Documenta Haematologica -
Revista Romana de Hematologie | 2023, Vol. 1, Nr. 4

Outcomes of allogeneic stem cell transplantation in acute leukemias – single centre study

Alexandra Oana ENACHE[1,2*], Mihail MATEI[1,3], Lavinia Eugenia LIPAN[1,4], Oana Gabriela CRACIUN[4], Laura Diana STEFAN[4], Andra Georgiana STOICA[4], Zsofia VARADY[4], Alina Daniela TANASE[2,4]

Abstract

Aim: *Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended in first complete remission (CR) for adverse and intermediate-risk acute myeloid leukemia (AML) and not recommended for AML patients with favourable disease. Allo-HSCT is standard of care in high-risk acute lymphoblastic leukaemia (ALL) and relapsed ALL but is not indicated for standard-risk ALL. Even though in many studies benefit for survival was proven for these patients, relapse rates (RR) at one year (32.9% for LAM and 34% for LAL) remains problematic. We want to report the outcomes of patients treated for acute leukaemia in our centre.*

Materials and methods: *We conducted a retrospective descriptive analysis of 215 patients with acute leukaemia treated with allo-HSCT between 2017 and 2022 in Fundeni Clinical Institute. Data analysis aimed the overall survival (OS) rate, progression free survival (PFS) and RR at one year based on genetic risk, number of CR, minimal residual disease (MRD) status and conditioning regimen used.*

Results: *At one year evaluation we observed OS rate of 64% and a 34% RR for ALL patients, while AML patients had a 74% OS rate and 13% RR.*

Conclusions: *The results obtained in our centre are similar to the ones reported in literature. The highest risk of relapse and smallest rate of survival are registered for patients who present with negative risk factors. The multifactorial influence over OS and RR impose the need for future studies in which different patient categories can benefit from an optimal therapeutic management.*

Keywords: allogeneic hematopoietic stem cell transplantation, acute leukaemia, lymphoblastic, myeloid, minimal residual disease, conditioning regimen

[1]University of Medicine and Pharmacy "Carol Davila", Bucharest

[2]Coltea Clinical Hospital – Hematology Department, Bucharest

[3]Central Military Emergency Hospital "Carol Davila" – Hematology Department, Bucharest

[4]Fundeni Clinical Institute – Bone Marrow Transplant Department, Bucharest

Corresponding author:
***Alexandra Oana Enache,** University of Medicine and Pharmacy "Carol Davila", Bucharest, Coltea Clinical Hospital – Hematology Department, Bucharest
email: oanaaaenache@gmail.com

Introduction

Acute myeloid leukemia (AML)

AML is highly heterogenous regarding disease characteristic (cytogenetics and mutational phenotype) which demands an individualised treatment approach. (Gilleece 2021) According to European LeukemiaNet (ELN) risk stratification, AML can be defined as either low, intermediate, or high risk. (Hartmut Döhner 2022) Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended in first complete remission (CR)

for adverse and intermediate-risk AML and not recommended for AML patients with favourable disease, except for those who have detectable minimal residual disease (MRD+). (Jentzsch 2021) (Gilleece 2021) (Snowden 2022) In addition to the risk category defined by the ELN, the most important reported predictor factors for the outcome of allo-HSCT in AML patients are MRD status and number of CR, with worse OS, PFS and RR reported for those who have MRD+ and more than CR1 at time of allo-HSCT. (Jentzsch M 2022) (Jentzsch 2021)
Acute lymphoblastic leukemia (ALL)
Allo-HSCT is standard of care in high-risk ALL and relapsed ALL but is not indicated for standard-risk ALL, especially if MRD-. (Snowden 2022) A retrospective study conducted by Satoshi Kaito et. al. in 2022 also revealed that adult patients with Philadelphia-negative B-ALL have worse outcomes when allo-HSCT is being performed in CR2 in comparison to patients in CR1 (3-year OS rate 51.8% vs 68.1%; 3-year RR 34.2% vs 17.6%). (Kaito S 2022)
Even though in many studies benefit for survival was proven for these patients, relapse rates (RR) at one year (32.9% for LAM and 34% for LAL) remains problematic. (J. Apperley 2012)

The aim of this paper is to report the outcomes of patients treated for acute leukaemia in our centre, with OS as primary endpoint and PFS and RR as secondary endpoints.

Materials and Methods

A retrospective descriptive analysis was conducted and 215 patients with acute leukaemia treated with allo-HSCT between 2017 and 2022 in Fundeni Clinical Institute were included in the study.
Clinical patient data were collected from Fundeni Clinical Institute database and patients' medical records. Microsoft Excel was used to build the database and statistical analysis was done through XLSTAT extension.
Inclusion criteria were diagnosis of either AML or ALL for patients undergoing allo-HSCT from a matched sibling donor (MSD), matched unrelated donor (MUD) or from a mismatched alternative donor [haploidentical donor (HAPLO)]. The conditioning regimens used were myeloablative (FluBu4 or BuCy) and reduced intensity conditioning (RIC) (FluBu2, FluBu3, TT/Flu/Mel and FluMel140).

Characteristic	AML (n=156)	B-ALL (n=50)	T-ALL (n=13)
Risk category			
Low	21	-	-
Intermediate	75	22	11
High-risk	23	10	2
FLT3-ITD pos.	37	-	-
Philadelphia pos.	-	18	-
Number of CR			
CR1	86	32	10
CR2	70	18	3
MRD status			
MRD-	64	23	10
MRD+	37	18	2
Not evaluated	55	9	1
Donor type			
MUD	102	24	10
MSD	35	24	2
HAPLO	19	2	1
Conditioning regimen			
MAC	33	12	7
RIC	123	38	6

Table 1. Patient population characteristics. MUD – matched unrelated donor, MSD – matched sibling donor, HAPLO – haploidentical donor, MAC – myeloablative conditioning regimen, RIC – reduced intensity conditioning regimen

https://doi.org/10.59854/dhrrh.2023.1.4.199

Our primary aim was overall survival (OS) rate and RR at one year based genetic risk, donor type and conditioning regimen used.

Progression free survival was defined as the time from transplantation until disease recurrence or death. If the patients were still alive, then OS and PFS were calculated according to the last follow-up. To estimate OS, PFS and RR the Kaplan-Meier method was used. The significance of differences in the probabilities obtained were tested using the log-rank test.

Data collection and analysis was conducted after approval by the Ethics Committee of Fundeni Clinical Institute, Bucharest in accordance with the Declaration of Helsinky.

AML subgroup analysis

Analysis of PFS in accordance with risk-group category showed better outcomes for patients with FLT3-ITD mutations than those observed in the high-risk group with mean survival time of 50.68 months (39.43-61.94 months; SD=5.73) vs 28.84 months (18.34-35.34 months; SD=4.33), without statistical significance (log-rank = 2.043, p=0.563). (Fig.3) Mean OS time for FLT3-ITD vs high-risk patients was 52.4 months (42.02-62.77 months, SD=5.29) vs 34.86 months (26.37-43.35 months, SD=4.33), without statistical significance (log-rank = 1.179, p=0.758). (Fig.4)

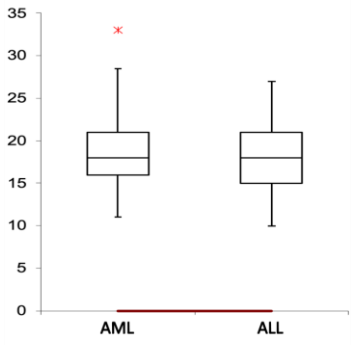

Fig.1 Median time to neutrophil engraftment – day +18

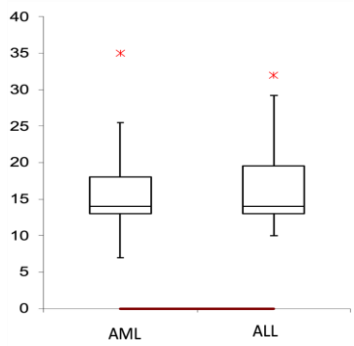

Fig. 2 Median time to platelet engraftment – day +14

Results

Patient population characteristic regarding risk category, number of CR, MRD status, type of donor cells and conditioning regimen are presented in Table 1. The female to male ratio in the AML-patient population was 1.08 (n=81 to n=75), and 1.03 in the ALL-patient population (n=32 to n=31). The patients received cryopreserved peripheral blood stem cells.

The median time to neutrophil engraftment was day +18 (day +10 to day +33) for both AML and ALL patients (Fig.1). The median time to platelet engraftment was day +14 (day +7 to day +35) for both patient populations. (Fig.2)

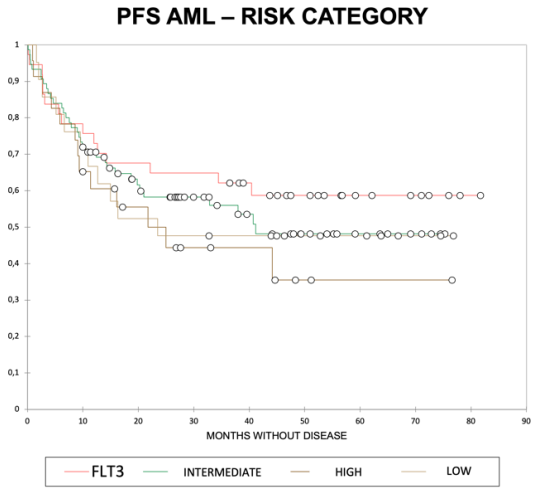

Fig.3 PFS – according to AML risk category

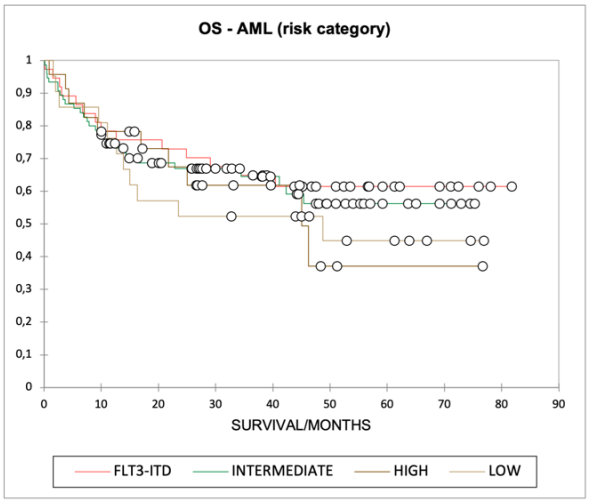

Fig.4 OS – according to AML risk category

Statistical significance was observed when the analysis for PFS and OS was performed in accordance with MRD status. MRD negative showed improved PFS (mean PFS time 52.86 months (44.61-61.11 months, SD=4.20) vs 33.68 months (22.55-44.81 months, SD=5.68) (log-rank = 8.026, p=0.005), as well as improved OS (mean OS time 56.51 months (48.22-64.80 months, SD=4.23) vs 41.23 months (29.97-52.49 months, SD=5.73) (log-rank = 3.955, p=0.047). (Fig.5 and Fig.6)

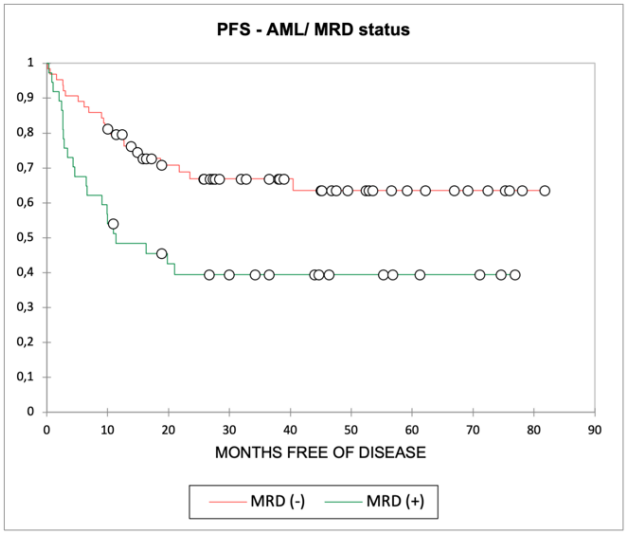

Fig.5 PFS – MRD status influence in AML patients

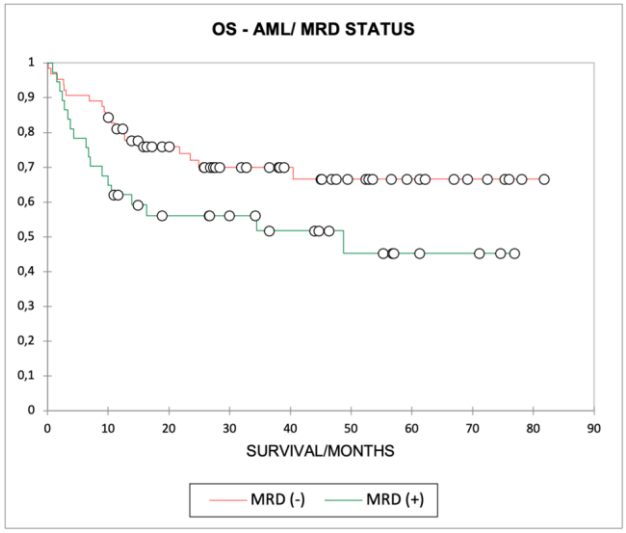

Fig.6 OS – MRD status influence in AML patients

No statistical significance was registered for PFS or OS when we compared patients with AML who underwent allo-HSCT in CR1 vs more than CR1, even though the results favour the ones who go through this procedure in the first CR (log-rank=0.945, p=0.331 for PFS and log-rank=0.738, p=0.390 for OS). (Fig.7 and Fig.8)

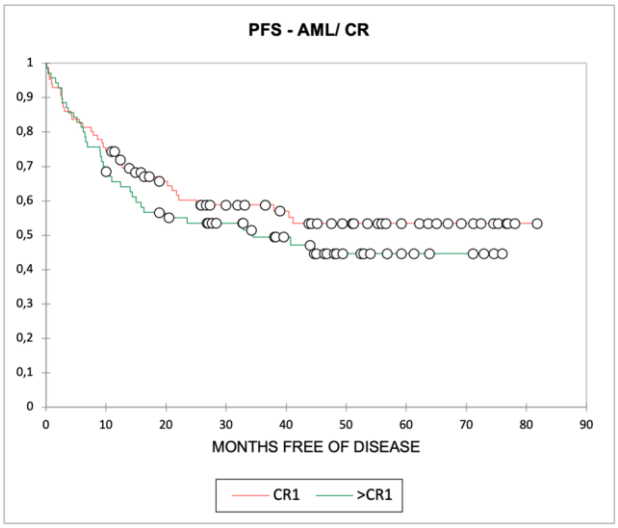

Fig. 7 Influence of number of CR on PFS in AML patients

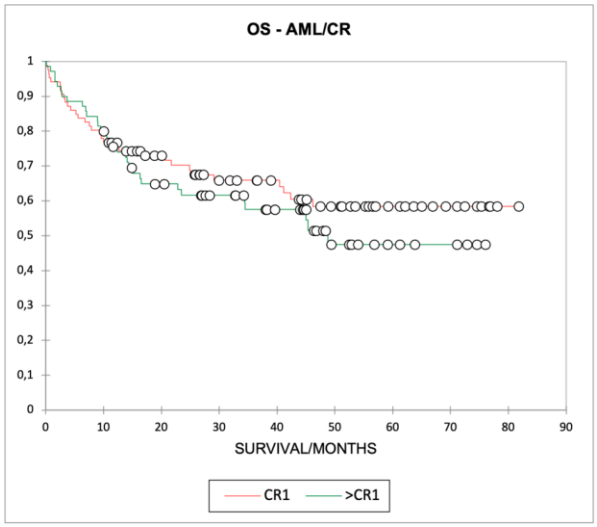

Fig.8 Influence of number of CR on OS in AML patients

An analysis was runed for MRD status and the conditioning regimen used for AML patients, and statistical significance was observed when comparing MRD (+) AML receiving MAC vs RIC both in PFS (mean survival time 50.321 months vs 23.19 months) (log-rank=7.508, p=0.006) and RR (mean survival time 66.151

https://doi.org/10.59854/dhrrh.2023.1.4.199

months vs 27 months) (log-rank=27.699, p<0.0001). (Fig.9 and Fig.10)

No statistical significance was observed for PFS (log-rank=1.792, p=0.181), OS (log-rank=5.320, p=0.150) or RR (log-rank=0.160, p=0.689) in patients who were MRD (-) at time of transplantation. (Fig. 9, Fig.10 and Fig.11)

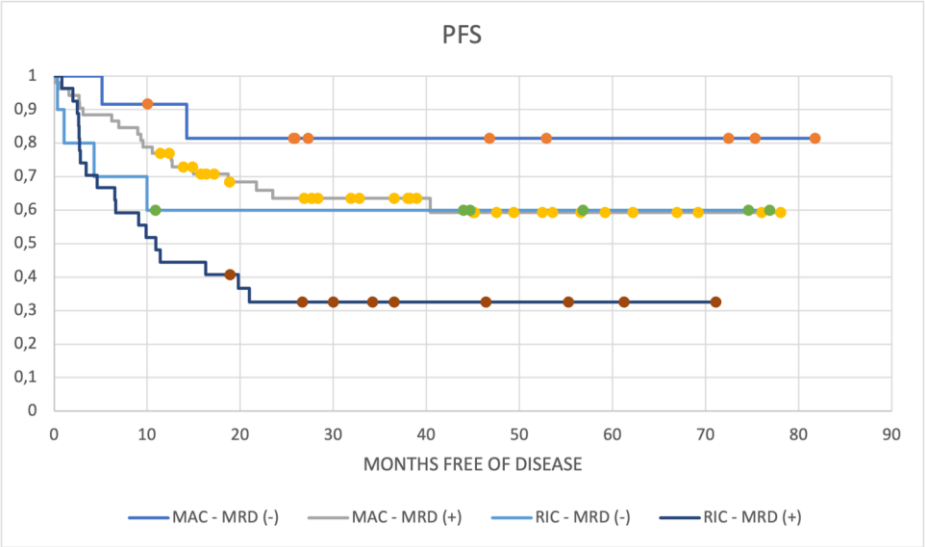

Fig.9 PFS in regard to MRD status and the conditioning regimen used in AML patients

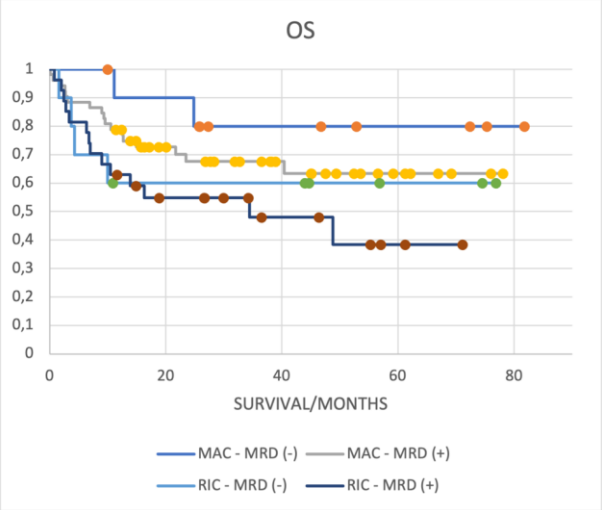

Fig.10 Relapse rate for AML patients in regard to MRD status and the conditioning regimen used

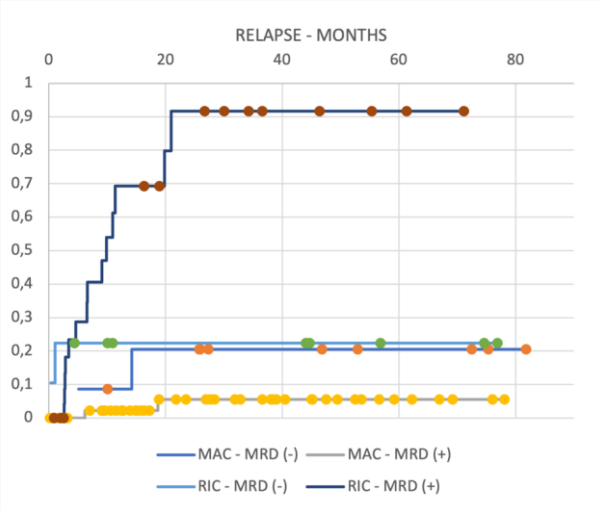

Fig.11 OS for AML patients in regard to MRD status and the conditioning regimen used

ALL subgroup analysis

Better OS was registered for patients with B-ALL than for T-ALL (mean OS time 43.83 months SD=4.743 vs 18.32 months SD=6.18 (log-rank=9.355, p=0.002). (Fig.12)

When comparing ALL patients according to risk category, poorer outcomes, without statistical significance were registered for patients with intermediate-risk with mean OS time 29.18 months SD=4.57 (log-rank=0.923, p=0.630) and mean PFS time 20.71 months SD=3.65(log-rank=0.923, p=0.630). (Fig. 13)

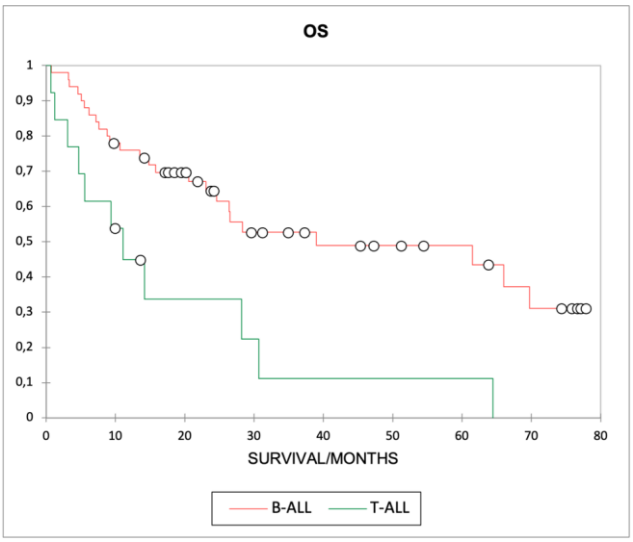

Fig.12 OS for B-ALL patients vs T-ALL patients

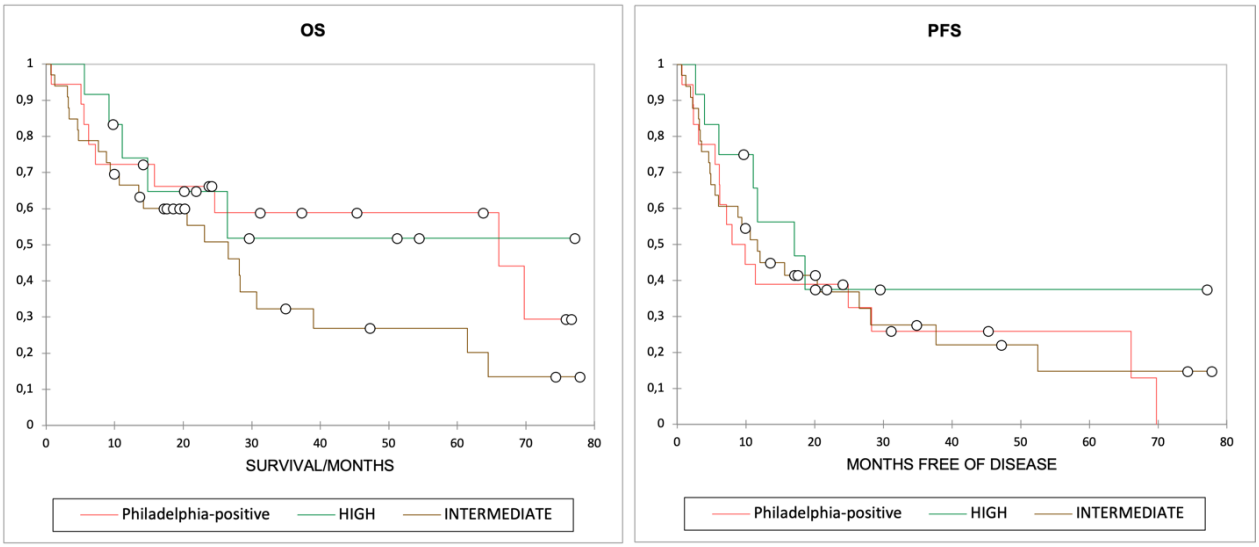

Fig.13 OS and PFS according to risk category for ALL patients

There was no statistical significance for OS and PFS observed when comparing patients in first CR vs those undergoing the allo-HSCT in more than first CR, even though the results favour for the first 18 months, and first 13 months, respectively, the ones in first CR at time of transplantation. Mean OS time for CR1 vs more than CR1 was 41.46 months SD=5.05 vs 30.82 months SD=6.71 (log-rank=1.449, p=0.229) and mean PFS time was 24.38 months SD=3.85 vs 26.11 months SD=6.97 (log-rank=0.325, p=0.568) (Fig.14)

PFS in MRD (+) ALL patients is worse than that observed for patients who are MRD(-) at time of transplantation (mean survival time 16.12 months SD=3.39 vs 24.14 months SD=4.67), without statistical significance (log-rank=0.496, p=0.481). (Fig.15)

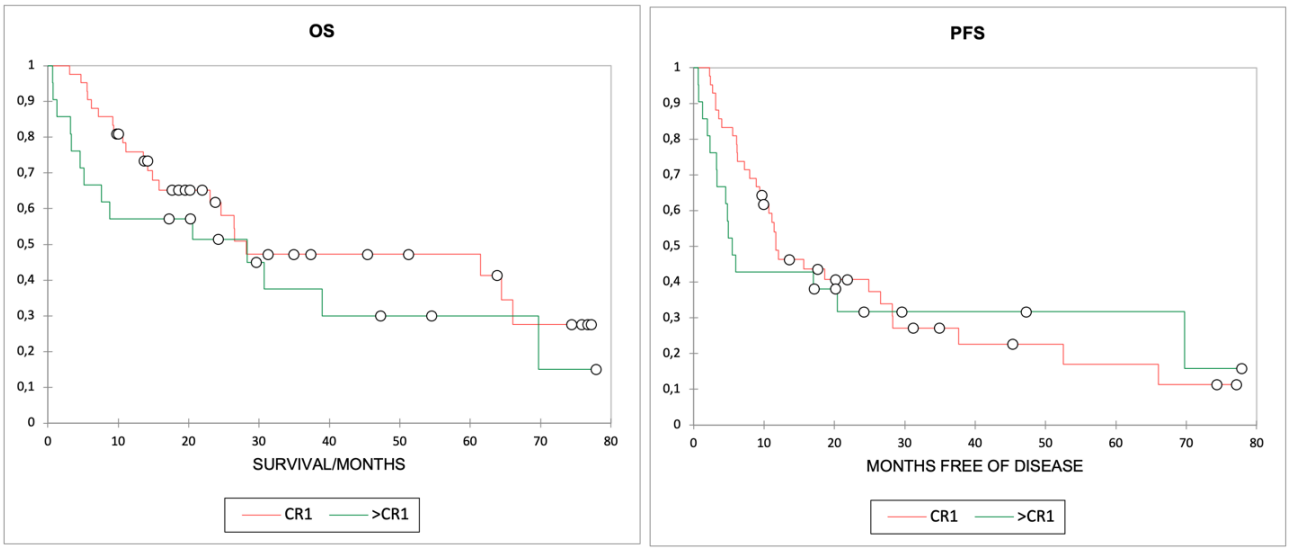

Fig.14 OS and PFS according to number of CR for ALL patients

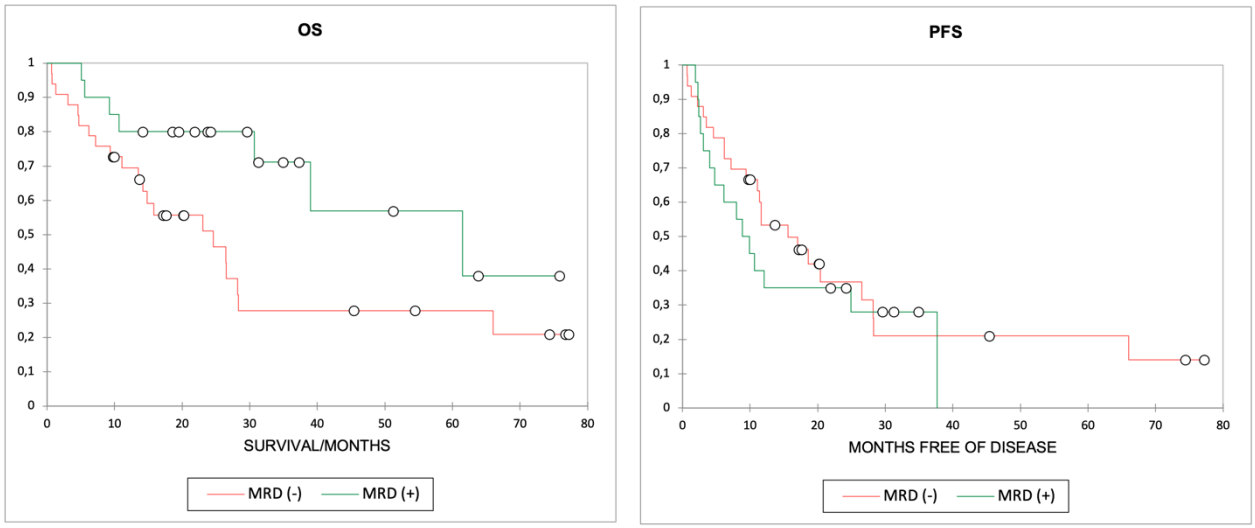

Fig.15 OS and PFS according to MRD status for ALL patients

Discussion

Patients diagnosed with AML carrying FLT3-ITD mutations experience advantages from post-transplant maintenance treatment involving tyrosine kinase inhibitors (like midostaurin, sorafenib, gilteritinib, quizartinib, etc.), leading to improved survival rates as depicted in the survival curves within the analysed patient population. These findings strongly support the ongoing administration of maintenance therapy post allo-HSCT for individuals with FLT3-ITD AML.

For patients with AML, regardless of risk-category, a survival benefit (better PFS and OS curves) was observed on univariate analysis for patients undergoing allo-HSCT in first CR.

Patients with undetectable MRD at time of transplantation had better outcomes both on univariate and multivariate analysis in the AML subgroup. Even with the myeloablative conditioning regimen MRD (+) brings worse PFS and OS for patients undergoing allo-HSCT.

Even though outcomes with the use of myeloablative conditioning regimens is better for patients who are MRD (+) at time of transplantation, a considerable number of these individuals are ineligible due to advanced age and a high-risk HCT-CI score (the majority of AML patient population is older than 55 years). In the case of MRD (+)

and reduced intensity conditioning regimen, the RR is greater than 50%. There were no statistical significant differences observed on multivariate analysis for PFS and OS in MRD (-) AML patients, indifferent of the conditioning regimen used.

The results observed for patients with B-ALL were better in terms of OS and PFS than the ones observed for T-ALL. Worse OS and PFS registered for ALL patients in the intermediate-risk category might be due to a higher rate of procedure related toxicity. Thus, transplant related mortality observed for intermediate risk ALL patients treated in our centre is high. The discussion emerges regarding the initiation of transplantation following the second CR among the individuals categorized as intermediate risk, contemplating the limited observed advantages of the procedure within the analysed cohort. This issue is reinforced when curves observed on the analysis for CR1 vs more than CR1 have crossing points. In the ALL subgroup, detectable MRD brings an important relapse risk, with a reduced benefit of the allo-HSCT procedure.

The study's limitations, stemming from its retrospective design, a small number of T-ALL patients registered, and the lack of available MRD status for a notable portion of the patient pool, might have impacted the obtained results.

Conclusion

The results obtained in our centre are similar to the ones reported in literature. The highest risk of relapse and smallest rate of survival are registered for patients who present with advanced age, higher HCT-CI scores, and especially detectable MRD at time of transplantation.

Better outcomes observed within the patient populations either FLT3-ITD positive AML or Ph-positive ALL underline the importance of tyrosine kinase inhibitors usage in this setting both in induction of remission and maintenance treatment after allo-HSCT.

The multifactorial influence over OS and RR brings up the need for future studies in which the therapeutic management of acute leukaemia patients can be optimized.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Jentzsch, M., Grimm, J., Bill, M. et al. 2021. "Prognostic relevance of remission and measurable residual disease status in AML patients prior to reduced intensity or non-myeloablative allogeneic stem cell transplantation." Blood Cancer J. 11 80.
2. Gilleece, M.H., Shimoni, A., Labopin, M. et al. 2021. "Measurable residual disease status and outcome of transplant in acute myeloid leukemia in second complete remission: a study by the acute leukemia working party of the EBMT." Blood Cancer J. 11 88.
3. Hartmut Döhner, Andrew H. Wei, Frederick R. Appelbaum, Charles Craddock, Courtney D. DiNardo, Hervé Dombret, Benjamin L. Ebert, Pierre Fenaux, Lucy A. Godley, Robert P. Hasserjian, Richard A. Larson, Ross L. Levine, Yasushi Miyazaki, Dietger Niederwieser,. 2022. "Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN." Blood 140 (12): 1345–1377.
4. Snowden, J.A., Sánchez-Ortega, I., Corbacioglu, S. et al. 2022. "ndications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022." Bone Marrow Transplant 57 1217–1239.
5. Jentzsch M, Bischof L, Backhaus D, Brauer D, Schulz J, Franke GN, Vucinic V, Niederwieser D, Platzbecker U, Schwind S. 2022. "Impact of MRD status in patients with AML undergoing allogeneic stem cell transplantation in the first vs the second remission." Blood Adv. 6 (15): 4570-4580.
6. Kaito S, Kurosawa S, Najima Y, Sakaida E, Shingai N, Fukuda T, Tachibana T, Uchida N, Ozawa Y, Sawa M, Nakazawa H, Ota S, Kato J, Nakamae H, Katayama Y, Eto T, Tanaka J, Kanda Y, Atsuta Y, Arai Y, Kako S. 2022. "Allogeneic Hematopoietic Stem Cell Transplantation for Adult Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia in Second Complete Remission." Transplant Cell Ther. 28(6): 326.e1-326.e10.
7. J. Apperley, E. Carreras, E. Gluckman, T. Masszi. 2012. The EBMT Handbook: Haematopoietic Stem Cell Transplantation. Vol. 6th Edition. EBMT.

 https://doi.org/10.59854/dhrrh.2023.1.4.199