HSCT may lower leukemia risk in ELANE neutropenia: a before–after study from the French Severe Congenital Neutropenia Registry

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Abstract 197/200

ELANE neutropenia is associated with myelodysplasia and acute leukemia (MDS–AL), and severe infections. Because the MDS–AL risk has also been shown to be associated with exposure to GCSF, since 2005, in France, patients receiving high daily GCSF doses (>15 μg/kg/day) are eligible for HSCT, in addition to classic indications (MDS–AL or GCSF refractoriness). We analyzed the effect of this policy. Among 144 prospectively followed *ELANE*-neutropenia patients enrolled in the French Severe Congenital Neutropenia Registry, we defined two groups according to period: "before 2005" for those born before 2005 and followed until 31/12/2004 (1588 person-years); and "after 2005" comprised of those born after 2005 or born before 2005 but followed after 2005 until 31/03/2019 (1327 person-years). Sixteen of our cohort patients underwent HSCT (14 long-term survivors) and six developed MDS–ALs. Six leukemic transformations occurred in the before-2005 group and none after 2005 (respective frequencies 3.8×10^{-3} vs 0; $P<0.01$), while four HSCTs were done before 2005 and 12 since 2005 (respective HSCT rates increased 2.5×10^{-3} vs 9×10^{-3}; $P<0.01$). Our results support early HSCT for patients with *ELANE* mutations who received high GCSF doses, as it might lower the risk of leukemic transformation.

Key words *ELANE*, neutropenia, HSCT, myelodysplasia, leukemia

Word count 2807

Introduction

Congenital neutropenia (CN) is a group of rare and inherited hematological disorders characterized by chronic profound neutropenia caused by impaired differentiation of neutrophilic granulocytes. Often diagnosed early in life, CN is defined as recurrent, life-threatening bacterial infections (e.g., skin infections, otitis, gingivitis, abscesses and sepsis) [1]. The elastase, neutrophil-expressed (*ELANE*) gene encodes neutrophil elastase, and is responsible for *ELANE* neutropenia, which is probably the most frequent and one of the most severe CN forms, based on its infection rate [2]. Two distinct *ELANE*-related CN phenotypes have been described: cyclic neutropenia (CyN), in which neutrophil counts classically oscillate with 21-day periodicity, and severe congenital neutropenia (SCN), with persistently low blood neutrophil counts [3,4]. The standard-of-care for *ELANE*-neutropenia patients consists of granulocyte-colony–stimulating factor (GCSF) administration, which increases the numbers of circulating neutrophils, thereby lowering infection-related mortality. Hematopoietic stem-cell transplantation (HSCT) is indicated for the rare patients with GCSF-refractory disease (i.e., no absolute neutrophil count (ANC) increase at ≥50 μg/kg/day) or those with myelodysplastic syndrome (MDS) [5-7].

Patients with *ELANE*-related CN are at risk of developing MDS–acute leukemia (MDS–AL). In 2005, our team showed [8] that the CN leukemia risk depends on two major features, the genetic defect and GCSF use, with the latter controlling the patients' infection rates. The relationship between high-dose GCSF exposure and leukemic transformation was confirmed in 2006 by the International Severe Chronic Neutropenia Registry (ISCNR), in which the USA, Canada, UK, the Netherlands, and Germany participate .[9]. Based on those results, guidelines were issued in France recommending HSCT for patients receiving high-dose GCSF, while the French Severe Chronic Neutropenia Registry has continued to collect data prospectively. This practice represents an extension of the validated indication of HSCT for CN.

This study was undertaken to analyze the effect of this policy on patients with the *ELANE*-gene mutation, as they are currently one of the most heavily GCSF-treated. In addition, even though HSCT has been proposed for CN since 1980 ,[10] it has been reported in only 11 patients with known *ELANE* status thus far [11-18]. Therefore, a comprehensive review of these cases appeared useful concerning HSCT indication and its impact.

Patients and Methods

Registry organization and data monitoring

The patients included in this study were all entered in the French Severe Chronic Neutropenia Registry (FSCNR). First created in 1993, with prospective enrollment of all CN types [1], the FSCNR was certified as a national registry by health authorities in 2008, and its case completeness was ascertained by verification through multiple sources. The database was approved by the French computer watchdog commission (CNIL certificate no. 97.075). Thirty-five French pediatric hematology–oncology units and ~50 adult hematology units participate in the FSCNR. A clinical research associate assured accurate data monitoring, based on annual on-site reviews of medical charts. The following parameters are currently recorded: sex, age at diagnosis, severe bacterial or fungal infections (septicemia, cellulitis, pneumonia, osteitis and liver abscess), complete blood cell counts, differential bone-marrow cell counts (smear method) and all information on HSCTs. Each patient had to provide written informed consent to be entered in the FSCNR. Several reports on the FSCNR are available elsewhere .[2;8;19-24].

Study design

This before–after study compared patients divided into two groups according to follow-up period: “before 2005”, for those born before 2005 and followed until 31/12/2004, and “after 2005”, for

those born after 2005 or before 2005 but still being followed after 2005 until the last update (31/05/2019). The main reason to separate these two periods was the HSCT-indication modification at the end of 2004. Since 2005, patients in France receiving a GCSF dose above the 15-μg/kg/day threshold become eligible for HSCT, in addition to patients with validated indications, such as MDS–AL or GCSF refractoriness (typically ≥50 μg/kg/day).

ELANE-neutropenia genetics

We classified variants according to American College of Medical Genetics and Genomics guidelines.[25]. Only pathogenic (class 5) and probably pathogenic *ELANE*-gene variants (class 4) were included in this study. The patients or their parents gave written informed consent for genetic testing. Standard procedures were used to extract DNA from blood. The *ELANE*-gene coding sequence and exon–intron boundaries were determined either by Sanger sequencing, as described previously[2;3], or by targeted sequencing of a gene panel including *ELANE*. Mutations were numbered as recommended by the Human Genome Variation Society (http://www.hgvs.org/), using the reference sequence NM_001972.2.

Literature review

To identify all publications related to *ELANE*-associated neutropenia and summarize reported cases, we first screened PubMed using the key words “ELANE” “ELA2” “Severe congenital neutropenia” “Congenital neutropenia”. Then the reference list of each article was checked to identify additional references and avoid duplicates.

Hematological events

AL, either acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), was defined

using WHO criteria (i.e., at least 20% blast cells in bone-marrow smears). Because these patients almost always had dystrophic cytological abnormalities, MDS was diagnosed when cytological abnormalities were associated with central anemia or central thrombocytopenia requiring blood transfusion, and when clonal cytogenetic abnormalities were present. Single-strand conformational polymorphism, as previously described[26], was used to screen for GCSF-receptor mutations, which were confirmed by sequencing. More recently, targeted next-generation sequencing was used.

GCSF exposure

To calculate GCSF exposure, we assumed dose equivalence between filgrastim and lenograstim. Because the unit dose and frequency of GCSF injections are individually tailored, each patient's overall treatment was estimated using several parameters calculated for each GCSF therapeutic period during which the dose and frequency of injections were stable: dose delivered per injection (dd_i, μg/kg); number of injections (n_i); cumulative dose, defined as the total dose received during the relevant period (mg/kg) = $dd_i \times n_i$; and duration of the relevant period in days. The total cumulative dose (μg) was calculated as the sum of cumulative doses for each therapeutic period, from day 1 of GCSF to the last day of follow-up. The cumulative duration of GCSF use (in years) was calculated as the sum of all therapeutic periods. For each patient, total GCSF-therapy follow-up (in years) since onset was calculated from the first injection to the last day. The time-averaged dose (μg/kg/day) was calculated by dividing the cumulative dose by the cumulative duration of treatment.

HSCT and engraftment

The conditioning regimen, donor, type of graft and number of cells injected were recorded.

Chimerism analysis was performed by means of cytogenetic or polymerase chain reaction (PCR) amplification of microsatellites on peripheral mononuclear blood cells.

Statistical methods

Demographic, clinical, biological and therapeutic data were recorded using an Access database (Microsoft). StataÒÒ version 13 software was used to compute all statistical analyses. The frequencies were calculated by dividing the numbers of events by the person-years observed for before and after periods. This before–after study compared medical intervention (HSCT) and medical complication (MDS–AL) frequencies between before- and after-2005 groups, using the Mantel–Haensel test [27;28]. Categorical data were compared with Fisher's exact test and quantitative data with the Mann–Whitney test. All tests were two-tailed, with $P<0.05$ defining significance. For survival analyses, the endpoints were death, bone-marrow transplantation and MDS–AL onset. The Kaplan–Meier method was used to estimate the probability of survival. Survival was compared between before and after groups with the log-rank test [29].

Results

Cohort description

As of 31 March 2019, among the 1032 CN patients enrolled in the FSCNR, 144 carry a heterozygous, pathogenic *ELANE* mutation. Ninety-five (66%) patients were diagnosed with SCN and 49 (34%) with CyN. The cohort comprised 70 males and 74 females. The median age of the entire cohort at diagnosis was 0.24 (range 0–42.9) years. Respective median ages at SCN or CyN diagnosis were 0.19 or 0.8 years ($P<0.002$). The cumulative observation times were 1588 person-years for the 89 patients in the before-2005 group and 1327 person-years for those in the after-2005 group (55 born after 2005 and 84 born before 2005 but followed since 2005). Five patients born before 2005 were not followed after 2005 because they developed MDS–AL, died or

underwent HSCT. GCSF treatments were individually tailored based on the recurrence of severe infections and GCSF tolerance. For the entire cohort, 112 patients received GCSF, at a mean dose of 9.8 μg/kg/day, and 32 patients were not given GCSF. The mean (range) total doses (μg/kg) were 9837 (0–115 431) for the entire cohort, 12 564 (0–115 431) for SCN patients and 3837 (0–25 038) for those with CyN. For the 112 treated patients, the maximum dose (μg/kg/day) was 0.1–4.9 for three (2.7%) patients, 5–9.9 for 47 (42%), 10–14.9 for 26 (23.2%), 15–29.9 for 14 (12.5%) or 30–49.9 for nine (8.0%) and >50 μg/kg/day for 13 (11.6%). Maximum doses (μg/kg/day) were <5 for 32 (22.2%) patients, 5–10 for 38 (26.4%), 10–20 for 32 (22.2%), 20–30 for 26 (18%) or >30 for 16 (11.1%). Five patients' neutropenias were considered GCSF-refractory (ANC <0.2 G/L after receiving ≥50 μg/kg/day).

Six leukemic transformations occurred, including one ALL. None of the patients followed after 2005 developed MDS–AL. For the entire cohort, the cumulative MDS–AL frequencies (SD) were 4.4% (1.9) at 10 years and 5.5% (2.2) at 20 years. Two patients initially diagnosed with MDS developed AL. No CyN patients developed MDS–AL. Diabetes insipidus with pituitary nodules was the first manifestation for two patients. Among the six MDS–AL patients, three had monosomy-7, and one a complex caryotype and 2 have no identified cytogenetic clone.. A *CSF3R* mutation was detected at the time of malignant transformation in 2 patients. [30] The mean GCSF dose before MDS–AL for the six patients was 18.9 μg/kg/day. Median age at AL onset was 10.75 (range 4.2–12.5) years. The two patients who did not undergo HSCT died of leukemia, while, among the four transplanted patients (two for AML, one for ALL and one for MDS); patient #3 died of HSCT-related complications, despite complete engraftment.

Seven of the 144 cohort patients died. The 20- and 40-year overall survival rates (95% CI) were 95.7% (90–98.2%) and 92.4% (79.1–97.2%), respectively (Fig. 1b). Five non-transplanted patients died. Before 2005, two deaths were attributed to AL complications without HSCT;

another died of sepsis. After 2005, one adult died of sepsis during a chemotherapy regimen for colon cancer and another died of septic shock and renal failure.

Description of the 16 patients who underwent HSCT

Six males and ten females underwent HSCT (Table 1). Median age at transplantation was 4.3 (range 0.6–20.4) years. All 16 underwent preparatory myeloablation: nine were given a combination of busulfan, cyclophosphamide and anti-thymocyte globulin (ATG); six were given fludarabine and busulfan, combined with ATG alone for four, and melphalan and ATG for one, and thiotepa and ATG for one. One patient underwent TAM12 (total body irradiation, cytarabine and melphalan). A *Gly214Arg* mutation was detected in 6/16 (37.5%) HSCT recipients. HSCTs were done in 4/89 before-2005 patients and 12/139 after-2005 patients (Table 2).

All 16 patients achieved complete hematological recovery with full engraftment, and have a normal neutrophil count after HSCT. The median time required for ANCs to reach 0.5×10^9/L was 21 (range 14–77) days; the longest engraftment time refers to an unrelated cord blood (UCB) HSCT in patient #3. After 9–42 (median 27) days, platelet counts reached 50×10^9/L, without further transfusion. Despite successful engraftment, patient **#13** developed autoimmunity (antinuclear factor (ANF) titer >1/640), lost his graft at 18 months, and was not amenable to immunosuppression. She underwent retransplantation complicated by severe varicella zoster but nonetheless achieved good and stable engraftment and is in good health, without sequelae, 4 years later.

All surviving patients are disease-free and no longer require erythrocyte and platelet transfusions, with normalized ANCs. Complete chimerism was found in all patients.

Median follow-up post-transplantation was 5.7 years and 5-year survival rate was 87.5% [95% confidence intervals (CI) 58.7–96.7%] (Fig. 1c).Two patients died after HSCT: patient #3 with

ALL for which HSCT was indicated, died of sepsis before 2005 and patient #11 with GCSF-refractory *ELANE* neutropenia, for which HSCT was indicated, died after 2005 of refractory grade-IV GVHD with transplant-associated thrombotic microangiopathy. In addition, six patients had grade-II GVHDs, including one with chronic skin GVHD and persistent livedo.

Comparison of HSCT rates and leukemia rates before vs after 2005

Comparing before 2005 to after 2005, respectively, median ages were 0.44 years and 0.15 years (non-significant difference) at diagnosis, and 7.3 (range, 1.6–12.4) and 3.4 (range, 0.6–9.3) years at transplantation. Median follow-up durations for the before- and after-2005 cohorts were 14.2 (range 0.1–53.4) and 10.4 (range 0.2–14.5) years, respectively (non-significant).

Before 2005, HSCT indications were AL for three patients and GCSF refractoriness for one, and GCSF refractoriness for six after-2005 patients: five taking high GCSF doses (15–30 μg/kg/day) and one with MDS (P<0.03). Neither the mean before- and after-2005 GCSF doses (8.5 vs. 11.6 μg/kg/day, respectively; P<0.09) nor the maximum doses (respectively, 14.4 vs. 13.6 μg/kg/day; P<0.15) received by these patients changed significantly with time. Finally, the major change between before and after 2005 was not the dose prescribed initially to treat the patients needing GCSF but the medical decision with regards to the indication of HSCT.

Discussion

The main finding issued from this population-based study on 144 patients with *ELANE* mutations was that slightly extending the HSCT indication to patients currently taking high-dose GCSF may lessen the risk of leukemia. In our FSCNR experience, leukemia has not been diagnosed in *ELANE*-neutropenia patients since 2005, when we extended the HSCT indication to patients receiving >15 μg/kg/day of GCSF. Analysis of administered GCSF doses showed no differences

between before-2005 and after-2005 mean doses, maximum doses or total doses for transplantation candidates. However, after 2005, the number of HSCTs increased significantly and patients were transplanted at a significantly younger mean age.

ELANE neutropenia was identified first in CyN,[31] and then shortly thereafter in chronic neutropenia. [32] Infections and hematological malignancies are the main life-threatening complications of *ELANE* neutropenia. Long-term use of GCSF to treat CN, which started in 1988, markedly limits the infectious risk, dramatically improving these patients' quality of life. However, it has also raised questions regarding the balance between the natural risk of severe infections and that of iatrogenic leukemic transformation. [8;9]

Patients carrying an *ELANE* mutation can develop MDS, AML or, more rarely, ALL. The leukemic transformation rate reported in the literature for *ELANE*-neutropenia patients is 15–25% by 20 years of age [2;3;33]. That risk is considered to be stable over time, affecting 25% of the 52 patients in a series from the NIH and US SCN registry.[33]. During the last 20 years, two large case series were reported; one from the ISCNR on 307 patients [4] and the other from the Hannover genetic laboratory on 213 patients [3]. Those reports mentioned that 40 HSCTs had been performed but no information was provided about the indications or outcomes. Among the largest series of HSCTs (136 including 39 *ELANE*-neutropenia patients) indicated for SCN [6], which includes our patients, the HSCT indication was not analyzed, and that series was not population-based. An exhaustive literature review of HSCT for CN identified only 11 cases with a known *ELANE* mutation (Table 3) and sufficient details about transplantation indications and outcomes).[11-18]. All the reported HSCT indications were 'classical' in the literature reviewed: three for MDS–AL and eight for GCSF refractoriness. None of those papers can be used to study the HSCT impact on the risk of developing MDS–AL, because only the numbers of HSCTs during follow-up of all *ELANE*-neutropenia patients are known but not the entire population.

Because our study was an exhaustive examination of a national cohort, with the participation of all French centers, we think that it could be representative of a non-biased sample of *ELANE*-neutropenia patients. Our first important observation is that the HSCT outcome for *ELANE*-neutropenia patients was good, with overall 95% engraftment survival and 90% long-term survival. Extending HSCT to a small number of patients requiring high-dose GCSF proved beneficial and may lower their risk of AL.

Many data have been collected on *ELANE*-neutropenia patients regarding clonal evolution. The first clonal event was shown to occur in the colony-stimulating factor-3 (*CSF3R*) clone, [34] but the ultimate clonal evolution involved a broader panel of mutations at the time of leukemic transformation. [35;36] Although such information is crucial to following patients with *ELANE*-germline mutations, the initial step of leukemogenesis in *ELANE*-neutropenia patients involved *CSF3R* mutations, which appear to be induced by GCSF therapy, and is sufficient to trigger MDS–AL. Taking into consideration the GCSF 'load', key information on early patient management may potentially help make the clinical decision about the HSCT indication.

Our results are limited by the small sample size. Further studies on larger populations could help improve our understanding the GCSF role and what dose can reasonably be considered low risk for leukemic transformation. However, HSCT remains a viable therapeutic option for patients who are difficult to manage and at high risk of severe infections.

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Conflict of interest The authors declare they have no conflict of interest concerning this study.

Authorship The original design of the study was conceived by JD and GAR. JD is the coordinator of the FSCNR and BB is responsible for data management. CB-C ran the genetic analyses. All the authors contributed to writing manuscript and its revision.

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Legends

Figure 1. Kaplan–Meier estimated probabilities of survival with 95% confidence intervals (CI) for (a) the entire French Severe Chronic Neutropenia Registry cohort of 144 patients, (b) the same cohort according to their dates of birth (before 2005 or after 2005) and (c) the 16 French *ELANE*-neutropenia cohort patients after hematopoietic stem-cell transplantation (HSCT).

Table 1. Main characteristics of 16 *ELANE*-neutropenia patients who underwent HSCT in France with situation pre HSCT, HSCT conditioning regimen and outcome.

Table 2. Results by period (Before and after 2005): This before–after study compared medical intervention (HSCT) and medical complication (MDS–AL) frequencies i.e. the number of events per person-years observed, between before- and after-2005 groups, using the Mantel–Haensel test.

Table 3. Literature review on HSCT for 11 *ELANE*-neutropenia patients.

Figure 1.

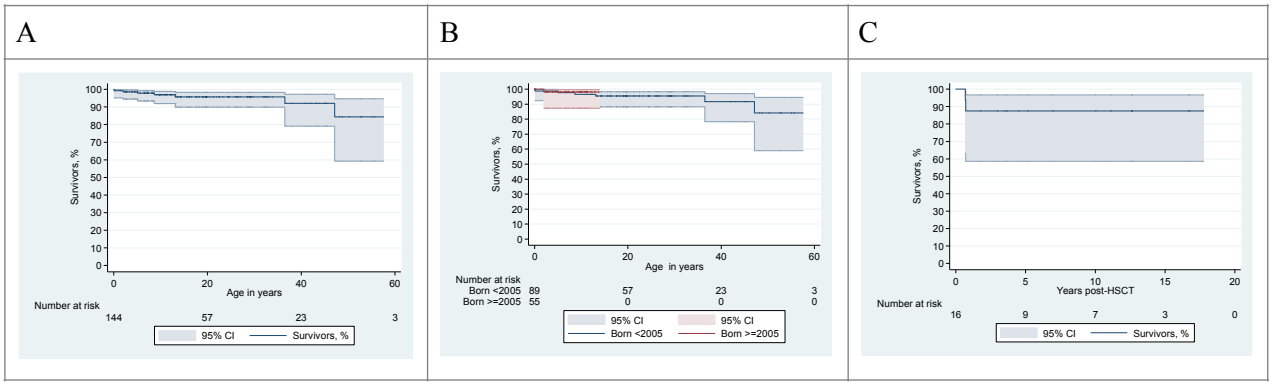
A
B
C
Survivors, %
Age in years
Number at risk
144 57 23 3
95% CI
Survivors, %
Age in years
Number at risk
Born <2005 89 57 23 3
Born >=2005 55 0 0 0
95% CI
95% CI
Born <2005
Born >=2005
Survivors, %
Years post-HSCT
Number at risk
16 9 7 3 0
95% CI
Survivors, %

Table 1

Patient Number	Mutation		Indication	HSCT year*/at age, y	Conditioning regimen	Graft; origin-matching	GVHD prophylaxis	Nucleated cells, n/kg	Highest GVHD grade	Complications	Post-HSCT status/follow-up, y
	DNA	Protein									
1	c.688delG	p.Asp230fs	MDS–AML	>2006/.92	Bu–Cy–ATG	MUD; 10/10	CSA–MTX	43	II	CMV	Alive/13
2	c.125C>T	p.Pro42leu	GCSF failure	>2005/9.28	Bu–Cy–ATG	MUD; 9/10	CSA	4.27×10^{8}	II	ARDS; cerebral abscess; seizure	Alive/12.6
3	c.640G>A	p.Gly214Arg	ALL	<2005/12.39	TAM12	UCB; 9/10	CSA–MTX	Unknown	IV	Sepsis	Died/0.7
4	c.158A>T	p.His53Leu	MDS–AML	<2005/4.72	Bu–Cy–ATG	UCB; 3/6	MMF–Pred	10.2×10^{7}	I	No	Alive/16.8
4	c.640G>A	p.Gly214Arg	GCSF failure	<2005/1.58	Bu–Cy–ATG	T-depleted MUD; 9/10	No	11.1×10^{6} (CD34+)	I	No	Alive/17.7
6	c.640G>A	p.Gly214Arg	MDS–AML	<2005/10.3	Bu–Cy–ATG	MUD; 10/10	CSA–MTX	3.45×10^{8}	I	CMV, EBV	Alive/16.6
7	c.199_207del	p.Ser67_Ala69del	GCSF failure	>2005/0.83	Bu–Cy–ATG	SIB	CSA	Unknown	Unknown	Unknown	Alive/14
8	c.170C>T	p.Ala57Val	High-dose GCSF	>2005/0.6	Bu–Cy–ATG	UCB; 4/6	CSA–Pred	15.8×10^{7}	None	No	Alive/10.3
9	c.377C>T	p.Ser126Leu	High-dose GCSF	>2005/3.98	Flu–Bu–ATG	MUD; 10/10	CSA	49.26×10^{6}	I	EBV	Alive/6.9
10	c.241_246del	p.Arg81_Val82del	High-dose GCSF	>2005/7.73	Flu–Bu–ATG	SIB	CSA	7.66×10^{8}	II (cGVHD)	Aplasia	Alive/6.4
11	c.193G>T	p.Val65Phe	High-dose GCSF	>2005/1.28	Flu–Bu–ATG	MUD; 10/10	CSA–MMF	19.8×10^{8}	IV	TAM, CMV, EBV *Pseudomonas*	Died/0.7
12	c.253G>A	p.Gly85Arg	High-dose GCSF	>2005/5.12	Bu–Cy–ATG	MUD; 10/10	CSA	Unknown	III	No	Alive/3
13	c.640G>A	p.Gly214Arg	GCSF failure	>2005/1.52	Flu–Bu–ATG	UCB; 5/6	CSA	8.3×10^{7}	None	Late-onset auto-immunity (ANF+) and late transplant loss	Alive/6.1 (4.2 y after 2nd HSCT)
			Late rejection despite full engraftment	> 2005/ 3.7	Flu–Cy–ATG	UCB; 5/6	CSA	0. 83 X 10^{8}/kg (0. 24 X 10^{6}/kg CD34).	I	Chickenpox	
14	c.640G>A	p.Gly214Arg	GCSF failure	>2005/1.44	Flu–Bu	SIB; 10/10	CSA	3.77×10^{8}	II	No	Alive/5.1
15	c.1A>T	p.Met1?	GCSF failure	>2005/0.73	Bu–Th–Flu–ATG	MUD; 12/12	CSA–MTX	Unknown	II	EBV	Alive/1.7

16	c.640G>A	p.Gly214Arg	GCSF failure	>2005/1.49	Bu–Cy–ATG	MUD	CSA	Unknown	II	EBV	Alive/3.5

HSCT hematopoietic stem-cell transplantation, *MDS–AML* myelodysplasia-acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *ANF* antineutrophil factor; *ARDS* acute respiratory distress syndrome, *Bu* busulfan, *Cy* cyclophosphamide, *ATG* anti-thymoglobulin, *Flu* fludarabine, *Th* thiotepa, *MUD* match unrelated donor, *UCB* unrelated cord blood, *SIB* sibling donor, *CSA* cyclosporine, *MTX* methotrexate, *MMF* mycophenolate mofetil, *Pred* prednisone, *cGVHD* chronic graft vs host disease, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *TAM* transplant-associated thrombotic microangiopathy, *TAM12* 12-Gy total body irradiation, cytarabine and melphalan

*<, before or >, after 2005

Table 2

Parameter	Before 2005	After 2005 to 2019	*P*
Patients at risk, *n*	89	139*	
Cumulative follow-up, person-years	1588	1327	
HSCT			
n	4	12	<0.01
Ratio, person-years	2.5×10^{-3}	9×10^{-3}	
MDS–AL			
n	6	0	<0.01
Incidence ratio, person-years	3.8×10^{-3}	0	
Deaths [cause], *n*	4 [2 AML, 1 sepsis, 1 HSCT-related]	3 [1 colon cancer, 1 sepsis, 1 HSCT-related]	
Median age at death, y	6.8	36	

HSCT hematopoietic stem-cell transplantation, *MDS–AL* myelodysplasia–acute leukemia, *AML* acute myeloblastic leukemia
*55 patients born after 2005; 84 patients born before 2005 and followed until 2019

Table 3

Ref.	Mutation Nucleotide effect	Mutation protein effect	Sex/age at diagnosis/age at HSCT	HSCT indication	Donor stem-cell source; matching	Conditioning regimen	GVHD prophylaxis	GVHD	Outcome/ follow-up
[11]	NR	Mutated, not specified	M/1 mo/9 mo	No response to GCSF	MUD CB; 4/6	**1)** Bu–Cy–ATG (MAC)	**1)** CSA–MTX	No	No engraftment/42 d
				No engraftment Rejection	MUD, CB; 4/6	**2)** Flu–ATG (RIC) **3)** Flu–Mel–Cam (RIC)	**2)** CSA–MMF **3)** CSA–MMF	No aGVHD	Rejection/5 mo Alive/20 mo
[12]	c.1287A>G	Met(–29)Val	M/1 mo/–	No response to GCSF	SIB, BM	MAC	NR	NR	Alive/47 d
[13]	NR	p.Leu121His	F/2 wk/28 y	*CSF3R* mutations	SIB, PBSC	Flu–Bu–Camp	Fk–Rapa	No	Alive/60 mo
	NR	p.His87del	M/3 mo/14 y	MDS–AML	MUD, PBSC	Bu–Cy–Mel–ATG	Low CSA–MTX	severe cGVHD	Alive/31 mo
	NR	p.Cys151Ser	M/1 wk/7 y	GCSF resistance, MDS	MUD, CB	Bu–Cy–Mel–ATG	CSA–Pred	Grade-IV aGVHD	Died of aGVHD/40 d
[14]	g.2253 A>C	p.Q73P	M/16 mo/3 y	No response to GCSF	MUD, BM	Flu–Mel–TBI–ATG	Fk–MTX	NR	Alive/15 mo
[15]	NR	p.Trp127Cys	M/1 mo/4 y	No response to GCSF	NR	NR	NR	No	Rejection, alive/5 y post-2nd HSCT
	NR	p.Gln208Ter	M/1 mo/31 y	AML	NR	NR	NR	Moderate	Alive/7 y
[16]	c.401A>C	p.Gln134Pro,	M/12 mo/2 y	No response to GCSF	SIB, BM	Mel–Flu–TBI	NR	NR	Alive
[17]	c.1 A>G	p.Met1Val	F/6 wk/6 mo	No response to GCSF	MUD, BM; 9/10	**1)** Flu–Mel–Cam–ATG (RIC)	Fk	No	Rejection/6 mo
				Rejection	MUD, BM; 9/10	**2)** Flu–Bu–rATG (MAC)	Fk–MTX	NR	Alive/1 y
[18]	c. 573_597+5 del		M/1 y/25 y	No response to GCSF	MUD, BM;10/10	Flu–Cy–ATG–TBI	CSA–MTX	Grade-IV aGVHD	Died of aGVHD/128 d

MUD match unrelated donor, *SIB* sibling donor, *CB* cord blood, *BM* bone marrow, *PBSC* peripheral blood stem cells, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *Bu* busulfan, *Cy* cyclophosphamide, *ATG* anti-thymoglobulin, *rATG* rabbit ATG, *Flu* fludarabine, *Camp* Campath (alemtuzumab), *Mel* melphalan, *CSA* cyclosporine, *MTX* methotrexate, *Fk* tacrolimus, *Rapa* rapamycin, *Pred* prednisone, *aGVHD* acute graft vs host disease, *cGVHD* chronic GVHD; *NR* not reported, *MDS–AML* myelodysplasia-acute myeloid leukemia, *TBI* total body irradiation, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning

*Patient carrying the familial Mediterranean fever *MEFV* mutation