Prophylactic and pre-emptive donor lymphocyte infusion in patients with acute myeloid leukemia and myelodysplastic syndrome: validation of current recommendations and proposal of a modified outcome assessment

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Abstract

Prophylactic and pre-emptive donor lymphocyte infusion (pro/preDLI) is used to prevent hematologic relapse of acute myeloid leukemia and myelodysplastic syndromes after allogeneic stem cell transplantation. Given the lack of prospective trials, outcome reports, risk factor analyses and published recommendations on DLI administration have had to rely on information from registry studies, frequently limited by inconsistent reporting and missing data. We, therefore, performed an extensive review of the charts of recipients of pro/preDLI in two German centers to investigate the clinical applicability of current guidelines in a well-defined cohort. Furthermore, as the outcome after pro/preDLI is unsatisfactorily described by conventional parameters, we constructed a model for "treatment success", defined as leukemia-free survival without intensive immunosuppressive treatment for graft-*versus*-host disease (GvHD). Eighty-three patients had received DLI: proDLI (N=36), preDLI for incomplete chimerism (N=27) and preDLI for persisting minimal residual disease/molecular relapse (N=20). According to current guidelines concerning initial T-cell doses and timing of DLI, 42% of patients had received DLI as recommended (standard intensity), whereas 30% had received DLI at lower cell doses and/or at a later timepoint (low intensity) and 28% had received DLI at higher cell doses and/or at an earlier timepoint (high intensity). Two-year rates of overall survival, leukemia-free survival, relapse incidence and non-relapse mortality within the entire cohort were 80%, 67%, 27% and 8%, respectively. One-year rates of high-grade acute/chronic GvHD were 34% and 27%, respectively, among all patients and 53% and 33% after high-intensity DLI. One-year treatment success rates were 72% and 69% after low- and standard-intensity DLI, respectively, in contrast to 34% after high-intensity DLI. Apart from advanced disease at the time of allogeneic stem cell transplantation, high-intensity DLI was the major risk factor for lower overall survival (hazard ratio [HR]=6.12), lower leukemia-free survival (HR=5.43), higher acute GvHD (HR=2.51), and lower treatment success (HR=0.41), supporting adherence to current recommendations.

Introduction

Recurrence of the underlying malignancy remains the most common cause of treatment failure in patients with high-risk acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) undergoing allogeneic stem cell transplantation (alloSCT).[1] After hematologic relapse, less than one third of patients achieve long-term remissions.[2-4] Therefore, for patients in complete hematologic remission after alloSCT with a high risk of relapse, prevention strategies are essential.

Donor lymphocyte infusions (DLI) are given after alloSCT to reinforce the graft-*versus*-leukemia reaction.[5] In overt hematologic relapse, therapeutic effects of DLI were limited.[6] In contrast, the efficacy of DLI given in complete hematologic remission was demonstrated after pre-emptive application (preDLI) to patients with incomplete donor chimerism, minimal residual disease (MRD) and molecular relapse, or as pure prophylaxis for patients with a high-risk of relapse, based on genetics or advanced stage at alloSCT (proDLI).[7-9] Long-term survival rates between 40% and 80% have been reported.[10-13] Pro/preDLI are thus considered effective strategies for relapse prevention in high-risk myeloid malignancies, especially for patients lacking targeted treatment options for post-SCT maintenance.[14,15]

The major clinical drawback of pro/preDLI is the risk of inducing graft-versus-host disease (GvHD), which might be difficult to manage, require prolonged immunosuppressive treatment, and can cause considerable morbidity and mortality.[12] Thus, the art of DLI consists of identifying the sweet spot in which pro/preDLI can be implemented both safely and effectively. In an approach towards standardization of the procedure, an international expert panel on behalf of the European Group for Blood and Marrow Transplantation (EBMT) has provided consensus-based recommendations on the indication, timing, and doses of DLI.[16] However, the level of evidence of such recommendations is limited to a certain extent, given that prospective trials are scarce in the setting of DLI, and most data come from retrospective registry analyses, which differ substantially in their inclusion criteria and methods, and are frequently limited by inconsistent reporting or missing data. Acknowledging these limitations, systematically increasing the number of patients with well-documented, detailed clinical courses before, during and after DLI, has been claimed as a prerequisite for a better understanding and improved clinical application.[16] Accordingly, we performed an exhaustive chart review and analysis of patients with AML and MDS with increased risk of post-transplant relapse, who had received DLI in complete hematologic remission in two German transplant centers. The goal of the study was to assess the role of recommended doses and schedules of DLI for established long-term clinical outcome parameters. Another challenge in the field of alloSCT, particularly after pro/preDLI, is to define clinically relevant outcome parameters. Interpretation of overall survival (OS) and leukemia-free survival (LFS) might be difficult outside of a randomized prospective trial, and outcome variables such as cumulative incidence of GvHD or GvHD-free, relapse-free survival do not consider that certain events such as GvHD might be transient and therefore of subsidiary importance for the final evaluation of treatment outcome. This is of particular relevance in patients with a high risk of relapse, who might be ready to accept a mild degree of GvHD or low-dose immunosuppression, as long as hematologic relapse can be avoided. To address this problem, multistate models, consisting of different states and transitions, have been proposed, as they offer a more comprehensive assessment with the advantage of capturing not only the final clinical outcome, but also assessing temporary states, such as GvHD.[17] These models are able to consider both sequential events and transient, i.e., non-absorbing states. Therefore, in a second part of our study, we constructed a multistate model to illustrate both transient and definitive clinical events occurring after pro/preDLI. Furthermore, we introduced the modified clinical outcome parameter "treatment success", which we defined as being free of leukemia, without GvHD requiring more than low-dose immunosuppressive medication, allowing unrestricted quality of life.

Methods

We included all consecutive adult patients from the centers in Augsburg and Tübingen (Germany) who fulfilled the following criteria: (i) AML or MDS in complete hematologic remission after alloSCT from a matched sibling, matched/mismatched unrelated, or haploidentical donor; (ii) proDLI or preDLI administered between 2007-2021; (iii) no anti-leukemic therapy for relapse prevention after alloSCT other than DLI; and (iv) follow-up after the first DLI (DLI1) ≥100 days. DLI for hematologic relapse or viral infections were excluded. All patients provided informed consent to the use of their clinical data for scientific purposes. The study was approved by the Ludwig-Maximilian University Munich ethics board (N: 22-0865).

Donor lymphocyte infusions

According to local standards, DLI consisted of unmodified $CD3^+$ lymphocyte concentrates. Routinely, donor lymphocytes were collected after alloSCT in a single, unstimulated apheresis, with the first portion (DLI1) administered immediately and the remaining cells cryopreserved in pre-defined, escalating doses. Alternatively, donor lymphocytes were harvested at stem cell collection and all portions were cryopreserved. As suggested,[11,18] prerequisites for pro/preDLI included: (i) cessation of immunosuppressive medication ≥4 weeks before DLI1; (ii) absence of active GvHD; (iii) no history of GvHD grade III/IV after alloSCT; and (iv) no active infection.

Pro/preDLI administration varied by local standards and over time. PreDLI was repeated until achievement of complete chimerism or MRD-negativity. Subsequent DLI were withheld in the case of GvHD grade I/II. No further DLI were given after development of GvHD grade >II. No prophylactic immunosuppression was used.

Intensity of donor lymphocyte infusions

Starting in 2019, expert panels from the EBMT recommended doses and intervals for pro/preDLI[19,20] that have recently been updated by the EBMT Practice Harmonization and Guidelines Committee (Table 1).[16] To validate these recom-

mendations, we defined the variable "DLI intensity" and retrospectively assigned patients to having received either standard-, low-, or high-intensity DLI based on time from alloSCT to DLI1, and the $CD3^+$ cell dose used for DLI1. Accordingly, standard-intensity DLI was defined by $CD3^+$ cell counts and time intervals from alloSCT to DLI1 as recommended. High-intensity DLI was defined as higher $CD3^+$ cell count for DLI1 or first administration earlier after alloSCT than recommended, and low-intensity DLI was defined by lower $CD3^+$ cell count for DLI1 or a longer interval from alloSCT than recommended.

Definitions

ProDLI was defined as DLI in complete hematologic remission with complete chimerism and undetectable MRD. PreDLI-MRD and preDLI-IC were defined as pre-emptive DLI for MRD or incomplete chimerism (without MRD), respectively. Standard-dose immunosuppression was immunosuppressive treatment as per international guidelines for acute or chronic GvHD,[21] whereas low-dose immunosuppression consisted of oral cyclosporine A ≤50 mg/day, or tacrolimus ≤1 mg/day, and/or prednisolone ≤20 mg/day. Treatment success was defined as being alive in complete hematologic remission without GvHD or with mild chronic GvHD not requiring immunosuppression or only requiring low-dose immunosuppressive treatment, without subjective quality-of-life impairment. Further definitions are provided in the *Online Supplementary Methods*.

Statistics

Endpoints included OS, LFS, relapse incidence (RI), leukemia-associated death, non-relapse mortality (NRM), acute and chronic GvHD and treatment success. Follow-up was calculated from the date of DLI1. Standard tests were used for differences in variable distribution, outcome probabilities, and risk factor analysis (details are provided in the *Online Supplementary Methods*). A Markov multistate model was constructed for the assessment of clinical events following DLI over time (Figure 1).

Table 1. Practical recommendations for prophylactic and pre-emptive donor lymphocyte infusion (DLI) by timing and cell dose for the first DLI after allogeneic stem cell transplantation (standard-intensity DLI).

DLI indication/ time since alloSCT	$CD3^+$ cells/kg		
	MSD	MUD	MMUD and haplo
Prophylactic DLI			
3 months	0.1×10^6	0.1×10^6	0.1×10^6
6 months	1×10^6	1×10^6	0.5×10^6
Pre-emptive DLI for IC or MRD			
3 months	$0.1\text{-}0.5 \times 10^6$	0.1×10^6	0.1×10^6
6 months	$1\text{-}3 \times 10^6$	1×10^6	0.5×10^6

DLI: donor lymphocyte infusion; alloSCT: allogeneic stem cell transplantation; CD: cluster of differentiation; MSD: matched-sibling donor; MUD: matched-unrelated donor; MMUD: mismatched-unrelated donor; haplo: haploidentical donor; IC: incomplete chimerism; MRD: minimal residual disease or molecular relapse; kg: kilogram. Modified from Pagliuca *et al.*[16]

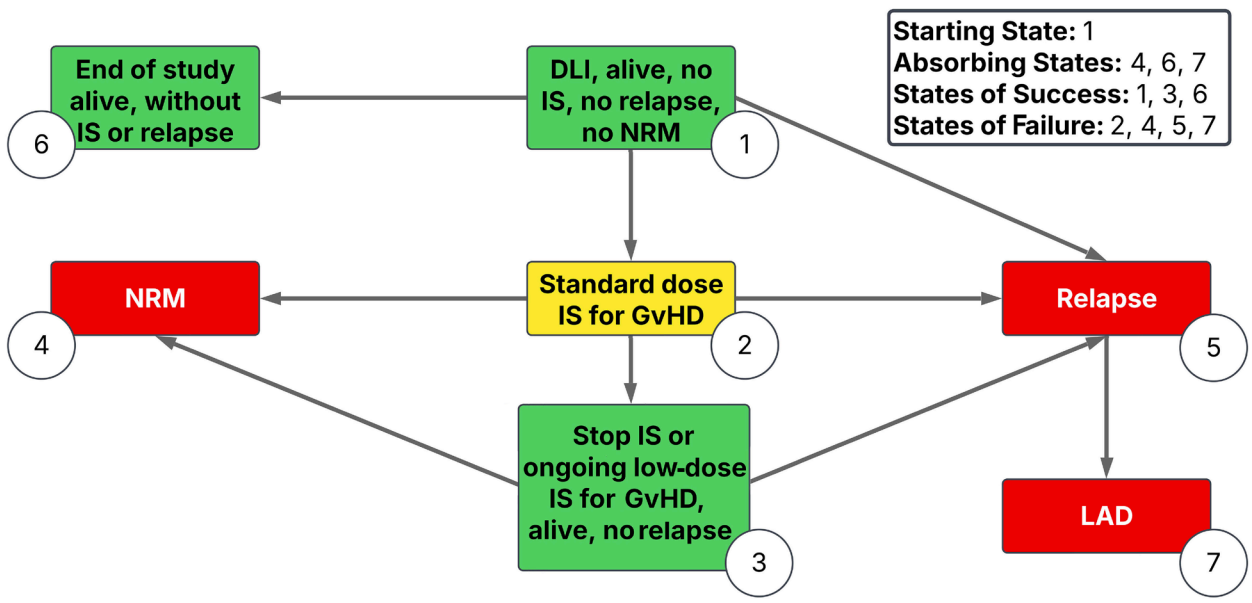

Figure 1. Structure of the multistate model. At time of their first donor lymphocyte infusion (DLI), all patients started in a state of being *alive, without graft-versus-host disease (GvHD) and without relapse* (1). From there, patients could transition into the following states: *standard-dose immunosuppression (IS) for GvHD* (2), *relapse* (5) or *being alive without having received IS for GvHD nor experiencing relapse* (6). Although clinically possible, a transition between state (1) and *non-relapse mortality (NRM)* (4) was not modeled because this transition was not observed in our cohort. Possible transitions for patients in the non-absorbing state (2) included either *stop IS or ongoing low-dose IS* (3), *NRM* (4) or *relapse* (5). From the non-absorbing state (3), patients could pass to *relapse* (5) or *NRM* (4). Patients with a relapse (non-absorbing) could only transition to *leukemia-associated death (LAD)* (7). The cumulative incidence of treatment success was assessed in a competing risk model with relapse, death or standard-dose IS regarded as competing events.

Table 2. Characteristics of the patients and donor lymphocyte infusions according to donor lymphocyte infusion intensity.

Variable	All DLI N=83	Low-intensity DLI N=25	Standard-intensity DLI N=35	High-intensity DLI N=23	*P*
Diagnosis, N (%)					0.7
Acute myeloid leukemia	75 (90)	22 (88)	31 (89)	22 (96)	
Myelodysplastic syndrome	8 (10)	3 (12)	4 (11)	1 (4)	
Center, N (%)					0.10
Augsburg	36 (43)	15 (60)	14 (40)	7 (30)	
Tübingen	47 (57)	10 (40)	21 (60)	16 (70)	
ELN + IPSS classification, N (%)					0.7
Low	6 (7)	3 (12)	2 (5.7)	1 (4.3)	
Intermediate	29 (35)	10 (40)	12 (34)	7 (30)	
High	48 (58)	12 (48)	21 (60)	15 (65)	
Patients' age, years, median (range)	59 (24-76)	62 (53-64)	58 (51-63)	58 (53-64)	0.6
Patients' sex, N (%)					0.1
Female	31 (37)	10 (40)	13 (37)	8 (35)	
Male	52 (63)	15 (60)	22 (63)	15 (65)	
Number of alloSCT, N (%)					0.9
1	75 (90)	22 (88)	32 (91)	21 (91)	
2	8 (10)	3 (12)	3 (9)	2 (9)	
Donor type, N (%)					<0.01
Matched sibling	20 (24)	0 (0)	9 (26)	11 (48)	
Matched unrelated, 10/10	47 (57)	15 (60)	22 (63)	10 (43)	
Mismatched unrelated, 9/10	10 (12)	7 (28)	3 (8)	0 (0)	
Haploidentical	6 (7)	3 (12)	1 (3)	2 (9)	
Donors' age, years, median (range)	39 (28-46)	37 (30-44)	32 (25-47)	45 (33-54)	0.093
CMV status in recipient and donor, N (%)					0.5
Donor neg/recipient pos	18 (22)	7 (28)	9 (26)	2 (9)	
Any other combination	54 (65)	15 (60)	22 (63)	17 (74)	
Unknown	11 (13)	3 (12)	4 (11)	4 (17)	
TCI score, N (%)					0.3
Low, 1-2/RIC	7 (8)	2 (8)	2 (6)	3 (13)	
Intermediate, 2.5-3.5	25 (30)	11 (44)	8 (23)	6 (26)	
High, >3.5/MAC	51 (62)	12 (48)	25 (71)	14 (61)	
T-cell depletion, N (%)					<0.01
Antithymocyte globulin	68 (82)	22 (88)	34 (97)	12 (52)	
No depletion	11 (13)	1 (4)	0 (0)	10 (44)	
PTCy	4 (5)	2 (8)	1 (3)	1 (4)	
Stage at alloSCT, N (%)					0.6
CR	34 (41)	11 (44)	12 (34)	11 (48)	
Active disease: upfront alloSCT, refractory, partial remission	49 (59)	14 (56)	23 (66)	12 (52)	
Year of alloSCT, median (range)	2016 (2014-2019)	2016 (2014-2019)	2016 (2014-2019)	2016 (2009-2019)	0.4
Status day 30+ after alloSCT, N (%)					<0.01
CR with MRD or IC	41 (49)	12 (48)	10 (29)	19 (83)	
Molecular CR and full chimerism	42 (51)	13 (52)	25 (71)	4 (17)	
Acute GvHD after alloSCT, before DLI, N (%)	34 (41)	13 (52)	14 (40)	7 (30)	0.3
Chronic GvHD after alloSCT, before DLI, N (%)	5 (7)	4 (17)	1 (3)	0 (0)	0.068
KPS before DLI, N (%)					0.046
<90	13 (16)	1 (4)	8 (24)	4 (18)	
90-100	68 (84)	24 (96)	26 (76)	18 (82)	
Indication for DLI, N (%)					<0.01
ProDLI	36 (43)	16 (64)	18 (52)	2 (9)	
PreDLI-IC	27 (33)	5 (20)	13 (37)	9 (39)	
PreDLI-MRD	20 (24)	4 (16)	4 (11)	12 (52)	

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Variable	All DLI N=83	Low-intensity DLI N=25	Standard-intensity DLI N=35	High-intensity DLI N=23	*P*
Time to DLI1, months, median (range)	5.9 (1.1-42.9)	8.4 (3.8-22.3)	5.4 (3.9-29.6)	4.7 (1.1-42.9)	<0.01
Total number of DLI, N (%) 1 2 3 4 5	 20 (24) 18 (22) 30 (36) 9 (11) 6 (7)	 3 (12) 5 (20) 12 (48) 5 (20) 0 (0)	 9 (26) 7 (20) 12 (34) 4 (11) 3 (9)	 8 (35) 6 (26) 6 (26) 0 (0) 3 (13)	0.12
DLI1 cell dose, x10^6 $CD3^+$ cells/kg, median (range)	0.20 (0.02-10.0)	0.2 (0.02-0.5)	0.2 (0.2-1.0)	2.4 (0.5-10.0)	<0.01

DLI: donor lymphocyte infusion; ELN: European LeukemiaNet; IPSS: International Prognostic System Score; alloSCT: allogeneic stem cell transplantation; CMV: cytomegalovirus; neg: negative; pos: positive; TCI: transplant conditioning intensity; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; PTCy: post-transplant cyclophosphamide; CR: complete remission; MRD: minimal residual disease; IC: incomplete chimerism; GvHD: graft-*versus*-host disease; KPS: Karnofsky Performance Status; ProDLI: prophylactic DLI; PreDLI-IC: pre-emptive DLI for incomplete chimerism; PreDLI-MRD: pre-emptive DLI for minimal residual disease or molecular relapse; DLI1: first DLI: CD: cluster of differentiation; kg: kilogram.

Results

Patients' characteristics

Eighty-three patients (AML, N=75; MDS, N=8) with a median age of 58.7 years (range, 24.5-76.1 years) were included (Table 2). At the time of alloSCT, all patients had fulfilled one or more of the following criteria defining high-risk disease: unfavorable genetics according to European LeukemiaNet 2022 classification[22] (N=48), secondary AML (N=2), primary induction failure (N=18), persistent MRD/molecular relapse (N=5) or hematologic relapse (N=4) after conventional therapy, and refractory disease or relapse after first alloSCT (N=8). Overall, 49 (59%) had active disease at the last alloSCT. Donors were matched siblings (N=20, 24%), matched unrelated 10/10 (N=47, 57%), mismatched unrelated 9/10 (N=10, 12%) and haploidentical (N=6, 7%).

No uniform conditioning for alloSCT was used; however, 57% of patients had received a sequential protocol based on the FLAMSA reducing intensity conditioning regimen[18] (*Online Supplementary Table S1*). *In vivo* T-cell depletion for GvHD prevention was performed in 72 patients (87%), using rabbit antithymocyte globulin in 68 patients, and post-transplant cyclophosphamide in four. More details are provided in the *Online Supplementary Result*s. Post-transplant immunosuppression included a calcineurin inhibitor in 93% of cases, either in combination with mycophenolate mofetil or methotrexate, to be tapered in the absence of GvHD from day +35 in haploidentical transplant recipients, and from day +56 in the setting of HLA matched donors.

Characteristics of the donor lymphocyte infusions

Fifty-six (67%) patients received unstimulated donor lymphocytes that were collected by a separate apheresis after alloSCT and 27 (33%) patients received donor lymphocytes collected at the time of donor stem cell harvest.

ProDLI was given to 36 (43%) patients, preDLI-IC to 27 (33%), and preDLI-MRD to 20 (24%). Overall, the median time from alloSCT to DLI1 was 5.9 months (range, 1.1-42.9); 6.6 months (range, 3.8-16.3) for proDLI, 5.6 months (range, 3.9-15.4) for preDLI-IC and 5.7 months (range, 1.1-42.9) for preDLI-MRD. The median number of infusions was three (range, 1-5). The reasons for limiting the number of DLI included GvHD (44%), treatment response (31%), physicians' decision/per protocol (17%), and disease progression (8%). The median number of $CD3^+$ cells/kg at DLI1 was 0.2x10^6 (range, 0.02-10.0x10^6). As described above, we retrospectively categorized pro/preDLI intensity based on recent international recommendations (Table 1). Standard-intensity DLI had been given to 35 (42%) patients, 23 (28%) had received high-intensity DLI, and 25 (30%) low-intensity DLI. At DLI1, high-intensity DLI contained a median $CD3^+$ cell count of 2.4x10^6 cells/kg, which was significantly different from that of both standard-intensity DLI (0.2x10^6), and low-intensity DLI (0.2x10^6) (*P*<0.001). Similarly, the median interval from alloSCT to DLI1 was shorter for high-intensity DLI (4.7 months) than for standard- intensity (5.4 months) and low-intensity (8.4 months) DLI (*P*<0.001) (Table 2).

Response to pre-emptive donor lymphocyte infusion

Forty-seven patients received preDLI, of whom 39 (83%) showed a primary response (preDLI-IC: 22/27 [82%]; preDLI-MRD 17/20 [85%]). Only 1/22 (5%) patients initially responding to preDLI-IC developed a hematologic relapse thereafter, in contrast to 5/17 (29%) responders to preDLI-MRD.

Survival and causes of death

The median follow-up from DLI1 among surviving patients was 40 months. The 2-year OS and LFS rates for the entire cohort were 80% (95% confidence interval [95% CI]: 71-90%) and 67% (95% CI: 57-78%), respectively. Divided by type of DLI, the 2-year OS and LFS rates were 81% (95%

CI: 69-96%) and 70% (95% CI: 56-88%), respectively, for proDLI, 88% (95% CI: 77-100%) and 74% (95% CI: 59-93%) for preDLI-IC and 65% (95% CI: 46-93%) and 48% (95% CI: 29-80%) for preDLI-MRD. The overall 2-year cumulative RI (regardless of DLI type) was 26% (24% after proDLI, 19% after preDLI-IC, and 49% after preDLI-MRD). The 2-year NRM for the whole population was 8% (Table 3, Figure 2). At last follow-up, 29 patients (35%) had died. Leukemia was the most frequent cause of death (N=20). Nine patients died in remission. GvHD induced by DLI was lethal in only one patient; however, all patients dying in remission had developed prior GvHD at some point after DLI. Other causes of NRM (N≤2 each) were infections, liver failure from iron overload, pulmonary hypertension, and secondary neoplasia.

Outcome according to donor lymphocyte infusion intensity

The 2-year OS and LFS rates were 87% (95% CI: 75-100%)

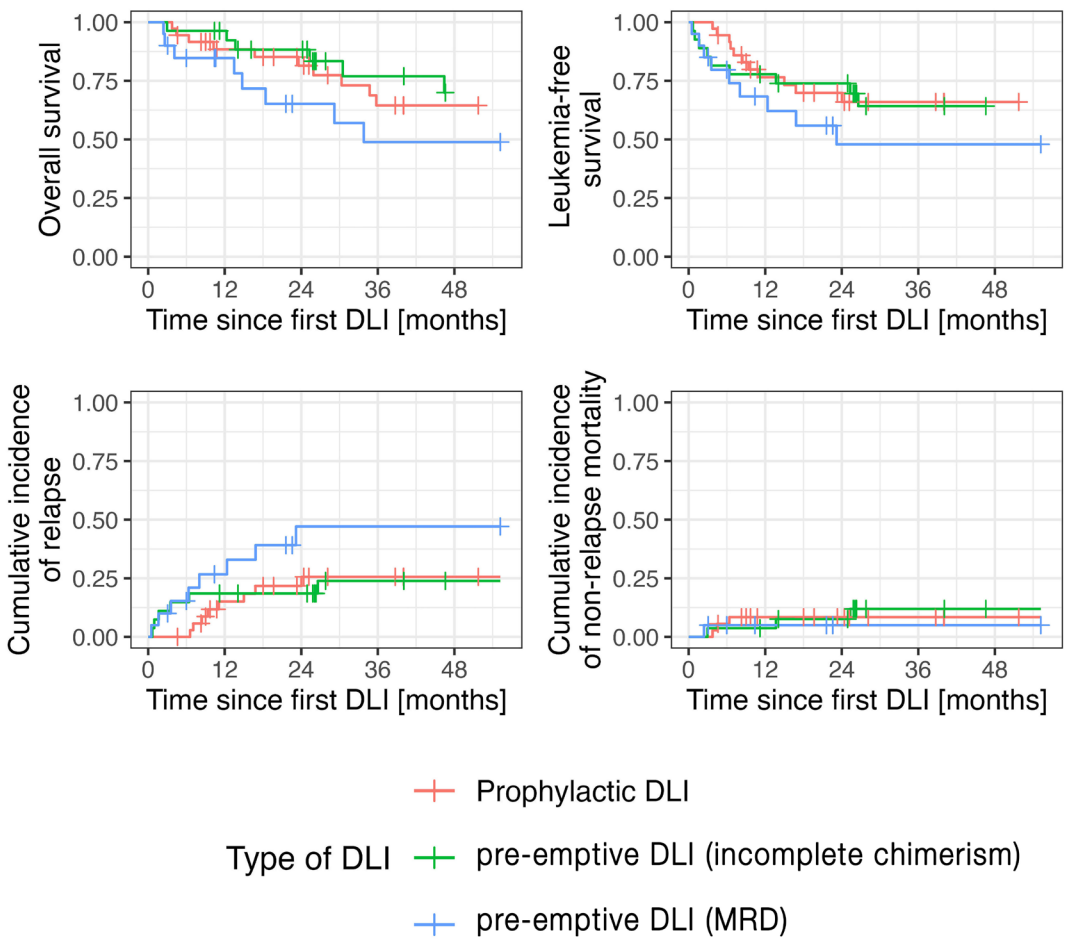

Figure 2. Overall and leukemia-free survival, cumulative incidence of relapse, and non-relapse mortality by indication for donor lymphocyte infusion. DLI: donor lymphocyte infusion; MDR: minimal residual disease or molecular relapse.

Table 3. Summary of clinical outcomes according to donor lymphocyte infusion intensity.

Outcome parameter	% (95% confidence interval)			
	All DLI N=83	Low-intensity DLI N=25	Standard-intensity DLI N=35	High-intensity DLI N=23
2-year OS	80 (71-90)	92 (82-100)	87 (75-100)	54 (35-82)
2-year LFS	67 (57-78)	88 (76-100)	72 (58-89)	30 (15-62)
2-year RI	26 (17-36)	8 (1-23)	22 (10-39)	55 (29-76)
2-year NRM	8 (3-15)	4 (0.3-17)	6 (1-17)	14 (3-33)
1-year acute GvHD grades II-IV	34 (24-44)	24 (10-42)	29 (15-44)	53 (30-72)
1-year chronic GvHD moderate/severe	27 (18-38)	20 (7-38)	30 (15-45)	33 (14-54)
1-year treatment success	61 (49-71)	72 (49-86)	69 (50-83)	34 (15-55)
2-year treatment success	71 (60-80)	84 (60-94)	76 (56-88)	NA

DLI: donor lymphocyte infusion; OS: overall survival; LFS: leukemia-free survival; RI: relapse incidence; NRM: non-relapse mortality; GvHD: graft-*versus*-host disease; NA: not applicable.

and 72% (95% CI: 58-89%), respectively, after standard-intensity DLI, 92% (95% CI: 82-100%) and 88% (95% CI: 76-100%) after low-intensity DLI, and 54% (95% CI: 35-82%) and 30% (95% CI: 15-62%) after high-intensity DLI. The 2-year RI after standard-, low- and high-intensity DLI were 22%, 8% and 55%, respectively. The corresponding figures for 2-year NRM were 6%, 4% and 14% (Table 3, Figure 3).

Graft-*versus*-host disease following donor lymphocyte infusion

The 1-year cumulative incidence of acute GvHD grades I-IV, II-IV, and III-IV were 50% (95% CI: 30-60%), 34% (95% CI: 24-44%), and 16% (95% CI: 9-24%), respectively. The 1-year cumulative incidences of limited, and moderate/severe chronic GvHD were 16% (95% CI: 9-25%) and 27% (95% CI: 18-38%), respectively. The median times from DLI1 to acute GvHD and chronic GvHD onset were 2.3 months (range: 0.1-9.0) and 5.2 months (range, 0.2-25.8), respectively. Of 32 patients requiring standard immunosuppressive treatment for acute or chronic GvHD, 25 (78%) could discontinue the treatment after a median of 10.7 months (range, 0.7-121). At last follow-up, seven patients (8%) still required low-dose immunosuppression as defined above. These patients had received immunosuppressive treatment for a median duration of 17.5 months (range, 9-121). The median time between the start of standard immunosuppressive treatment and transition to low-dose treatment was 8.7 months (range, 1.3-16.7). With respect to DLI intensity, the 1-year cumulative incidence of acute GvHD grades II-IV was 29% (95% CI: 15-44%) after standard-intensity DLI, 24% (95% CI: 10-42%) after low-intensity DLI, and 53% (95% CI: 30-72%) after high-intensity DLI. The 1-year cumulative incidence of moderate/severe chronic GvHD was 30% (95% CI: 15-45%) after standard-intensity DLI, 20% (95% CI: 7-38%) after low-intensity DLI, and 33% (95% CI: 14-54%) after high-intensity DLI (Table 3).

End organs affected by graft-*versus*-host disease and response to immunosuppressive treatment

Clinically significant GvHD requiring systemic immunosuppressive treatment most often affected skin (31%), liver (19%), and oral mucosa (14%). Other organs affected in less than 10% of patients were the lower or upper gastrointestinal tract (7% and 6%, respectively), joints and muscles (7%), eyes (5%) and lungs (5%). Rare manifestations included autoimmune hemolytic anemia, nail dystrophy, sexual organ involvement, and serositis (all 1%) (*Online Supplementary Figures S1* and *S2*).

Regarding the response of GvHD in different organs to treatment in the 32 patients requiring systemic immunosuppressive therapy (most frequently based on steroids and a calcineurin inhibitor), we observed an overall response rate of >80% in most organs. Treatment-refractory GvHD rarely occurred but was observed in the lower gastrointestinal tract (N=2), eyes (N=1), oral mucosa (N=1), liver (N=2), and skin (N=2) (*Online Supplementary Table S2*).

Risk factor analyses

As described above, no major differences in outcome pa-

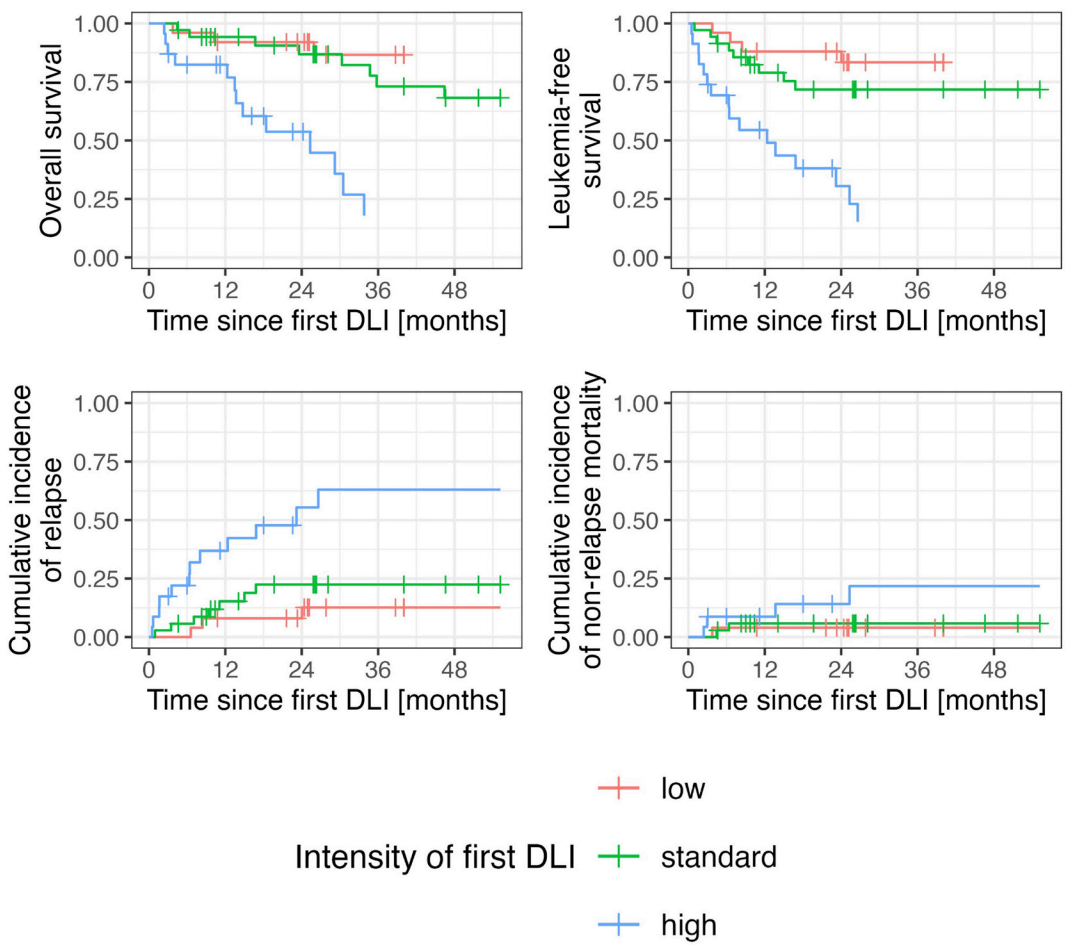

Figure 3. Overall and leukemia-free survival, cumulative incidence of relapse, and non-relapse mortality by donor lymphocyte infusion intensity. See Methods section for definitions of donor lymphocyte infusion intensity. DLI: donor lymphocyte infusion.

rameters were observed between recipients of standard- or low-intensity DLI. Therefore, the two cohorts (N=60) were combined for risk factor analysis and compared to patients receiving high-intensity DLI (N=23). Univariate analysis of risk factors for OS, LFS, NRM and GvHD are shown in *Online Supplementary Table S3*.

In multivariable analysis, active disease before alloSCT and high-intensity DLI were associated with worse outcomes. The hazard ratios for OS, LFS, and RI in patients with active disease were 2.81 (95% CI: 1.2-6.5; *P*=0.018), 2.88 (95% CI: 1.2-6.4; *P*=0.010) and 3.19 (95% CI: 1.3-7.7; *P*=0.011), respectively. The hazard ratios for OS, LFS, and RI in patients given high-intensity DLI were 6.1 (95% CI: 2.7-13.6; *P*<0.001), 5.43 (95% CI: 2.6-11.2; *P*<0.001); and 4.77 (95% CI: 1.9-11.4; *P*<0.001) for OS, LFS and RI, respectively. A multivariable risk factor analysis for NRM could not be performed due to the low number of events.

High-intensity DLI was the only significant risk factor for acute GvHD grades II-IV (HR=2.51, 95% CI: 1.2-5.2; *P*=0.015). Low numbers of affected patients precluded a risk factor analysis for chronic GvHD. The results of multivariable analysis for clinical outcome parameters are shown in Table 4.

Although MRD status after alloSCT was not a significant factor for RI in multivariable analysis, we conducted an exploratory risk factor analysis excluding patients who had received preDLI-MRD (N=20) to analyze the effects of DLI intensity on outcome parameters in a more homogeneous cohort. In this selected subgroup (proDLI and preDLI-IC, N=63), results obtained in the entire cohort were confirmed, with active disease before alloSCT and high-intensity DLI remaining significant risk factors for worse OS and LFS. DLI-induced GvHD (acute or chronic, any grade, calculated as a time-dependent covariate) was associated with a significant reduction of RI among these patients (HR=0.27, 95% CI: 0.08-0.9; *P*=0.039). Again, a low number of events precluded a risk factor analysis for NRM (see *Online Supplementary Table S4* for details). Finally, consistent with the results described above, among recipients of preDLI-MRD (N=20), relapse rates were 0% after low- or standard-intensity DLI, and 67% after high-intensity DLI.

Exploratory analyses of donor lymphocyte infusions after haploidentical and HLA-mismatched allogeneic stem cell transplants

Sixteen patients had received DLI after alloSCT from a haploidentical or a 9/10 HLA-mismatched donor. Clinical outcomes in this selected cohort were not remarkably different from those of the whole cohort of patients. A detailed description is provided in *Online Supplementary Table S5*.

Multistate model analysis and proposal of treatment success as an outcome parameter

A multistate Markov model was constructed to evaluate important clinical events after DLI. Figure 4 shows the probabilities over time of being in the previously described

Table 4. Multivariable analyses of overall survival, leukemia-free survival, relapse incidence, graft-*versus*-host disease and treatment success.

Variable	HR	95% CI	*P*
Overall survival			
Stage before alloSCT Complete remission (baseline) Active disease	- 2.81	- 1.2-6.5	- 0.018
DLI intensity Low or standard (baseline) High	- 6.12	- 2.74-13.6	- <0.001
Indication for DLI ProDLI or preDLI-IC (baseline) PreDLI-MRD	- 1.92	- 0.78-4.75	- 0.159
Stage at day +30 after alloSCT Molecular CR, full chimerism (baseline) CR with MRD or IC	- 1.27	- 0.54-2.97	- 0.589
Leukemia-free survival			
Stage before alloSCT Complete remission (baseline) Active disease	- 2.88	- 1.29-6.40	- 0.010
DLI intensity Low or standard (baseline) High	- 5.43	- 2.64-11.2	- <0.001
Relapse incidence			
Stage before alloSCT Complete remission (baseline) Active disease	- 3.19	- 1.31-7.78	- 0.011
DLI intensity Low or standard (baseline) High	- 4.77	- 1.99-11.4	- <0.001
Indication for DLI ProDLI or preDLI-IC (baseline) PreDLI-MRD	- 1.44	- 0.59-3.53	- 0.420
DLI-induced GvHD No GvHD (baseline) GvHD	- 0.46	- 0.18-1.20	- 0.110
Acute GvHD grades II-IV			
Patients' age, every 10-year increase	1.62	0.95-2.75	0.077
DLI intensity Low or standard (baseline) High	- 2.51	- 1.20-5.27	- 0.015
Treatment success			
Stage before alloSCT Complete remission (baseline) Active disease	- 0.55	- 0.38-0.81	- 0.002
DLI intensity Low or standard (baseline) High	- 0.41	- 0.2-0.84	- 0.016

HR: hazard ratio: 95% CI: 95% confidence interval; alloSCT: allogeneic stem cell transplantation; DLI: donor lymphocyte infusion; proDLI: prophylactic DLI; preDLI-IC: pre-emptive DLI for incomplete chimerism; preDLI-MRD: pre-emptive DLI for minimal residual disease or molecular relapse; CR: complete remission; GvHD: graft-*versus*-host disease.

absorbable and non-absorbable states, out of which the states marked in green represent "treatment success" as defined above. Accordingly, in the entire cohort the 1- and 2-year probabilities of treatment success were 61% (95% CI: 49-71%) and 71% (95% CI: 60-80%), respectively, thereby increasing over time due to improving/resolving GvHD. With respect to DLI intensity, the rates of treatment success at 1 and 2 years were 69% and 76% after standard-intensity DLI, and 72% and 84% after low-intensity DLI, respectively. In contrast, the treatment success rate after high-intensity DLI was 34% at 1 year (2-year analyses were not possible due to the low number of events) (Table 3). In multivariable analysis, active disease before alloSCT (HR=0.55, 95% CI: 0.3-0.8; *P*=0.002) and high-intensity DLI (HR=0.4, 95% CI: 0.2-0.8; *P*=0.016) were associated with significantly reduced probabilities of treatment success (Table 4, univariate analysis in *Online Supplementary Table S3*).

Discussion

Patients with high-risk AML and MDS achieving complete hematologic remission after alloSCT require effective and safe relapse prevention strategies. Particularly in patients without targeted treatment options, pro/preDLI is a frequently used strategy, but carries the risk of severe, potentially life-threatening GvHD, or might be detrimental for the patients' quality of life. The concept of separating graft-*versus*-leukemia effects from GvHD through delayed DLI administration until establishment of complete donor chimerism and by escalating dose schedules has optimized DLI use and mitigated the risk of (severe) GvHD. As a general problem in the field, the lack of prospective trials, as well as missing data and inconsistencies within retrospective registry studies (e.g., concerning cellular composition of the inoculum, cell-subset selection, timing and dosing) complicate the interpretation of reported results and treatment standardization. During recent years, expert panels have developed consensus-based recommendations for the use of pro/preDLI focusing on $CD3^+$ doses and the interval from alloSCT to the first DLI. Nevertheless, these guidelines remain limited by the absence of systematic validation studies and the overall low degree of supporting evidence. Against this background, we took advantage of extremely detailed documentation for 83 consecutive pro/preDLI recipients at two transplant centers that have used DLI for relapse prevention in high-risk AML and MDS for many years. Variations in local DLI standards over time allowed us to compare different strategies with respect to DLI timing and cell dosing, facilitating validation of current recommendations. Overall outcomes in our study confirmed published data on pro/preDLI,[12] demonstrating the representativeness of our cohort. With respect to DLI intensity, earlier application or higher $CD3^+$ cell doses were clearly associated with an increased risk of clinically significant GvHD and inferior OS and LFS. Hence, in the setting investigated here (infusion of unmodified $CD3^+$ cells without GvHD prophylaxis), higher $CD3^+$ cell doses or administration earlier than recommended after alloSCT[16] (Table 1) should definitively be avoided. An estimated higher

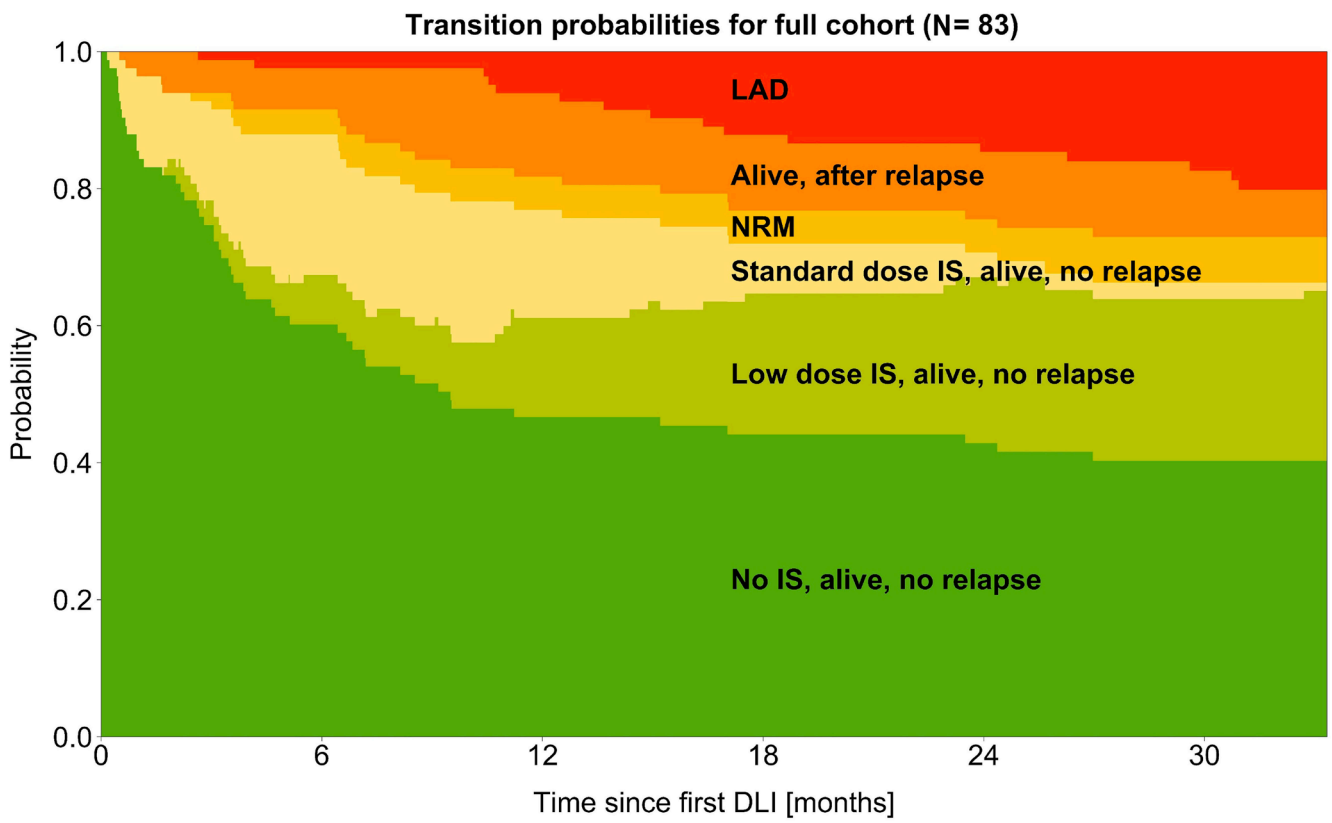

Figure 4. Multistate model for the analysis of clinical events over time after prophylactic or pre-emptive donor lymphocyte infusions. The green areas represent states fulfilling the criteria for treatment success, defined as being alive, without relapse and with no or only low-dose immunosuppression for graft-*versus*-host disease. LAD: leukemia-associated death; NRM: non-relapse mortality; IS: immunosuppression; DLI: donor lymphocyte infusion.

relapse risk, even in the case of MRD or molecular relapse, may not justify the decision to increase pro/preDLI intensity, since it does not improve outcomes, but substantially increases the risk of GvHD and its associated toxicity.

In contrast, excellent outcomes could be demonstrated when DLI was administered according to the recommended schedule and dosing. Among patients receiving either standard- or low-intensity DLI, 2-year OS and LFS rates were 92% and 88%, respectively, after low-intensity DLI, and 87% and 72% after standard-intensity DLI, underscoring the safety and the promising outcomes that can be obtained by following current recommendations. Although the overall incidence of GvHD after pro/preDLI was considerable (50%), systemic immunosuppression was only required by about two-thirds of affected patients and, over time, 78% could either discontinue or switch to low-dose immunosuppressive treatment. All patients requiring low-dose immunosuppressive treatment at last follow-up (8%) reported no or minimal complaints related to GvHD or its treatment.

Clinical results were comparable among patients receiving DLI as recommended and those receiving low-intensity DLI, suggesting - within the limitation of small numbers - the possibility of eventually further reducing recommended cell doses. Alternative DLI modifications, such as granulocyte colony-stimulating factor-mobilized DLI, infused as early as day +30 after alloSCT, together with ongoing or newly initiated immunosuppression[23,24] or low-dose DLI, repeated without dose escalation up to a median number of eight infusions over a period of up to 36 months,[25] have been proposed.

In a second part of our study, we applied a Markov multistate model to illustrate the clinical course after pro/preDLI over time and introduced the outcome variable "treatment success" to allow for a more real-life based estimate of patients' outcomes. In the DLI setting, the value of classical endpoints might be limited due to their inability to consider that certain events, in particular GvHD, might be either transient or at least well controlled in a way that they do not impair the quality of life of affected patients. Patients with a high risk of relapse might be ready to accept a certain degree of GvHD or low-dose immunosuppression, as long as hematologic relapse can be avoided. In contrast, induction of severe GvHD might profoundly reduce quality of life, even in the absence of leukemia relapse, thereby questioning DLI as a relapse prevention strategy with acceptable side effects.

Taking advantage of the pioneering work by the group from Leiden,[17] we analyzed treatment success as an outcome parameter, defining it as being free of leukemia without GvHD requiring more than mild immunosuppressive medication, and with unrestricted quality of life. With a median follow-up of 40 months from DLI1, treatment success at 2 years was achieved by 71% of patients, with a considerable proportion of patients entering the success state after developing transient high-grade GvHD. Within the model, both the direct transition from start to final success and the transient state of "standard-dose immunosuppression for GvHD" contributed most to the differences in outcome between the two intensity groups (*Online Supplementary Table S6*). The model also showed how a subset of patients who relapsed early after pro/preDLI (hence not fulfilling the definition of treatment success) were alive at last follow-up, reflecting the potential of the model for further analyses of long-term outcomes even after relapse.

Our model differs from the application introduced by the colleagues from Leiden, which had been designed to describe how alloSCT outcomes are influenced by subsequent DLI. In contrast, our model was developed to consider transient events occurring after DLI. In general, the outcome parameters illustrated by multistate models are more flexible and informative than rigid endpoints such as LFS or the cumulative incidence of relapse or GvHD/RI, which are terminal. By allowing a more real-life based description of treatment success following pro/preDLI, the approach underscores the model's applicability for the description of events and outcome parameters in the context of maintenance treatments after alloSCT.

Regarding the influence of DLI intensity on treatment success, in the cohort of patients who had received pro/preDLI in line with current recommendations, treatment success rates after 2 years were 76% and 84% among those receiving standard- and low-intensity DLI, respectively (difference not statistically significant), with limited requirement of standard immunosuppression for the treatment of GvHD, and very low NRM rates. Exploratory analyses showed successful and early discontinuation (>90%) of immunosuppression for GvHD in patients receiving standard- or low-intensity DLI.

Limitations of our study include its relatively small sample size, its essential restriction to the setting of *in vivo* T-cell depletion, and its retrospective nature, which did not allow identification of why other transplant recipients had not been assigned to pro/preDLI. Hence, no comparative analysis of the clinical efficacy of pro/preDLI could be performed. Furthermore, a certain heterogeneity in DLI1, i.e., cryopreserved *versus* fresh infusion, with some products obtained following administration of granulocyte colony-stimulating factor stimulation to the donor, needs to be accounted for. Nevertheless, although a theoretical influence of these inconsistencies on the efficacy and safety of DLI cannot be excluded, this is not supported by the literature.[5,26] In addition, due to the study design, which excluded patients who had received additional medical treatment, no data about potential synergisms between DLI and other types of maintenance therapy can be provided, although they are suggested by published data.[5,27] In particular, in patients with *FLT3* mutations, the use of sorafenib or gilteritinib might confer synergistic effects with regard to relapse prevention.[28,29] Finally, patients' quality of life was not systematically evaluated using questionnaires or scores established in the alloSCT setting, which, however,

have not been validated in the context of DLI.
In summary, with respect to overall outcome, our results confirm previous observations on pro- and preDLI with high rates of treatment success. Adherence to current EBMT recommendations[16] can significantly reduce the risk of GvHD and its associated morbidity and mortality, and leads to superior outcomes. The application of a multistate model might help to describe the clinical course and treatment success of DLI recipients more precisely.

Disclosures
No conflicts of interest to disclose.

Contributions
GFV and CS obtained ethical approval and performed the literature search. GFV and JFW collected data from clinical charts. MM, CL, WB, MT, MC and CS contributed clinical data and provided logistical support for data collection. AR, TA, SS and GM performed statistical analyses. AR served as the primary statistician, supervised by GM. GFV, JFW and AR created and edited the tables and figures. Figures were mainly prepared by AR with support from TA and SS. GFV, JFW, AR, MC and CS were involved in study conception, data analysis, and interpretation. MC and CS supervised the study as senior authors. GFV and CS drafted the manuscript. JFW, AR, WB, MM and MC revised it critically. All authors approved the final version and submission.

Data-sharing statement
All data generated or analyzed during this study are included in this published article and its supplementary information files. Additional data are available from the corresponding author upon reasonable and justified request.

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