one would normally think that the sooner the treatment for relapse is delivered, the better. This finding may be related to the particular natural course and biology of the disease, as CML is usually a slowly evolving disease and patients in cytogenetic or hematologic relapses will still have some months or years before advancing to blast phase and death. Another contributing factor might be a certain degree of residual GvL effect that would differentiate this situation from a molecular relapse occurring after first-line TKI therapy.

We should very cautiously limit our interpretation to patients who after relapse remain in molecular, cytogenetic or hematologic chronic phase and should not translate our findings into the more advanced phases since there were too few patients in accelerated or blastic phases in our cohort and we could not, therefore, specifically examine these categories. Nevertheless, previous studies have shown that DLI given to patients in CML chronic phase resulted in a better outcome with a survival of approximately 76-79% compared to 12-28% in advanced phases.[5,7]

Another interesting question that follows on from this is that the best moment to give DLI after molecular detection of relapse might not be immediately after it occurs. Our results suggest that it might be possible to follow the patient closely and decide to treat him at a later time point, even after progression to cytogenetic or hematologic chronic phase relapse. This strategy might impact favorably on the DLI-associated mortality as, according to our findings, having DLI later than six months after the detection of molecular relapse might be safer. It seems that, although there is no clear time point that we could recommend, DLI could be postponed despite molecular evidence of relapse and be given no later than in hematologic chron-

ic phase relapse, in line with previous reports that showed that DLI given at least two years after allogeneic HSCT had a lower risk of leading to GvHD.[14,19]

This issue now becomes even more complicated in the era of TKI. Patients could receive TKI for posttransplant relapse[20,21] or DLI or both.[1] If one plans to give both therapies, should they be given sequentially (and in which order) or concomitantly? In addition, whether the use of a TKI at the very early signs of molecular relapse or simply observing untreated molecular relapse could jeopardize the efficacy of subsequent DLI is also an important question.

Nevertheless, these data should constitute the benchmark for a future comparative study of patients treated with TKI at the time of molecular relapse.

Appendix: EBMT centers [center number]

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Authorship and Disclosures

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