Development of leukemia in donor cells after allogeneic stem cell transplantation–a survey of the European Group for Blood and Marrow Transplantation (EBMT)

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Leukemia in donor cells (donor cell leukemia; DCL) has been reported as a rare but severe complication of allogeneic stem cell transplantation (SCT). However, the incidence, potential pathogenetic factors, therapeutic options and outcome of patients suffering from DCL and the leukemia risk of their donors are not well defined. A questionnaire survey was carried out within European Blood and Marrow Transplantation Group (EBMT) centers. Ninety-one EBMT centers participated in this survey, covering 10489 allogeneic SCT between 12/1982 and 09/2003. Fourteen cases of DCL, most with a myeloid phenotype (7 cases of acute myeloid leukemia, 3 each of acute lymphocytic leukemia and 1 case of chronic myeloid leukemia) were identified. Demonstration of donor cell origin included molecular analysis of chimerism in most cases. DCL type and cytogenetic alterations were independent from the original disease. The median time between transplantation and diagnosis of DCL was 17 months (4–164). No type of conditioning, donor, graft manipulation, graft-versus-host disease prophylaxis or subsequent complications were identified as risk factors for DCL. Chemotherapy induced remissions in DCL and 2 of 5 patients remain alive in remission after a second transplant. None of the stem cell donors developed hematologic malignancies (median follow-up period of 9 years; range 6-30 years). DCL is an extremely rare complication of allogeneic SCT in which treatment attempts with chemotherapy and a second SCT are justified. Donors are not at an increased risk of developing hematologic malignancies.

Key words: donor cell leukemia, bone marrow transplantation, stem cell transplantation, relapse.

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Hematopoietic stem cell transplantation (SCT) may be complicated by disease relapse or the development of secondary malignancies.[1] A rare complication is the occurrence of leukemia or myelodysplasia in donor cells. Since the first publication describing a case of a donor cell leukemia (DCL) in 1971,[2] several other cases of DCL have been reported.[3-15] However, taking into account the increasing number of stem cell transplants, DCL appears to be a very rare complication.[16] Despite its rarity, this complication has attracted great interest from both basic researchers and clinicians as the development of leukemia or myelodysplasia in apparently healthy donor cells after transplantation into a leukemic host may provide some insights into the mechanisms of leukemogenesis. Early reports on leukemia development in donor cells resulted in a debate on the appropriate methods for demonstrating the donor type of the relapsed leukemia. Cases in which donor cell leukemia was suspected based on the demonstration of the opposite sex chromosomes at relapse in sex mismatched transplantation could not be confirmed by more sensitive tests, such as fluorescent *in situ* hybridizatioon (FISH) and molecular testing of chimerism.[17-19] On the other hand, more frequent monitoring of hematopoietic chimerism after SCT and at the time of relapse by these molecular techniques could lead to the detection of a higher number of DCL, which were not suspected using other techniques.[20]

Other important questions regarding DCL are whether donors have an increased risk of developing leukemia and whether donors should be informed, closely monitored and eventually treated. These questions are of special interest in

the setting of unrelated transplants. Finally, treatment options for patients with DCL are presently unclear. To provide some insights into these questions, the subcommittee on complications within the *Chronic Leukemia Working Party* of the *European Group for Blood and Marrow Transplantation* (EBMT) carried out a questionnaire survey within EBMT centers to evaluate this rare complication.

Methods

A questionnaire was sent by e-mail to all centers registered at the EBMT. Centers were asked to report whether a proven or suspected case of donor cell leukemia/myelodysplasia had been observed in their center and to report the total number of allogeneic SCT performed during the observation period. Centers in which a case of DCL had been observed or suspected were asked to fill in a second detailed questionnaire including information about the characteristics of the original disease, the DCL, the patient and donor, the transplantation procedure, the methods used to demonstrate the donor cell origin of the leukemia/myelodysplasia and the treatment given. EBMT centers which had published a case of DCL were asked to provide the above listed information in addition to the data already published. In a second round, the centers reporting a case were again contacted to provide updated information or clarify unclear topics in the original questionnaire.

Ninety-one centers responded and 12 DCL cases from 11 centers were reported. Two centers which initially reported not having observed any DCL cases, each later reported one current case. Thus, a total of 14 DCL cases were identified, 7 of which had been published prior to this survey or were published during it and 7 *new* cases. All centers contributing DCL cases to this survey are listed in Table 1.

Results
Cases of donor cell leukemia/myelodysplasia

A total of 14 cases of donor cell leukemia/myelodysplasia from 13 centers were identified. The cases are listed in Table 1 in order of the year that the DCL was diagnosied. The 91 centers that responded to the questionnaire reported having performed a total of 10489 allogeneic stem cell transplantations at the time of evaluation, which results in an estimated incidence of 124 DCL per 100,000 transplants. The transplants were performed between 1975 and 1998 and the DCL cases occurred between December 1982 and September 2003. Six cases of DCL occurred prior to 1991 and eight cases since 1991. Considering the increasing number of allogeneic stem cell transplants performed within this time period, the data do not indicate an increase in the incidence of DCL in more recent years.

Characteristics of donor cell leukemia/myelodysplasia

Of the 14 cases of donor cell leukemia / myelodysplasia, seven were acute myeloid leukemia (AML), three were acute lymphoblastic leukemia (ALL), three were myelodysplasia (two of these patients progressed to develop AML and one later received chemotherapy for AML; see below) and one was chronic myeloid leukemia (CML). The original diseases for which transplants were performed included AML (n=6), ALL (n=2), aplastic anemia (n=2) and CML (n=4). The relationships between original disease and DCL are shown in Figure 1. This figure indicates that AML, ALL and myelodysplasia occurred after transplantation for AML, ALL, severe aplastic anemia and CML. The single case of donor cell CML was diagnosed in blast crisis and occurred after transplantation for CML in blast crisis.

The median age of the patients developing DCL was 27 years at transplant, with a range from 12 to 56 years. Nine patients were female and five male. The median time between transplantation and the occurence of DCL was 17 months, with a range of 4 to 164 months. The time spans for the different types of DCL with respect to the original disease are shown in Table 1.

Demonstration of donor cell origin

Centers were asked whether the donor cell origin of the observed leukemia/myelodysplasia after transplantation was considered to be proven or suspected. Twelve centers reported their case as proven, one center as suspected and one center did not give a statement.

The diagnosis of DCL was based on sex mismatch in six cases. Sex mismatched SCT was performed in 10/14 cases. In seven cases a male donor was used in female patients and in three cases transplants from female donors were given to male recipients. In two cases, the demonstration of female cells in male recipients was used to show donor origin. In four cases, male leukemic cells in female recipients were considered evidence for the donor cell type. To exclude an overgrowth of normal donor cells, attempts were made to demonstrate that the male cells represented the malignant cell population. In two cases, this was achieved by demonstrating additional abnormalities together with the Y chromosome. In one of these patients with AML, an add(3) and a del(12) was demonstrated in the male cells. The other patient developed B-ALL and showed a 6q- aberration in the male cells. In one patient, the Y chromosome was directly demonstrated in the blasts by FISH analysis. Molecular techniques (variable number of tandem repeats, VNTR; short tandem repeats, STR) were used

Table 1. Characteristics of the patients, the donor cell leukemia and tthe methods used to demonstrate the donor type. DCL cases are listed in order of the year of diagnosis.

Case	CIC/City	DCL	Diagnosis of DCL	Transplant Date	Prim. Diagnosis	Time (months) Transpl.-DCL	Age (yrs.) at transplant	Sex R	Sex D	Donor	Cytogenetic analysis	Molecular analysis	Additional Tests
1	217/ Genova	CML (BC)	12/82	08/82	CML (BC)	4	25	F	M	id brother	46xy t(9;22)	MS/STR	–
2	256/ Kiel	ALL	09/84	05/82	ALL	28	25	F	M	id brother	46xy 6q-	no	cytogenetic aberration in cells with donor karyotype
3	281/ London	ALL	04/88	03/87	AML	13	18	F	M	id brother	46xy	no	FISH
4	258/ Jerusalem	AML	12/88	09/87	ALL	15	24	F	M	id brother	46xy t(8;21)	no	cytogenetic aberration in cells with donor karyotype
5	202/ Basel	ALL	01/89	02/75	AML	164	16	M	F	id sister	46xx	no	
6	257/ Dublin	AML	02/90	05/89	SAA	9	21	M	F	id cousin	46xx t(9;11)	STR	cytogenetic aberration in cells with donor karyotype
7	258/ Jerusalem	MDS	07/91	03/91	AML	4	28	F	M	id brother	46xo	STR	
8	279/ Monza	AML	08/92	01/91	SAA	19	12	F	F	id sister	46xx	STR	STR in BFU-E and CFU-E
9	234/ Brussels	AML	07/97	02/97	AML	5	35	F	M	id brother	46xy add3, del 12	no	cytogenetic aberration in cells with donor karyotype
10	614/ Hamburg	MDS→AML	11/97	08/94	AML(M6)	39	34	M	F	id sister	46xx	VNTR	
11	259/ Essen	AML	07/99	12/92	AML	78	47	F	F	id sister	46xx	VNTR	
12	295/ Hannover	AML	01/00	11/98	CML (CP)	14	40	M	M	MUD	46xy	VNTR	VNTR in sorted cells BCR-ABL PCR negative
13	311/ Wiesbaden	AML	07/01	05/98	CML (BC)	39	35	M	M	MUD	46xy t(15;17)	STR	cytogenetic aberration in cells with donor karyotype BCR-ABL-RT PCR negative
14	808/ Dresden	MDS→AML	09/03	02/98	CML (CP)	67	56	F	M	id brother	45xy,-6,-7,- 11, der(17),-18	STR	–

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; SAA: severe aplastic anemia; CP: chronic phase; BC: blast crisis; CIC: center identification code; DCL: Donor cell leukemia; id: HLA-identical; MUD: matched unrelated donor; M: male; f: female; FISH: fluorescence in situ hybridization; MS: microsatellites; PM: polymorphism marker; STR: short tandem repeats; VNTR: tandem repeats.

to demonstrate the donor cell origin of the leukemia in nine cases. In five cases these analyses were performed in addition to demonstration of the donor cell origin by sex mismatch. In one patient who developed AML after transplantation for chronic phase CML, the absence of BCR-ABL mRNA demonstrated by reverse transcription polymerase chain reaction was used as an additional marker for the occurrence of a new leukemia in donor cells. The methods used to demonstrate the donor cell origin in the individual patients are shown in Table 1.

Donors and transplant procedure

Donors were HLA-identical siblings in 11 cases, an HLA-identical cousin in 1 case and unrelated to the recipients in two cases. The median age of the donors was 35 years (range 16-57). A bone marrow examination was performed in three of the donors and an additional cytogenetic analysis was carried out in one patient. The results were normal in all cases. Additionally, there was no report on the development of a leukemia or myelodysplasia in any of the donors. This finding was confirmed by a second

Table 2. Initial transplantation and treatment of DCL.

Case	Conditioning	Graft	TCD	GvHD-Prophylaxis	GvHD Acute/chronic	Chemotherapy	Result	2nd BMT	Outcome	References
							Treatment of DCL			
1	TBI/CP	BM	no	CSA	no/no	no	progression	no	death	7,28
2	TBI/CP	BM	yes	MTX	no/no	ARA-C/ MITOX	CR	no	CR (1.6 years) relapse, death	10
3	CP/TBI/ARA-C	BM	yes	none	grade II/no	LASP/VCR	CR	no	CR (1.9 years) relapse, death	23
4	CP/VP/MEL/ ARA-C/TBI/TLI	BM	yes	CSA	no/no	CP/IL-2/ ARA-C/DNR		no	death	—
5	CP/TBI	BM	no	MTX	no/no	Local irradiation	remission	yes	death, VOD	—
6	CP/ATG	BM	no	CSA/MTX	no/no	TAD	CR	yes	death, MOF	15
7	CP/VP/MEL/ ARA-C/TBI/TLI	BM	yes	CSA	no/no	no	—	no	alive (9+ years)	22
8	CP-CP/ TLI/ ATG	BM	no	CSA	no/no	DNR/ARA-C	progression	no	death	29
9	BU/CP	PBPC	no	CSA/MTX	no/no	no	—	yes	Progression, death	—
10	BU/CP/VP	BM	no	CSA/MTX	no/no	HAM	CR	yes	CCR (5.2+ years)	—
11	BU/CP	BM	no	CSA	no/limited	HAM	aplasia	no	death	—
12	BU/CP	BM	no	CSA/MTX	grade I/no	MTC	CR	yes	CCR (4+ years)	24
13	BU/TT/CP	BM	no	CSA/MTX	grade II/no	TAD/ATRA	CR	no	CCR (2.5+ years)	—
14	BU/CP	PBPC	no	CSA/MTX	grade II/limited	Rapamycin	progression	no	death	

TBI: total body irradiation, TLI: total lymphoid irradiation, CP: cyclophoshamide, ARA-C: cytarabine, VP: etoposide, MEL: melphalan, ATG: antithymocyte globulin, BU: busulfan, TT: thiotepa, BM: bone marrow, PBPC: peripheral blood progenitor cell, CSA: cyclosporine A, MTX: methotrexate, MITOX: mitoxantrone; LASP: L-asparaginase, VCR: vincristine, IL-2: interleukin 2, DNR: daunorubicin, TAD: thioguanine, cytarabine and daunorubicin, HAM: high-dose cytarabine and mitoxantrone, MTC: mitoxantrone, topotecan and cytarabine, ATRA: all-trans retinoic acid, VOD: veno-occlusive disease, MOF: multi-organ failure.

request to the centers contributing a case and not providing follow-up information in the first questionnaire. The median follow-up of the donors was 9 years after transplant (range 6-30) and 7.5 years (range 1-16) after development of leukemia in donor cells in the recipient.

The conditioning consisted of total body irradiation (TBI)-containing regimens in six patients. Busulfan and cyclophosphamide were used in six patients and cyclophosphamide and antithymocyte globulin in the two patients with severe aplastic anemia. Additionally total lymphoid irradiation was given to three patients. Bone marrow cells were used as the graft in 12 cases and peripheral blood stem cells in two patients. Ten patients received an unmanipulated graft and either methotrexate (n=1), cyclosporine A (n=3) or the two drugs together (n=6) for prophylaxis against graft-versus-host disease

(GVHD). A T-cell-depleted graft was given to 4 patients. One of these patients received no further GVHD prophylaxis, one patient received methotrexate and two patients cyclosporine. The overall GVHD-incidence was low with only four patients developing grade II acute GVHD and two patients developing limited chronic GVHD. There were no reports of other uncommon complications after transplantation. Except for the methotrexate used for GVHD prophylaxis, the only cytotoxic drug given after transplant prior to DCL diagnosis was intrathecal methotrexate, which was administered to one patient.

Treatment of donor cell leukemia/myelodysplasia and outcome

An attempt to treat DCL was made in 12 of the 14 patients. One patient with AML received no treatment

and died of progressive leukemia. One patient with MDS was reported to be alive without treatment 9 years after diagnosis of donor type MDS.

Nine patients received chemotherapy as initial treatment for DCL. Six of these patients entered remission (5 AML, 1 ALL), one patient died from progressive leukemia and two patients died of complications during aplasia. Three of the six patients received a second transplant. Of the three patients treated with chemotherapy only two patients with ALL (#2, #3) entered long lasting remission (1.6 and 1.9 years), but eventually relapsed. Patient #13 with AML M3 t(15;17) remains in complete remission 2.5 years after chemotherapy and all trans retinoic acid (ATRA) treatment. One patient with donor type MDS (#14) received experimental treatment with rapamycin but progressed to develop AML and died.

A second transplant was given to five patients (3 after initial chemotherapy as described above, one after local irradiation and one without prior treatment). A different donor was used in three patients (cousin 1, sister 1, alternative unrelated donor 1). Conventional myeloablative conditioning was used in 3 patients, one patient received conditioning consisting of thiotepa and cyclophosphamide (#10) and one patient received a non-myeloablative conditioning regimen (#12; 2Gy TBI, fludarabine). Three patients died after second transplantation (progressive disease 1, vaso-occlusive disease 1, multi-organ failure 1). Two patients were reported to be alive and in remission 5 and 11 months after the second transplant. Overall four patients remain free of disease at +2.5 years.

Discussion

The results of this EBMT center survey demonstrate that the occurrence of leukemia or myelodysplasia of donor cell origin is a rare complication of allogeneic SCT. A total of 14 cases occurring between 1982 and 2003 were identified. Based on the number of transplants performed in the centers, the absolute risk is about 124 per 100,000 transplants. An exact determination of the annual risk of developing leukemia in donor cells after allogeneic bone marrow transplantation would require a detailed analysis of the survival of all patients transplanted within the participating centers. However, taking into account that 12 of the 14 DCL cases occurred within 4 years after transplantation, it can be concluded that the annual incidence of developing a leukemia of donor cell type after transplantation is moderately increased compared to that of developing leukemia in the general population. The fact that the number of observed DCL has not increased in recent years, despite the more frequent use of chimerism studies after transplantation, argues against the hypothesis that the occurrence of leukemia in donor cells may be much more frequent than suspected from the published

case reports. While we cannot completely rule out under-reporting of DCL cases in this study, it is our opinion that this is unlikely as our questionnaire asked for suspected as well as proven cases.

A major problem in the analysis of DCL is that demonstration of the donor cell origin of leukemic *relapse* after allogeneic transplantation is difficult and hampered by many pitfalls.[18,19,21] The simplest evidence for donor cell type of a leukemia occurring after transplant is the demonstration of the opposite sex in the leukemic cells in sex-mismatched SCT. It is, however, well known that leukemic blasts from male patients sometimes lose their Y-chromosome and that doubling of an X chromosome can also occur. If this happens in the setting of allogeneic BMT with a female donor in a male patient, one might erroneously suspect the development of leukemia in donor cells.[19,21] In two cases (#5 and #10) of this survey, a female phenotype of the leukemia provided evidence of donor origin, but in case #10, donor origin was further confirmed by molecular chimerism analysis. Molecular confirmation was also gained in case #7, in which the 46XO karyotype could otherwise have simply reflected the loss of one X chromosome in the female recipient.[22] Another problem of the demonstration of donor cell origin of the leukemia by cytogenetics is preferential growth of the normal donor hematopoiesis in the cytogenetic analysis. This is, however, extremely unlikely in patients showing additional cytogenetic abnormalities together with the donor karyotype (case #2, 4, 6, 9, 13). In case #3, the donor type was further demonstrated by FISH of the Y-chromosome in the blast cells.[23] The most reliable techniques for demonstrating donor type are molecular techniques using different polymorphism markers to differentiate donor and recipient cells (VNTR, STR). These techniques were used in 9 of 14 DCL cases in this analysis. In case #12, the leukemic cells were additionally sorted and enriched prior to VNTR-analysis.[24] Based on the techniques used for demonstrating donor cell origin by the EBMT centers, we believe that the evidence in the majority of the cases included in this study convincingly support the belief that the leukemia did indeed arise in donor cells.

The majority of DCL were myeloid (11/14). The underlying disease for which the transplants were performed was leukemia in the majority of cases, but DCL also occurred after transplantation for aplastic anemia. The development of DCL is neither an early nor a late complication of SCT; rather, it represents an intermediate complication occurring at a median of 17 months after the transplant, but with a wide range of 4 to 164 months. With a median age of 27 years and an equal sex distribution, patients developing DCL do not differ greatly from the general population of SCT recipients. Interestingly, DCL did not exhibit the same phenotype as the original disease for which the transplant was per-
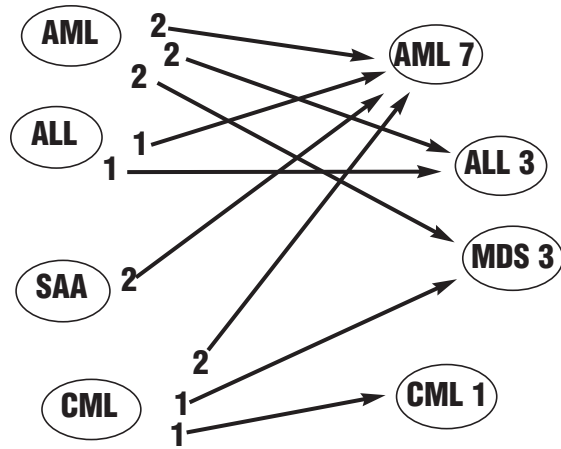
Figure 1. Relationship between the type of original disease and DCL.

formed (Figure 1).

The reported cases of DCL following SCT still attract much interest, since it is suspected that analysis of this phenomenon could provide insight into the mechanisms of leukemogenesis. Since the first reported case of DCL,[2] many hypotheses about the underlying mechanism have been generated. These include the continued antigenic stimulation of a susceptible donor lymphoid cell clone, the induction or facilitation of leukemia development by aberrant homeostasis, the fusion of normal donor cells with leukemic cells followed by diploidization resulting in a cell with host leukemic factors and the donor chromosomes, the transfer of an etiologic agent such as a virus or genetic material from host to donor cells and factors of the microenvironment, e.g. stromal cell alteration.[25,20] According to the multiple hit hypothesis of leukemogenesis, one might also speculate that leukemia arises due to a second hit in the recipient cells that have already received a first hit in the donor.[26] In addition, patients with prolonged pharmacological immunosuppression associated with chronic GVHD are at an increased risk for secondary malignancies,[1] which may also be true for the development of leukemia. The data of our survey neither support nor refute any of these hypotheses. While our survey does not identify the mechanism of the development of DCL, it can resolve some critical issues. One hypothesis on the development of DCL is the transfer of an occult leukemia from the donor to the recipient. The inadvertent transfer of an acute myeloid leukemia from donor to his HLA-identical sister suffering for chronic myeloid leukemia has been described,[27]

but in this case the donor had overt leukemia in the marrow graft. In our study, no leukemias were verified in the donors following DCL. A bone marrow examination was performed in three donors and additional cytogenetic analysis in one donor. In all cases, normal findings were obtained. Nevertheless, the donors may have an increased risk for leukemia development with longer follow-up. Since the follow-up period in the published case reports is usually limited, we were especially interested whether leukemia had occurred in any of the donors in our survey. The development of leukemia was, however, not reported in any of the donors in the 14 cases of DCL of this survey and this was confirmed in a second request to all centers which provided a median follow up of 9 years (6-30 years) after transplant. Thus the median follow up of the donors exceeds the median time to occurrence of DCL. The potential risk for the donor was of special importance in case #12, which represented the first case of DCL after transplantation from an unrelated donor. While most of the donors in the setting of family/related transplantation are aware of the history of the recipient, the situation is different in transplantation from unrelated donors. The question whether an unrelated donor should be informed about the development of leukemia in his/her cells in the recipient and the potential consequences for the donor represent a major ethical and medical challenge. Based on the results of this survey we conclude that the donors do not have an increased risk of leukemia. Another question is whether risk factors for the development of DCL can be identified from the transplantation procedure or from treatment or complications after transplantation. Our data indicate that neither a special conditioning or GVHD-prophylaxis regimen nor the occurrence of GVHD or the use of cytotoxic therapy after transplant represent a special risk for the occurrence of DCL.

It remains to be determined whether DCL can be successfully treated. The data collected by this survey indicate that the use of chemotherapy for treatment of DCL can induce remissions but that the treatment-related mortality is high. However, secondary SCT can induce long-lasting remissions in some patients.

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