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CLINICAL STUDY

Allogeneic hematopoietic stem cell transplantation from matched related donors for acute myeloid leukemia

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ABSTRACT

INTRODUCTION**:** In patients with acute myeloid leukemia (AML), allogeneic hematopoietic stem cell transplantation (HSCT) remains the priority treatment option as the most effective prevention of relapse. When an HLA-matched sibling is available, these transplants are preferred.

OBJECTIVES: We stratificated patients according to risk, disease state (an active disease, the 1st or 2nd complete remission – CR1, CR2, which was achieved after the 1st or 2nd induction) and type of graft (from brother or sister). Finally, the overall survival (OS) of patients in individual groups was evaluated.

MATERIAL AND METHODS: The retrospective single-center study included 104 transplantations in 97 adult patients with AML who underwent HSCT from matched sibling donor in a period of 10 years between January 2011 and December 2020.

RESULTS: 54 patients (55.7%) were alive as of the January 1, 2022. The median OS of the entire group, as well as the cohort with favorable (5y-OS 75.0%) and intermediate prognosis risk (5y–OS 78.5%) was not reached. We found that patients, who required second induction therapy to achieve CR, had poorer OS after allogeneic HSCT, median 20.7 months (95% CI, 6.5-35.5) than those who achieved CR after first induction, median not reached (95% CI, 63.5–63.5, p=0.0048). Statistically significant effect on OS shows transplantation in CR2 (HR 6.76, CI 95% 2.19–20.80, p=0.0009), In addition, this parameter influenced OS more than achieving CR up to the 2nd induction course (HR 2.44, CI 95% 1.17–5.11; p=0.0180) or entry to transplantation without CR (HR 2.81, CI 95% 1.09–7.26; p=0.0326).

CONCLUSION: The results presented in the work show the high efficiency of HSCT in each risk group. The number of induction therapies required to achieve CR is a good prognostic factor. The gender of a sibling has no impact on OS *(Tab. 11, Fig. 7, Ref. 18)*. Text in PDF www.elis.sk

KEY WORDS: acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, overall survival, remission status, donor tender.

Introduction

Acute myeloid leukemia (AML) is a clinically and biologically heterogeneous group of clonal neoplasias and, at the same time, the most common acute leukemia in adults. In the last decade, a significant progress in the research of molecular and cytogenetic changes in patients with AML has been observed. These findings have gradually become part of important decision-making processes. The identification of pathogenic variants in selected genes helped to refine the individual prognosis, to monitor the effectiveness of treatment using the measurement of minimal residual disease (MRD), and thus also choose the optimal treatment strategy. The basis of AML therapy is a combination of cytarabine and anthracycline-based regimens with allogeneic HSCT for suitable candidates. A novelty for elderly and morbid patients is a semi-intensive regimen with azacitidine and venetoclax, which opens the door for another spectrum of AML patients to achieve CR with acceptable toxicity, and subsequently some of them can undergo allogeneic HSCT after reduced intensity conditioning (RIC). According to the definition, the diagnosis of AML is made based on the presence of more than 20% blasts in the bone marrow or peripheral blood or a proven genetic abnormality, e.g., fusion *PML::RARA*, *RUNX1::RUNX1T1*, *CBFB::MYH11*, *DEK::NUP214* or *RBM15::MRTFA*, rearrengement of *KMT2A*, *MECOM* or *NUP98* and *NPM1* mutation – in these situations the diagnosis can be made regardless of the percentage of blasts in the bone marrow (1).

The diagnosis of AML can also be established in the presence of extramedullary tissue infiltrates. Treatment is divided into induction

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(with the aim of inducing remission) and consolidation (with the aim of strengthening remission). This also includes allogeneic HSCT, which, thanks to the complex immunological, so-called graft-versus-leukemia (GvL) effect, can maintain remission for a long time. The average age of transplant recipients is increasing due to the development of anti-infective treatments and the introduction of less toxic conditioning regimes (reduced intensity conditioning). When choosing suitable donors, the first option is always an HLA-compatible sibling. The European Leukemia Net (ELN) classification (Tab. 1) divides acute myeloid leukemia into 3 risk groups according to the results of genetic analysis – favorable, intermediate, and adverse risk (2).

Prognostically more important than genetic features is the response to treatment, and especially the presence of the aforementioned MRD. Currently, 2 methods are used to monitor minimal residual disease, i.e. for the purpose of assessing the depth of remission and possible choice of post-remission therapy, as well as for the early detection of disease relapse: multiparameter flow cytometry (the advantage of this method is the fact that it can be used even in patients without a genetic marker suitable for monitoring MRD) and RT-qPCR. In the case of AML (apart from the APL subtype), several targets are identified for simple monitoring of MRD by PCR, e.g., mutated *NPM1*, *CBFB-MYH11* or the *RUNX1-RUNX1T1* fusion gene (3).

The applicability of PCR testing for MRD in other situations is problematic, as the sensitivity of the method and the kinetics of the markers are different. Due to the high risk of relapse, patients with the aforementioned, otherwise prognostically favorable molecular changes, yet without achieving MRD negativity after 2 courses of intensive chemotherapy, should undergo allogeneic HSCT already in the 1st complete remission (CR1) (4).

For the standard-risk patients with MRD negativity, non-transplantation therapy with 3–4 consolidation courses of high-dose cytarabine or autologous HSCT is chosen (5, 6).

Tab. 1. ELN2017 risk stratification by genetics in AML.

Risk category*	Genetic abnormality
Favorable	t(8;21) (q22;q22.1); *RUNX1-RUNX1T1*
	inv(16) (p13.1q22) or t(16;16) (p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†}
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high†}
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†} (without adverse-risk genetic lesions)
	t(9;11) (p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9) (p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22) (q34.1;q11.2); *BCR-ABL1*
	inv(3) (q21.3q26.2) or t(3;3) (q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high†}
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Thus, using this approach, we do not expose patients to the risk of allogeneic transplantation (transplant-related mortality or TRM), such as graft-versus-host disease (GvHD), infectious complications during immunosuppressive treatment or organ toxicity. The key parameter is, therefore, the depth of remission. Without rigorous monitoring of MRD, we cannot select this group of patients.

Conversely, in case of an adverse-risk patient, we prefer to consolidate the disease with at least 1 cycle of cytarabine in high or intermediate doses and subsequent allogeneic HSCT. There are no unequivocal recommendations on the transplantation of patients at intermediate risk; each transplant center decides their therapeutic approach individually.

Patients and methods

In this retrospective study, we have focused on the evaluation of overall survival using Kaplan-Meier curves in patients with AML who underwent allogeneic transplantation at the University Hospital in Bratislava between January 2011 and December 2020. We have stratified patients into three risk groups according to the results of the genetic analysis. We used the ELN model. In the group of adverse-risk patients, we also included those in whom the disease was initially manifested by hyperleukocytosis above $100x10^9$/l, as well as secondary leukemias, most often AML after previous cytostatic treatment for another oncological disease (t-AML) or AML after transformation from myelodysplastic syndrome or myeloproliferative neoplasia. We also considered patients with extramedullary involvement (mucous membrane, skin, central nervous system, etc.) and chemoresistant (primary refractory) forms to be adverse-risk patients. We defined chemoresistance as failure to achieve CR or CRi after two courses of induction therapy. Understandably, these groups often overlapped: patients with secondary leukemia arising from MDS often had chromosomal changes that put them at adverse risk according to the aforementioned classification, and extramedullary AML was also more often chemoresistant, in addition to having adverse genetics.

We focused on other important characteristics of the patient and donor, respectively, and their influence on the success of the transplant. We analyzed the OS of patients according to disease status before transplantation and type of graft (from a brother or sister). In the case of death, we searched for the cause of death. The statistical evaluation was carried out on the January 1, 2022.

In the period of 2011–2020, a total of 104 transplantations in patients with AML with a median age of 45, in the age range of 19–71 years, underwent a matched sibling transplant. We did not include haploidentical transplants performed at our department in the given period.

Patients between the ages of 41–50 clearly dominated ten years ago; in recent years, the average age has been gradually increasing. Thanks to the use of reduced-intensity conditioning regimens

with significantly reduced toxicity, the number of elderly patients has increased since 2016 (Fig. 1). In our group of 104 patients, men (59 patients, 56.7%) predominated over women (45 patients, 43.3%) in a ratio of 1.3.

Results

Reviewing the number of patients in cohorts stratified by risk we observed a predominance of high-risk patients (Tab. 2). The presence of a smaller number of patients in favorable and intermediate-risk cohorts is indicated by the recommendations for AML treatment, since in these groups it is possible to choose autologous HSCT versus consolidation chemotherapy.

Secondary leukemias occurred in 24 cases (Fig. 2), or 24.74%. Transformations from myelodysplastic syndrome (9 patients), leukemia with MDS cytogenetic abberations (4 patients) and AML with multilineage dysplasia (3 patients) predominated. Two patients developed AML on the basis of previous cytotoxic therapy (t-AML), another progressed from another myeloid neoplasia such as chronic myelomonocytic leukemia (3 patients) or chronic eosinophilic leukemia (1 patient). In two cases, a blast crisis of chronic myeloid leukemia was recorded.

Extramedullary disease occurred in 14 patients (14.43%), presented as myelosarcoma (4 patients), skin infiltration by myeloid cells (4 patients), meningeal leukemia (3 patients) and gingival hyperplasia (3 patients). Myeloid sarcoma manifested in different ways: involvement of the pancreas, exocervix, paravertebral space, lung tip, nasopharynx, extrahepatic bile duct or infiltration in the fossa poplitea.

Hyperleukocytosis above 100 x 10^9/l was present in 16 patients at the time of diagnosis.

Chemoresistance, i.e. failure to achieve CR after 2 induction chemotherapy courses, was noted in 9 patients. 19 patients achieved remission after only two inductions. We observed worse overall survival in these two cohorts.

87 patients underwent transplantation *once*, another ten *twice*, but the 1st transplantation in the case of 3 patients is not part of the study, as they were performed either outside the observed period (1 case, in 1995), outside our department (1 case, in Italy) or it was an autologous transplant (1 case).

Nine of 10 patients were retransplanted for relapses of leukemia, two of whom had isolated extramedullary relapses. In one patient, the reason for the second transplant was primary graft failure after the first transplant. In that case, we used a different conditioning regimen, and the graft yield was noted to be higher. Without exception, the donor of hematopoietic cells was the same sibling as in the case of the first transplant. The time between two

Tab. 2. Risk stratification.

Risk	Number of patients
favorable	16
intermediate	21
adverse	56
unknown	4

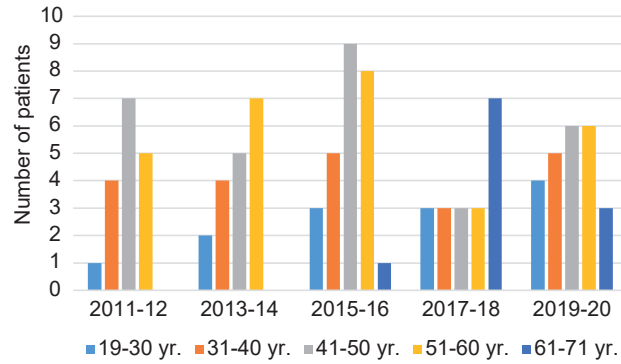

Fig. 1. Age structure of patients before transplantation.

transplants was 1–276 months with a median of 20 months (Tab. 3; living patients are bold).

The remission status before transplantation also significantly affects the prognosis (Tab. 4). Complete remission with incomplete regeneration of the blood count was included in the group of CR.

AB0 compatibility was the most common (56 transplants), followed by minor incompatibility (19 transplants), major incompatibility (15 transplants), bidirectional incompatibility (7 transplants).

The *age* of the stem cell donor ranged between 12–68 years, with a median of 44 years. Twice, it was an underage sibling (12 and 14 years old). 63 times the patient's brother and 41 times the patient's sister donated.

In 75 transplant patients, the conditioning regimen consisted of standard myeloablative chemotherapy (busulfan and cyclophosphamide). In seven patients, we provided myeloablation with a combination of cyclophosphamide and total body irradiation (TBI); another nine patients were prepared with a reduced regimen, i.e. administration of busulfan, cyclophosphamide and fludarabine (Bu+Flu, Bu+Flu+Cy and once Flu+Cy). 13 patients received a sequential regimen, mainly according to the FLAMSA-RIC protocol (fludarabine, cytarabine, amsacrine, TBI and cyclophosphamide

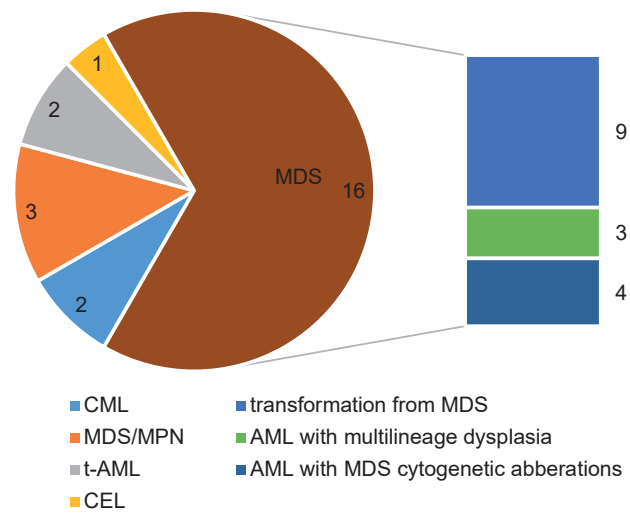

Fig. 2. Secondary AML – review.

Tab. 3. Twice transplanted patients.

	1.Tx	Risk	Cause of 2.Tx	2.Tx	Time btw Tx
1	**6/1995 (alo)**	**adverse**	**relapse 7/2016**	**6/2018**	**276 months**
2	**1/2012 (alo)**	**adverse**	**relapse 1/2015**	**5/2015**	**40 months**
3	6/2012 (alo)	adverse	relapse 3/2013	5/2013	11 months
4	9/2012 (alo)	adverse	relapse 3/2013	7/2013	10 months
5	9/2013 (alo)	adverse	extramed.relapse 5/2016	9/2017	48 months
6	8/2015 (alo)	adverse	relapse 2/2016	3/2016	7 months
7	**11/2015 (alo)**	**intermediate**	**relapse 12/2017**	**3/2018**	**28 months**
8	**3/2017 (alo)**	**adverse**	**prim.failure**	**4/2017**	**1 month**
9	**4/2018 (alo)**	**adverse**	**extramed.relapse 10/2019**	**7/2020**	**27 months**
10	**9/2019 (auto)**	**favorable**	**relapse**	**10/2020**	**13 months**

±ATG). It concerned patients with active disease, incipient relapse or MRD-positive patients.

The graft from the donor consisted of peripheral hematopoietic cells in 101 cases (97.1%) and 2x bone marrow; in 1 patient the cells came from both sources. Following the recommendations of the EBMT, from 2020 the graft was in all cases cryopreserved and only then was the preparation regimen started in the patient. In this way, the risk of donor failure due to COVID-19 infection was reduced.

The stem cell graft *yield* ranged between 1.4–15.1x10^6 $CD34^+$ cells per kilogram of patient body weight; median yield was 4.6x10^6.

As *prevention of GvHD*, we most often combined cyclosporine A with methotrexate, or mycophenolate mofetil. Rarely, solo cyclosporine A was used. Three cases were not treated with any immunosuppression. (Tab. 5).

The median time to achieve an *absolute neutrophil count above 0.5x10^9/l* was 16 days after transplantation and varied between 10-41 days. Four transplant recipients had a late engraftment of more than 30 days; these were patients with dysplastic changes and patients with inhibited regeneration by infection. The number of *platelets above 20x10^9/l* and thus independence from transfusions was achieved after 7–56 days, in the median after 13 days after transplantation. Three patients were dependent on platelet substitutions at the time of death.

During chemotherapy-induced cytopenia, patients received a median of 5 *transfusion units* of erythrocytes and platelets, yet in a few patients we noticed enormously high transfusion requirements. Erythrocyte concentrates were administered 0–33x and platelet concentrates 1–56x. The reason for the extreme numbers was refractoriness to administered platelets, intracranial hemorrhage, suppression of hemopoiesis due to a septic condition or bone marrow fibrosis in the underlying disease, or admission to the hospital as dependent on transfusions in a non-remission status of the disease. More than 15 erythrocyte units were received by 6 patients and more than 20 platelet units by 8 patients.

Patients were *discharged* 16 to 58 days after transplantation, with a median of 22 days. Late discharge, more than 40 days after transplantation (2 patients), was due to neutropenic enterocolitis with septic shock and drug-induced hepatopathy with renal failure.

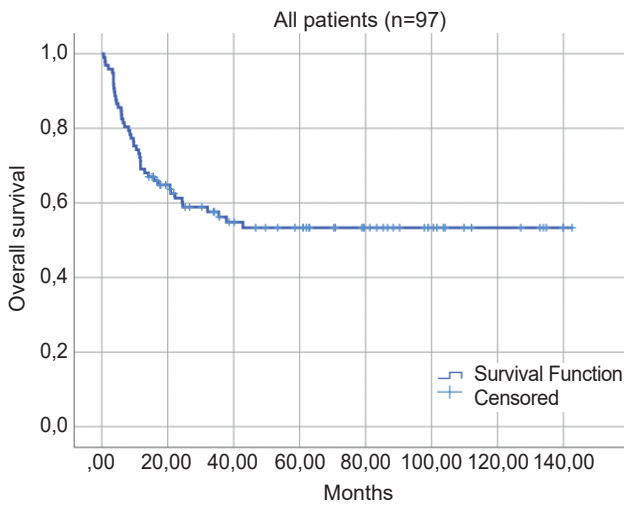

Fig. 3. Overall survival of all patients.

Tab. 4. Remission status before HSCT.

Remission status	n	%
CR1	77	79.4
CR2	6	6.2
without CR	14	14.4

Tab. 5. Immunosuppressive drugs.

Immunosupp.	n	Comment
CsA + MTX	88	standard profylaxis
CsA + MMF	10	9x at condioning FLAMSA-RIC, 1x for methotrexate hepatotoxicity
CsA	3	for inducing GvL effect
without immunosuppression	3	2x for inducing GvL effect, 1x syngeneic transplantation

Overall survival of patients and causes of death

Out of the entire study of 97 patients as of January 1, 2022, 54 patients (55.7%) are alive and 43 patients (44.3%) have died. Median overall survival was not reached. 5-year survival is 54.5% (Fig. 3).

In the majority, 24 patients, non-relapse mortality was recorded (55.81% of patients who died, 24.74% of all transplanted). GvHD (10 patients) and infectious complications (5 patients) dominate as the causes of death. In 4 patients, the cause of death was unknown, 1 patient died due to capillary leak syndrome, 1 patient due to intracranial hemorrhage after trauma, 1 patient due to intestinal perforation,

Tab. 6. Overall survival according to risk groups.

	n	Medián OS (months)	5-y OS (%)	CI 95% lower	CI 95% upper	HR (CI 95%)
favorable risk	16	not reached	75.0	–	11.8	–
intermediate risk	21	not reached	78.5	–	32.1	2.88 (1.38–6.01)
adverse risk	56	20.7	40.6	11.5	63.5	4.38 (2.23–8.62)

Tab. 7. Overall survival according to remission.

	n	Medián OS (months)	5-y OS (%)	CI 95% lower	CI 95% upper	HR (CI 95%)
1.CR	77	not reached	60.2	42.8	63.5	–
2.CR	6	6	42.9	1.1	14.1	2.81 (0.56–14.18)
without CR	14	6	28.6	3.6	11.5	3.73 (1.21–11.53)

Tab. 8. Overall survival according to the number of induction courses.

	n	Medián OS (months)	5-y OS (%)	CI 95% lower	CI 95% upper	HR (CI 95%)
CR after 1.induction	69	not reached	64.4	63.5	63.5	–
CR after 2.induction	19	20.7	36.8	6.5	35.5	2.20 (0.95–5.09)
chemoresistant	9	11.5	22.2	3.6	15.9	3.21 (0.90–11.48)

1 patient due to veno-occlusive disease (VOD) with sepsis, and 1 patient committed suicide. 19 patients died of a relapse of leukemia (44.2% of deaths, 19.6% of all transplanted). We observed 100-day mortality in 7 patients (7.2% transplanted).

We observed, that the differences in OS between the risk groups are statistically significant (p=0.002) (Fig. 4, Tab. 6). In patients who underwent two allogeneic transplants, we included parameters from the first transplant in the statistical evaluation of OS only. The exception were two patients in whom the first transplant was performed outside of Slovakia or outside the monitored period – 23 years before the second transplant with the development of another clone. Four patients with unknown genetics were excluded from the statistical evaluation.

We used the Cox proportional hazard model to conduct the multivariable analysis of overall survival (Tab. 9). Statistically significant effect on OS shows transplantion in CR2 (HR 6.76, CI 95% 2.19–20.80, p=0.0009), In addition, this parameter influenced OS more than achieving CR up to the 2nd induction course (HR 2.44, CI 95% 1.17–5.11; p=0.0180) or entry into transplantation without CR (HR 2.81, CI 95% 1.09–7.26; p=0.0326). The effect of high-risk status was lower with no statistical significance (HR 2.22, CI 95% 0.77–6.42; p=0.1425).

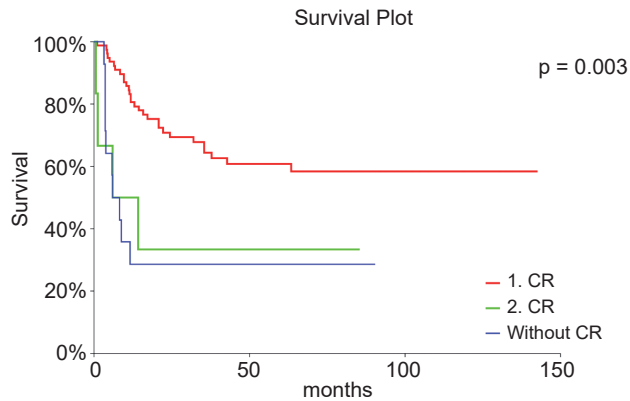

Fig. 5. Overall survival according to remission.

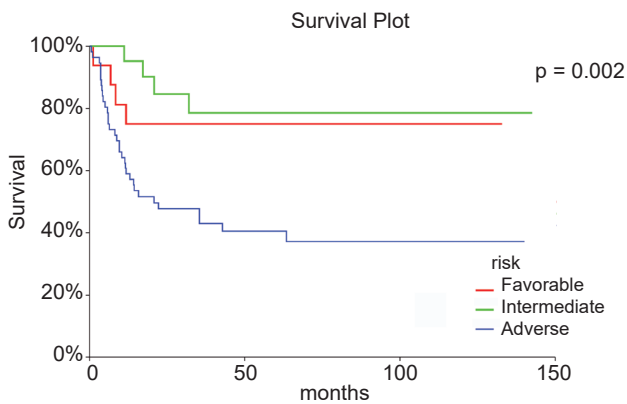

Fig. 4. Overall survival according to risk groups.

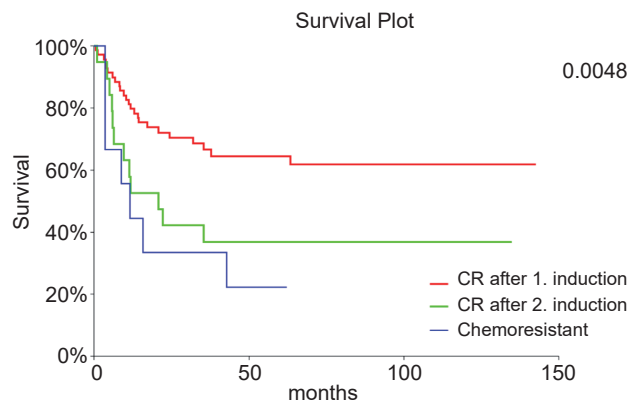

Fig. 6. Overall survival according to the number of induction courses.

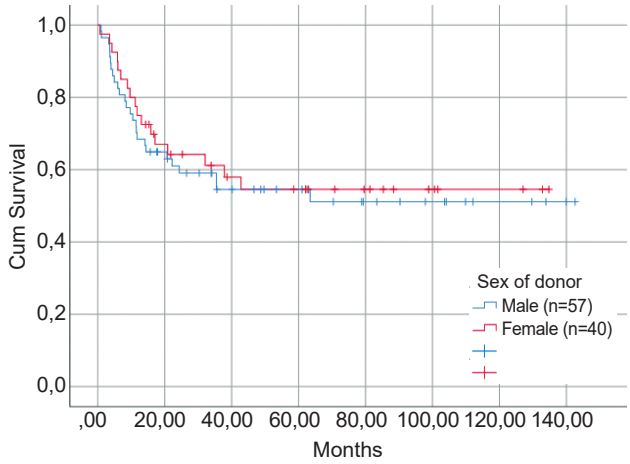

Fig. 7. Overall survival according to the gender of donor.

Graft-versus-host disease

Acute GvHD was manifested in 33 patients (34.02%), of whom 15 are alive (45.45%). We have no data on 1 patient; the others (63 patients) did not develop acute GvHD. Grade I had 8 patients, which represents 8.25% of transplantations (5 patients are alive, 62.50%). Grade II had 16 patients, 16.49% transplanted (5 patients alive, 31.25%). Grade III had 7 patients, 7.22% transplanted (4 patients alive, 57.14%) and Grade IV had 2 patients, 2.06% (0 patients alive, 0%). Clinical manifestations of acute GvHD are listed in Table 10.

Tab. 9. Multivariate analysis of overall survival.

	HR	p	95,0% CI	
			Lower	Upper
High risk	2.2167	0.1425	0.7651	6.4219
2.CR before Tx	6.7563	0.0009	2.1949	20.7976
Without CR	2.8118	0.0326	1.0893	7.2583
CR after 2.induct.	2.4413	0.0180	1.1655	5.1139

Tab. 10. Clinical manifestations of acute GvHD.

Acute GvHD	n	Alive n (%)
Skin	26	12 (46.2%)
Liver	9	3 (33.3%)
GI	10	4 (40.0%)
Ocular	4	2 (50.0%)
Oral mucosa	7	3 (42.9%)

Tab. 11. Clinical manifestations of chronic GvHD.

Chronic GvHD	n	Alive n (%)
Skin	29	21 (72.4%)
Ocular	28	20 (71.4%)
Oral mucosa	25	16 (64.0%)
Liver	32	21 (65.6%)
Lung	8	6 (75.0%)
GI	4	3 (75.0%)
Joints and fasciae	5	3 (60.0%)

44 patients (45.36%) had chronic GvHD (cGvHD), and 30 of them are alive as of the January 1, 2022 (68.18%). We have no data on two patients. 51 patients (52.58%) did not develop chronic GvHD; 24 of them are still alive (47.06%). Mild cGvHD was diagnosed in 9 patients, 9.28% transplanted (7 patients alive, 77.78%). We observed moderate cGvHD in 11 patients, 11.34% transplanted (8 patients alive, 72.73%). Severe GvHD in 24 patients, 24.74% (15 patients alive, 62.50%). The main clinical manifestations represented the skin, eyes, mucous membranes of the oral cavity and liver; we noticed it less often in the lungs, GI tract or joints (Tab. 11).

Of the ten patients who died of GvHD, three had respiratory failure in a cGvHD-affected field, and three patients had severe cGvHD of the liver. One patient had a hepatic form of acute GvHD, and another patient had acute GvHD of the gastrointestinal tract. We have no data on one patient, and one patient died of acute GvHD of the GI tract and liver after the second transplant.

Discussion

The improvement of the overall survival of patients with AML is related to the development of transplantology and supportive, mainly anti-infectious treatment. The reduced intensity of the conditioning regimes and the evolution of techniques for monitoring MRD and HLA typing contributed significantly to making the selection of patients and donors for HSCT optimal. Nowadays, the procedure itself is more widely available and safer, even in older age categories.

Compared to the 54.5% 5-year survival of our cohort, a similar 56% 2-year OS was observed in the work of Hansen et al. (7). According to our results, deaths occur rarely 2 years after transplantation. The median OS of our patients in favorable (16 patients) and moderate risk (21 patients) was not reached. Better results in patients with intermediate risk than in patients with favorable risk are attributed to the error of small numbers; the difference is not statistically significant (p=0.5742). In our cohort of high-risk patients, the median OS is 20.7 months and the 5-year OS is 40.6% (according to the mentioned study, 45%).

The 5-year OS of our patients transplanted in CR2 (6 patients) was 42.9%, according to a multicenter analysis by German authors (8) with a significantly larger cohort (128 patients) with a median follow-up of 6.5 years, the OS is around 49%. Regarding refractory patients transplanted without CR, in our group of 14 patients 5-year OS was 28.6%, according to the mentioned German analysis (297 patients) 23%.

Patients transplanted in CR2 had worse OS, median 6 months (CI 95% 1.1–14.1) than patients in CR1, median not reached (CI 95% 42.8–63.5), difference was statistically significant (p=0.0003) (Fig. 5, Tab. 7).

Whether the number of induction therapies required to achieve CR affects the prognosis after allogeneic HSCT is not entirely clear (9, 10, 11, 12). We found that patients who required two induction therapies to achieve CR had a poorer OS after allogeneic HSCT, median 20.7 months (95% CI, 6.5–35.5) than those who achieved CR after one induction course, median not reached (95%

CI, 63.5–63.5), difference was statistically significant (p=0.0048). This may be due to several factors, including the higher burden of disease and a more resistant form of leuemia requiring more intensive treatment (Fig. 6, Tab. 8).

Despite some literature data on the higher risk of GvHD and mortality associated with allogeneic HSCT in patients transplanted from women (13, 14, 15), in our group as well as in some other studies (16, 17, 18), there was no effect on overall survival. In our study, patients who received a graft from a sister achieved a better OS, yet the difference is not statistically significant (Fig. 7) (p=0.686).

When looking at the causes of death, relapses of leukemia prevail. Better traceability of genetic markers causes earlier detection of incipient relapse of the disease and gives the possibility of early therapeutic intervention in the form of induction of GvL by donor lymphocytes or reduction of immunosuppression. Treatment of corticosteroid-resistant GvHD represents a worldwide problem. Infectious causes of death in the cohort also included complications caused by CMV reactivation, which are expected to be significantly reduced by the prophylactic administration of letermovir.

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