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Prognostic factors affecting the outcome after allogeneic haematopoietic stem cell transplantation for myelodysplastic syndrome

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ABSTRACT

In the present study, we retrospectively analysed the results of HSCT in 47 consecutive patients with MDS diagnosed at our department between 2002 and 2019, with a focus on possible predictive factors influencing overall survival (OS), the development of relapse, infections, and the occurrence of graft versus host disease (GvHD). In a univariate analysis, the pre-transplantation value of blasts in the marrow < 5% ($p = 0.006$), the revised International Prognostic Scoring System (IPSS-R) ($p = 0.041$), and karyotype ($p = 0.009$) were predictive of OS. Neither the elevation of serum ferritin (> 1000 ug/ml) nor increased C-reactive protein (CRP) (> 5 mg/l) was associated with shorter OS. In contrast, elevated serum lactate dehydrogenase (LDH) (> 213 U/l) was associated with shorter OS ($p = 0.04$).

1. Introduction

Myelodysplastic syndrome (MDS) represents a group of clonal myeloid stem cell disorders with a heterogeneous spectrum of presentations, ranging from an indolent course over several years to rapid progression to acute myeloid leukaemia (AML). Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only available curative method. [1,2]

Unambiguous risk factors for relapses of MDS are higher age, a higher number of blasts in the marrow, advanced bone marrow fibrosis, a complex karyotype (more than three cytogenetic aberrations), and the presence of some somatic mutations (ASXL1, RUNX1, and TP53). [3]

2. Patient population

The cohort under evaluation includes 47 consecutive patients (24 females, 23 males) who underwent HSCT for MDS at our department between October 1st, 2002 and November 31st, 2019. The median of the age was 58 years (range, 26 – 68) at the time of HSCT and the median of the period from the diagnosis to HSCT was 5 months (M) (range, 2 - 42 M); the median follow-up from HSCT was 24 M (range, 1–185 M). The analysis was carried out in January 2021, with 21 patients (45%) still alive.

3. Disease characteristics and treatment of MDS

In the present cohort, four cases (8%) were secondary forms of MDS (primary malignity: carcinoma of the testicle, colon cancer, acute promyelocytic leukaemia, acute myeloid leukaemia). The diagnosis was established according to the 2016 World Health Organization criteria (WHO) and the representation of individual subtypes was as follows: MDS with multilineage dysplasia (MDS-MLD) $n = 10$ (22%), MDS with excess blasts 1 (MDS-EB1) $n = 5$ (10%), MDS-EB2 $n = 24$ (51%), and chronic myelomonocytic leukaemia (CMML) in eight patients (17%). [4] According to IPSS-R, 16 patients (34%) were medium-risk, 24 patients (51%) high-risk, and seven (15%) very high-risk (see Table 1). Patients with ≥ 20% blasts in the marrow at any time in the course of treatment were classified as AML and were not included in the present analysis. On the basis of the cytogenetic findings, the patients were divided into four groups: 21 patients (45%) with a normal karyotype, five patients (10%) with chromosome 7 abnormalities, and six (13%) with a complex karyotype, while in 15 patients (32%) other changes were found: +8, del 5, del Y, del 12, t(3;3), t(1;6), t(2;7), and t(16;21). The presence of a TP53 mutation was analysed in 22 patients, TP53 mutation was present in four patients with a complex karyotype.

Prior to the performance of HSCT, seven patients (15%) did not undergo any treatment, 13 patients (26%) were treated with a hypomethylating agent (azacitidine, AZA), and 13 patients (28%) with

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Table 1
Demographic and clinical characteristics of the patients who underwent HSCT.

Number of patients	$N = 47$ (%)
Median age (years)	58 (26–68)
Male (M)	24 (51%)
Female (F)	23 (49%)
Time from diagnosis to HSCT (months)	5 (2 – 42)
WHO classification	
MDS-MLD	10 (22%)
MDS-EB1	5 (10%)
MDS-EB2	24 (51%)
CMML1/2	8 (17%)
Type of MDS	
Primary	43 (92%)
Secondary	4 (8%)
Treatment	
None	7 (15%)
Azacitidine	13 (28%)
Chemotherapy	13 (28%)
Azacitidine + chemotherapy	7 (15%)
Other	7 (15%)
Transfusion dependency	
Yes	35 (74%)
No	12 (26%)
Conditioning	
Myeloablative	18 (38%)
RIC	29 (62%)
Donor type	
HLA-matched siblingHLA-matched unrelated	12 (26%)
HLA-matched unrelated	30 (64%)
HLA-mismatched unrelated	5 (10%)
Occurrence of GvHD	
Acute	21 (45%)
Chronic	12 (26%)
Severe infection <6 M	
Yes	20 (43%)
No	27 (57%)
Relapse	
Yes	16 (34%)
No	31 (66%)

Abbreviations: HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; MDS-EB, myelodysplastic syndrome with excess blasts; CMML, chronic myelomonocytic leukaemia, GvHD, graft-versus-host disease.

induction chemotherapy. In seven patients (15%), AZA therapy was introduced first with subsequent administration of induction chemotherapy aiming to reduce the number of blasts. Other treatment (15% of the patients) included immunosuppressive therapy ($n = 5$), lenalidomide ($n = 1$), and erythropoiesis-stimulating agents ($n = 1$) (see Table 1). The median OS from HSCT was 24 M (range, 1–185 M).

On the basis of comorbidities, the Haematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was established, with the median being 1 (range, 0–3). In 18 cases (38%), myeloablative preparation was administered; 29 patients (62%) underwent reduced intensity conditioning (RIC). HLA-matched siblings were the donors of stem cells in 12 cases (26%), while in five cases (10%) the donors were HLA-mismatched unrelated. Peripheral blood stem cells were used as the graft in all the patients (see Table 1).

4. Statistical analysis

Statistical analysis was performed with the R software, version 4.0.2. OS was analysed using the "survival" library version 3.2.7. OS was defined as the interval from transplantation to death from any cause or follow-up. NRM was defined as the probability of any death in the absence of relapse since HSCT. The univariate probabilities of OS were calculated using the log-rank test and survival curves were constructed using the Kaplan-Meier method. NRM was estimated using the cumulative incidence method. P-values smaller than 0.05 were considered statistically significant; all p-values are two-sided.

5. Results

At the median follow-up of 24 months, 26 patients (55%) had died and the causes of death were as follows: relapse in ten cases (42%), infectious complications in nine (38%), acute GvHD in four (16%), and lung cancer in one patient (4%). A total of 16/47 patients (34%) relapsed with the median progression free survival (PFS) of 6 M (range, 3–22 M), ten patients have died, and six are alive: four patients have active disease, two patients are in complete remission after second allogeneic transplantation.

The two-year OS and non-relapse mortality (NRM) were 53% and 23%. Univariate analysis demonstrated the impact of the value of blasts (<5%) on OS (four-year OS 55% vs. 13% with a high value of blasts ($p = 0.006$). Likewise, cytogenetic findings had a significant impact on OS: (four-year OS: 58% vs. 48% vs. 32% vs. 0% in the group with a normal karyotype, other cytogenetic findings, complex karyotype, and abnormalities of chromosome 7) ($p = 0.009$). The four-year OS according to IPSS-R was 70% vs. 42% vs. 16% for the medium- vs. high- vs. very high-risk groups ($p = 0.04$). The impact of HCT-CI on the results of HSCT was evaluated by the division of the cohort into two groups: patients with HCT-CI 0 – one point and HCT-CI ≥ two points. Survival after four years in both groups under evaluation was 48% vs. 39% without demonstration of statistical significance ($p = 0.23$).

With regard to biological parameters, the significance of pre-transplantation serum levels of LDH, CRP, and ferritin was analysed. The pre-transplantation median LDH value was 254 U/l (range, 137–592 U/l); 60% of the patients had elevated LDH prior to HSCT. Univariate analysis demonstrated an impact of the LDH value on OS ($p = 0.041$): four-year OS was 70% versus 32% in the patients with elevated LDH (Fig. 1). We have demonstrated statistically significant relapses in the group of patients with high LDH as relapses appeared here in 14/28 cases vs. 2/19 in the group with a low LDH value ($p = 0.013$) (Fig. 2). The impact of the LDH value on the occurrence of acute and chronic forms of GvHD was not demonstrated (data not shown). In the patients with elevated LDH, however, a trend was found towards more frequent development of serious infections ($p = 0.067$).

The median of the CRP value prior to HSCT was 5 mg/l (range, 0.3–58 mg/l) and a pre-transplantation increase in CRP was present in 22/47 patients (47%). The importance of the CRP value for OS or PFS was not demonstrated in our cohort ($p = 0.92$; $p = 0.20$). In the group of patients with an elevation of CRP, however, there was a significantly higher occurrence of both forms of GvHD: aGvHD (13/22; $p = 0.042$) and chGvHD (14/22; $p = 0.009$). Similarly, in the group of patients with an elevation of CRP a higher occurrence of serious infections was observed (13/22 vs. 7/25; $p = 0.02$) in the course of 6 M after HSCT.

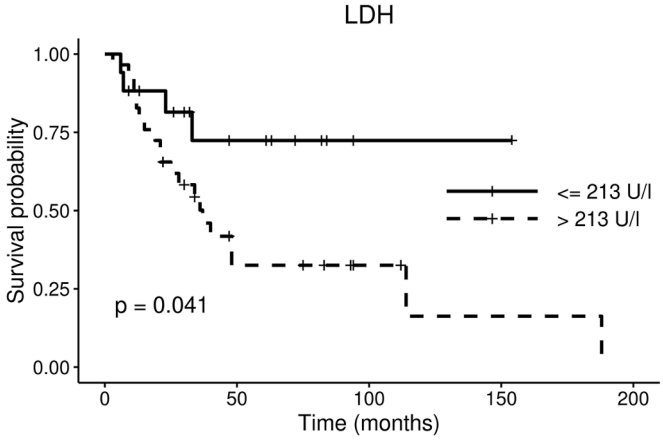

Fig. 1. Kaplan-Meier survival estimates showing overall survival and progression free survival. Overall survival of cohort stratified by pre-transplant level of LDH (≤ 213 U/l or > 213 U/l).

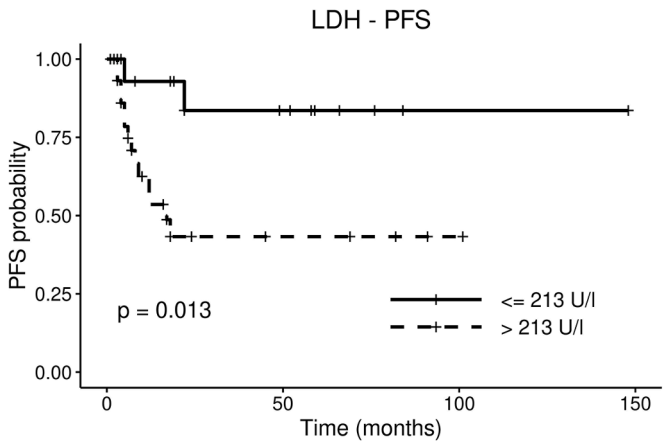

Fig. 2. Progression free survival according to LDH.

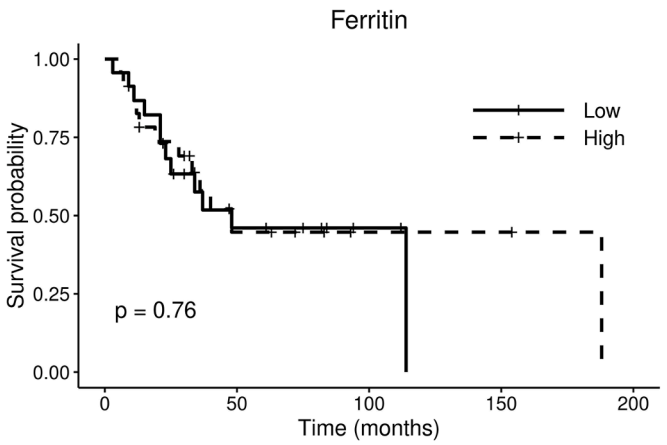

Fig. 3. Overall survival of cohort stratified by ferritin ($\leq$ 1000 ng/ml or $>$ 1000 ng/ml).

The median pre-transplantation value of ferritin was 1010 ng/ml (1010–8317 ng/ml). For the sake of analysis, the cohort was divided into two subgroups: the cut-off for an elevated level was $>$ 1000 ng/ml. Patients with a higher ferritin level had similar four-year OS compared to patients with a ferritin level below 1000 ng/ml (46% vs. 48%; p = 0.76) (Fig. 3). The significance of ferritin for PFS was not demonstrated (p = 0.55). Likewise, no association of ferritin with the development of GvHD or occurrence of relapses was found. Patients with elevated ferritin levels had a trend towards more frequent serious infections (sepsis, mycotic infections) (p = 0.07).

6. Discussion

We analysed prognostic factors for the outcome of HSCT in patients with MDS, including the disease- or patient-related factors (number of blasts, IPSS-R, cytogenetic aberrations, HCT-CI). At the same time, our attention was focused on some biological pre-transplantation markers (LDH, CRP, ferritin) which could help stratify patients prior to HSCT. In agreement with the literature, we have confirmed the significant importance of the values of blasts in the marrow. This fact has been known for a long time and confirms the necessity of achieving remission of the disease prior to the performance of HSCT. [4, 5]

The principal role of the cytogenetic finding in the survival of patients with MDS after HSCT, including its important impact on the development of relapse, has already been demonstrated. The results of our analysis are in accord with these publications. In the cohort under evaluation, the patients with chromosome 7 abnormalities displayed even worse OS after HSCT than the patients with the complex karyotype. Very unfavourable results of HSCT are also known in patients with the monosomal karyotype, but in our cohort this cytogenetic finding was not present. [6, 7] Our analysis has not demonstrated the importance of HCTI-CI for the results of HSCT. This result, however, is influenced by the fact that only 26% of the patients had HCT- CI $\geq$ 2 and only two patients had HCT-CI = 3. [8]

A higher LDH in haematological malignities is generally associated with an unfavourable prognosis. In MDS, elevation of LDH is explained by a higher disintegration of myeloid cells, damaged tissues, residual disease or haemolysis of erythrocytes. In our cohort, 20 patients had elevated LDH in spite of being in CR; hence we presume that a high pre-transplantation LDH is always a warning signal for a possible early relapse of MDS after HSCT. [9, 10]

CRP represents a sensitive marker of the inflammatory process. It follows from some studies that a higher pre-transplantation value of CRP may have a negative prognostic impact on survival, which, however, has not been demonstrated in our cohort of patients. On the other hand, in agreement with some published results, we have demonstrated a higher rate of occurrence of GvHD and serious infections in patients with increased values of CRP prior to HSCT. [11, 12]

Patients with MDS frequently develop iron overload as a result of repeated red cell transfusion, as well as other mechanisms. Several papers have already been devoted to the importance of the pre-transplantation value of ferritin on the results of transplantations. Individual papers, however, differ with regard to the cut-off value of ferritin (1000–2500 ug/l) and the heterogeneity of the patients in the cohorts. The majority of published papers have demonstrated the impact of ferritin on OS and several papers also on the development of relapse or GvHD. Surprisingly, in our cohort we have not confirmed the impact of the elevation of ferritin on OS, NRM, or the development of GvHD, either. [13–15]

In conclusion, the results of our analysis are in concordance with the literature regarding the importance of traditional and known prognostic factors for the results of HSCT (number of blasts, IPSS-R, and cytogenetic findings). Nevertheless, we have not demonstrated the prognostic significance of HCT-CI. Considering biological markers, we have demonstrated the impact of LDH on OS and the occurrence of relapses after HSCT; on the other hand, elevation of CRP seems to be connected with a higher risk of the development of GvHD or serious infections.

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Declaration of Competing Interest

The authors declare no financial or personal conflict of interest.

References

[1] U. Platzbecker, Treatment of MDS, Blood 133 (10) (2019) 1096–1107, https://doi.org/10.1182/blood-2018-10-844696.
[2] T. de Witte, D. Bowen, M. Robin, L. Malcovati, D. Niederwieser, I. Yakoub-Agha I, et al., Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel, Blood 129 (13) (2017) 1753–1762, https://doi.org/10.1182/blood-2016-06-724500.
[3] R. Bejar, K.E. Stevenson, B. Caughey, R.L. Coleman, B.G. Mar, P. Stojanov, et al., Somatic mutations predict poor outcome in atients with myelodysplastic syndrome after hematopoietic stem-cell transplantation, J. Clin. Oncol. 32 (25) (2014) 2691–2698, https://doi.org/10.1200/JCO.2013.52.3381.
[4] P. Kebriaei, J. Kline, W. Stock, K. Kasza, M.M. Le Beau, R.A. Larson, K. van Besien, Impact of disease burden at time of allogeneic stem cell transplantation in adults with acute myeloid leukemia and myelodysplastic syndromes, Bone Marrow Transplant 35 (10) (2005) 965–970, https://doi.org/10.1038/sj.bmt.1704938.
[5] E.D. Warlick, A. Cioc, T. Defor, M. Dolan, D. Weisdorf, Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden, Biol. Blood Marrow Transplant 15 (1) (2009) 30–38, https://doi.org/10.1016/j.bbmt.2008.10.012.
[6] F. Onida F, R. Brand, A. van Biezen, M. Schaap M, P.A. von dem Borne PA, J. Maertens, et al., Impact of the International Prognostic Scoring System cytogenetic risk groups on the outcome of patients with primary myelodysplastic syndromes undergoing allogeneic stem cell transplantation from human leukocyte antigen-identical siblings: a retrospective analysis of the European Society for

blood and marrow transplantation-chronic malignancies working party, Haematologica 99 (10) (2014) 1582–1590, https://doi.org/10.3324/haematol.2014.106880.

[7] T.J. Nevill, H.C. Fung, J.D. Shepherd, D.E. Horsman, S.H. Nanteet, H. G. Klingemann, et al., Cytogenetic abnormalities in primary myelodysplastic syndrome are highly predictive of outcome after allogeneic bone marrow transplantation, Blood 92 (6) (1998) 1910–1917, https://doi.org/10.1182/blood.V92.6.1910.

[8] M.L. Sorror, B.M. Sandmaier, B.E. Storer, Michael B Maris, Frédéric Baron, et al., Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation, J. Clin. Oncol. 25 (27) (2007) 4246–4254, https://doi.org/10.1200/JCO.2006.09.7865.

[9] F. Wimazal, W.R. Sperr, M. Kundi, A. Vales, C. Fonatsch, R. Thalhammer-Scherrer R, et al., Prognostic significance of serial determinations of lactate dehydrogenase (LDH) in the follow-up of patients with myelodysplastic syndromes, Ann. Oncol. 19 (5) (2008) 970–976, https://doi.org/10.1093/annonc/mdm595.

[10] F. Wimazal, W.R. Sperr, M. Kundi, P. Meidlinger, C. Fonatsch, J.H. Jordan, et al., Prognostic value of lactate dehydrogenase activity in myelodysplastic syndromes, Leuk. Res. 25 (4) (2001) 287–294, https://doi.org/10.1016/s0145-2126(00)00140-5.

[11] A.S. Artz, A. Wickrema, S. Dinner, L.A. Godley, M. Kocherginsky M, O. Odenike, et al., Pretreatment C-reactive protein is a predictor for outcomes after reduced-intensity allogeneic hematopoietic cell transplantation, Biol. Blood Marrow Transplant. 14 (11) (2008) 1209–1216, https://doi.org/10.1016/j.bbmt.2008.08.004.

[12] A.S. Artz, B. Logan, X. Zhu, G. Akpek, R.M. Bufarull, V. Gupta, et al., The prognostic value of serum C-reactive protein, ferritin, and albumin prior to allogeneic transplantation for acute myeloid leukemia and myelodysplastic syndromes, Haematologica 101 (11) (2016) 1426–1433, https://doi.org/10.3324/haematol.2016.145847.

[13] P. Armand, H.T. Kim, J.M. Virtanen, R.L. Parkkola, M.A. Itälä-Remes, N.S. Majhail, et al., Iron overload in allogeneic hematopoietic cell transplantation outcome: a meta- analysis, Biol. Blood Marrow Transplant. 20 (8) (2014) 1248–1251, https://doi.org/10.1016/j.bbmt.2014.04.024.

[14] E.M. Cremers, A. van Biezen, L.C. de Wreede, M. Scholten, A. Vitek, J. Finke, et al., Prognostic pre-transplant factors in myelodysplastic syndromes primarily treated by high dose allogeneic hematopoietic stem cell transplantation: a retrospective study of the MDS subcommittee of the CMWP of the EBMT, Ann. Hematol. 95 (12) (2016) 1971–1978, https://doi.org/10.1007/s00277-016-2802-z.

[15] S. Prem, E.G. Atenafu, W. Lam, A. Law, F.V. Michelis, D. Kim, et al., Allogeneic stem cell transplant in myelodysplastic syndrome-factors impacting survival, Eur. J. Haematol. 104 (2) (2020) 116–124, https://doi.org/10.1111/ejh.13353.