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Application of standard and novel prognostic systems in patients with myelodysplastic syndrome undergoing allogeneic hematopoietic stem cell transplantation

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Summary

Several prognostic indexes were developed to predict outcome in patients with myelodysplastic syndrome (MDS). The aim of our study was to evaluate prognostic impact of disease- and transplant-specific indexes on the results of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in MDS patients.

Patients and methods

A retrospective cohort of fifty-nine MDS patients (excluding secondary acute myeloid leukemia) and treated with allo-HSCT was used to evaluate the predictive value of the following prognostic indexes: IPSS, IPSS-R, WPSS, Disease Risk Index (DRI), prognostic systems developed by Kroeger et al., Armand et al., Pretransplant Assessment of Mortality Score (PAM), EBMT risk score and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI).

Results

There was a significant difference in risk estimation between indexes ($p<0.001$). Clinical factors significant for overall survival (OS) in the univariate and multivariate analyses were as follows: acute graft-versus-host disease (GVHD) grade I-II (HR 0.223, 95% CI 0.059-0.721, $p=0.0134$) and occurrence of sepsis during aplasia (HR 3.636, 95% CI 1.438-8.673, $p=0.0059$). Despite significant impact of CD34+ cell contents in hematopoietic graft ($p=0.006$) revealed in ROC analysis, only DRI remained a significant predictor of 5-year OS in the multivariate model (HR 1.857, 95% CI 1.036-3.328, $p=0.037$). Inferiority of other MDS-specific indexes to predict the outcome for allo-HSCT seems to be associated with adverse results in the intermediate risk group. In conclusion, we presume a need for further characterization of the intermediate risk patients when predicting the therapy outcomes.

Keywords

Myelodysplastic syndrome, allogeneic hematopoietic stem cell transplantation, prognostic indexes, risk estimation.

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal bone marrow disorders characterized by ineffective hematopoiesis, and increased propensity to evolve to acute myeloid leukemia (AML). Currently allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only treatment option with curative potential in MDS patients. However, allo-HSCT is associated with risk of significant toxicity – 1-year non-relapse mortality (NRM) is reaching 17% to 25% [1, 2]. Thereby transplant- and disease-related risks should be carefully weighed against the benefits of transplantation. Several prognostic scoring indexes such as International prognostic scoring system (IPSS) [3], revised IPSS [4], WHO-classification-based IPSS (WPSS) [5] are widely used to predict MDS disease course and optimize timing of allo-HSCT according to disease related factors. Allo-HSCT is indicated in patients with high/very high and even in very low/ low or intermediate IPSS-R risk with poor features (poor risk cytogenetics, life-threatening cytopenias, severe transfusion dependence and persistently increasing blast count) [6]. Multiparametric prognostic models IPSS, WPSS and IPSS-R were developed to assess disease risk at diagnosis. In contrast disease related index (DRI) [7] and prognostic models defined by Kroeger et al. [8] and Armand et al. [9] were designed directly for the posttransplant outcome evaluation. Patient-related risk factors such as comorbidities and age should be also taken into consideration. They are included in several prognostic scoring systems such as EBMT score [10], Pretransplant Assessment of Mortality score (PAM) [11] or Hematopoietic Cell Transplantation-specific Comorbidity Index HCT-CI [12]. Here we evaluate aforementioned disease- and transplant-related prognostic indexes in MDS patients treated with allo-HSCT in one center.

Patients and methods

All consecutive primary allogeneic transplants performed for the diagnosis MDS in the time period 2002-2018 and complete information to calculate all of the prognostic indexes were included in the analysis. Pediatric patients and patients transformed to AML were excluded. Main patient characteristics, transplantation parameters, outcomes and complications are summarized in Table 1.

Median of age was 44 years (range 18-67). Twenty four percent of patients were grafted from a matched related donor, and 73% were transplanted from the 9-10/10 HLA-matched unrelated donors. MDS with excess blasts I or II was documented in seventy-six percent of the patients. Twenty-two percent were treated with hypomethylating drugs before transplant. Conditioning regimen was myeloablative in 1/4 of patients, and consisted of oral busulfan 16 mg/kg and cyclophosphamide 120 mg/kg. Reduced-intensity conditioning comprised fludarabine 180 mg/m^2 and oral busulfan 8-10 mg/kg. The reduced-intensity conditioning was used in all the patients after first analysis of the RICMAC trial [2] in 2012. Graft-versus-host disease (GVHD) prophylaxis included posttransplant cyclophosphamide in 37% of patients, while the rest of them received calcineurin-based prophylaxis with short-course methotrexate, or mycophenolate mofetil and antithymocyte globulin in case of unrelated grafts.

Clinical outcomes

Time-to-disease relapse, acute GVHD (aGVHD), moderate to severe GVHD (chGVHD), non-relapse mortality (NRM), overall survival (OS), event-free survival (EFS), and GVHD-relapse free survival (GRFS) were defined as the time from transplantation to the event. Graft failure without evidence of the disease after transplantation was not considered an event. Patients were censored at the time of last contact or a second transplantation for all outcomes. The disease relapse was defined as morphologic or cytogenetic evidence of disease with pre-transplant characteristics. Disease staging, including bone marrow aspirate, was routinely performed on days +30,+60,+100, +180, +365 post-transplant. Primary graft failure was defined as the complete absence of donor chimerism in bone marrow aspirate by day +40. Time to engraftment was calculated as time from HSCT to unsupported neutrophil count >500/ul and white blood cell count >1000/ul for 3 consecutive days. Toxicity was assessed with CTCAE ver. 4.03. Sepsis and severe sepsis were diagnosed based on International Guidelines for Management of Severe Sepsis and Septic Shock [13]. Invasive mycosis was diagnosed in case of probable or proven infection according to EORTC/MSG guidelines [14]. HCT-CI [12], DRI [7], IPSS [3], IPSS-R [4], WPSS [5], PAM [11], Armand et al. risk score [9], Kroeger et al. risk score [8] were calculated based on the published scoring systems.

Statistical Analysis

All tests were two-sided, and differences with p values less than 0.05 were considered significant. The difference in grading between indexes was accessed using Friedman test. The survival distributions for OS, EFS, GRFS were calculated using Kaplan-Meier methodology with 95% confidence intervals. Appropriate survival curves are provided in Supplementary files (see online version) Cumulative incidence analysis with competing risks was used for relapse and NRM. Five-year OS was used as an outcome to test all prognostic systems, because most of them were created based overall survival with follow up for 5 years and more [3, 4, 5, 9]. The univariate comparisons were made using the log-rank test. Proportional hazard modeling was used for the multivariate analysis. Based on the number of events 3 most significant factors from univariate analysis were included in the model. The MDS risk indexes were added in the series of tests. The final multivariate confidence intervals are the result of meta-analysis with fixed effect modeling. The heterogeneity of confidence intervals was tested with Cochran Q test. The C-statistic for the predictive factors was produced from logistic regression with death during five years after transplantation as an outcome. The predictive values were presented as area under the curve (AUC) with confidence intervals. Analyses were conducted in R 3.4.1 and SAS 9.3 (SAS Institute, Inc.).

Table 1. Patient characteristics and overall transplantation outcomes

Characteristic	Value
Patient median age, y (range)	44 (18-67)
Median no. of CD34 infused stem cells/kg BW (range)	$4.6x10^6$ (1.4-16.4)
Sex of patient, M/F	30/29
Donor type	
Related	14 (24%)
Unrelated	43 (73%)
Haploidentical	2 (3%)
HLA matching	
Full	48 (81%)
Single mismatch	11 (19%)
Disease status	
MDS with ring sideroblasts (MDS-RS)	4 (7%)
MDS-RS and multilineage dysplasia	1 (2%)
MDS with multilineage dysplasia	4 (7%)
MDS with isolated del(5q)	1 (2%)
MDS with excess blasts 1	12 (20%)
MDS with excess blasts 2	33 (56%)
MDS, unclassifiable	2 (3%)
Chronic myelomonocytic leukemia	2 (3%)
Risk profile according to IPSS score	
Low	4 (7%)
Intermediate-1	20 (34%)
Intermediate-2	23 (39%)
High	12 (20%)
Risk profile according to IPSS-R score	
Very low/Low	8 (14%)
Intermediate	19 (32%)
High	19 (32%)
Very high	13 (22%)
Risk profile according to WPSS score	
Very low	1 (2%)
Low	4 (7%)
Intermediate	9 (15%)
High	26 (44%)
Very high	19 (32%)
Risk profile according to Kroeger et al. score	
Low	15 (25%)
Intermediate	27 (46%)
High	13 (22%)
Very high	4 (7%)
Risk profile according to Armand et al. score	
Low	31 (53%)
Intermediate	19 (32%)
High	9 (15%)
Risk profile according to PAM score	
Score <10	11 (20%)
Score ≥10	43 (80%)

Characteristic	Value
Risk profile according to DRI score	
Intermediate	33 (56%)
High	19 (32%)
Very high	7 (12%)
Risk profile according to HCT-CI score	
Score 0	32 (54%)
Score ≥1	27 (46%)
Risk profile according to EBMT score	
Score 0	0 (0%)
Score 1	2 (3%)
Score 2	6 (11%)
Score 3	5 (8%)
Score 4	15 (25%)
Score 5	18 (31%)
Score ≥6	13 (22%)
Conditioning	
Reduced intensity	44 (75%)
Myeloablative	15 (25%)
AGVHD prophylaxis	
Cyclosporine A	10 (17%)
Tacrolimus	42 (71%)
Methotrexate	17 (29%)
Posttransplant cyclophosphamide	22 (37%)
Antithymocyte globulin	33 (56%)
AGVHD	51%
Grade 0-2	35%
Grade 3-4	15%
Chronic graft-versus-host disease	30%
Limited	2%
Extensive	28%
Graft failure	**9 (15%)**
Toxicity grade 3-4	
Liver	9 (15%)
Renal	2 (3%)
Mucositis	8 (15%)
Neurotoxicity	1 (2%)
Thrombotic microangiopathy	**3 (6%)**
Hemorrhagic cystitis	**4 (7%)**
Veno-occlusive disease	**3 (6%)**
Sepsis	**13 (24%)**
Severe sepsis	7 (13%)
Invasive fungal infection after bone marrow transplant	**10 (18%)**
Cytomegalovirus reactivation	**25 (46%)**

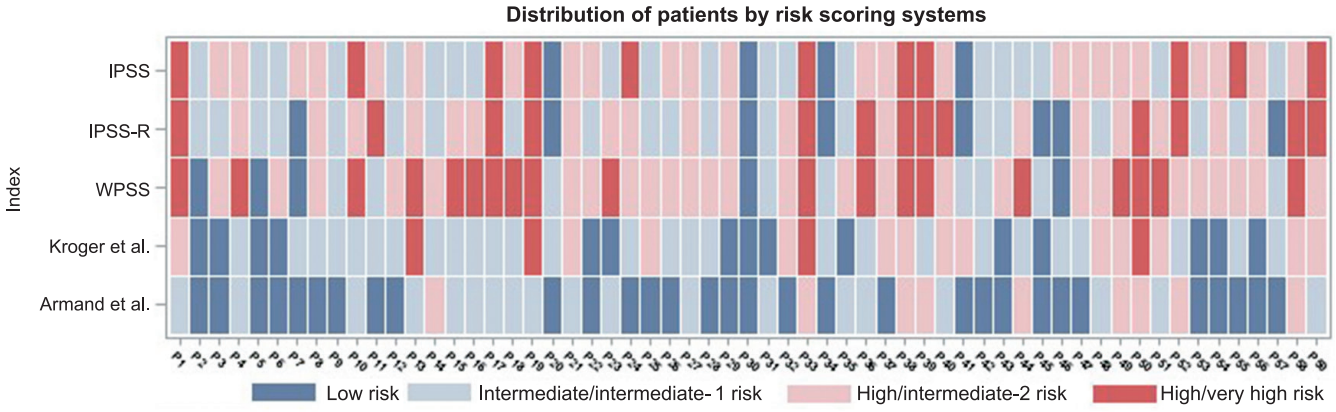

Figure 1. Distribution of patients by different prognostic scoring systems

Results

Distribution of patients by different scoring systems

We analyzed the distribution of patients by disease specific scoring systems such as IPSS, WPSS and IPSS-R and MDS prognostic indexes for patients undergoing allo-HSCT developed by Kroeger et al. and Armand et al. (Fig. 1). Fifty-four percent of patients were transplanted in high or very high IPSS-R risk. Forty-eight percent of patients with high/very high WPSS or IPSS-R risk were reclassified into intermediate risk according to pretransplant Kroeger et al. MDS score and 60% into intermediate risk, according to pretransplant Armand et al. score. There was a difference between disease- and pretransplant prognostic systems especially in distinction between high/very high and intermediate risk ($p<0.001$).

Clinical outcomes

Platelet and leukocyte engraftment was documented in 48 (81%) of patients. Primary graft failure was observed in six cases (10%). Four patients out of them died (in one case, due to disease progression, and three patients deceased due to infections). The median time to leukocyte engraftment was 18 days (range 11-30), neutrophil engraftment, 20 days (range 10-30), platelet engraftment, 17 days (range 11-130). Overall, 50% of patients developed aGVHD with severe aGVHD grade 3-4 registered only in 15% of cases. The rate of chronic GVHD was 30%, which proved to be extensive in 28% of the patients (Table 1).

Cumulative incidence of relapse at 5 years was 37% (95% CI 25-57%). The cumulative incidence of non-relapse mortality (NRM) at 1 year was 25% (95% CI 16-40%). Thirty patients died during the follow-up study. The main reasons of death were disease progression or relapse in 26%; GVHD, 26%; infections, 37%; hemorrhagic events, 7%; acute myocardial infarction, in 4% of cases.

With a median follow-up of 36 months (range 3 to 135), the 5-year OS, EFS and GRFS was 34%, 33% and 29%, respectively. In univariate analysis, the significant factors for prolonged OS were as follows: aGVHD grade 1-2 (62% *vs* 18% $p=0.004$), quantities of donor CD34+ cells ($p=0.006$), and absence of septic episodes before engraftment (44 % *vs* 17%,

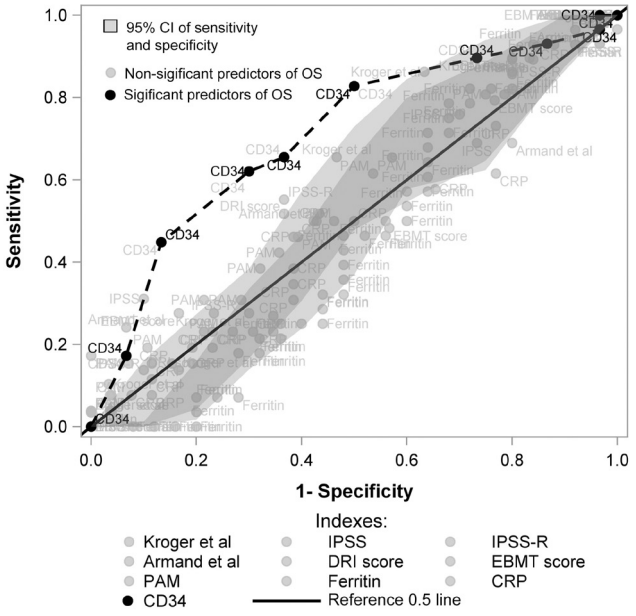

Figure 2. Influence of different prognostic systems and factors on OS in MDS patients, receiver-operating-curve (ROC) analysis

Note: C-statistics for the potential predictors of overall survival. Results of the ROC analysis treated in logistic regression with 5-year overall survival as an outcome. The non-significant parameters ($p>0.05$) are shown in grey. The significant ($p<0.05$) parameters are shown in black. The 95% confidence intervals of sensitivity and specificity are produced from individual results of all the parameters tested. C-statistic values of the variables were: CD34 positive cells in the graft 0.7080 (95% CI 0.5740-0.8421), Kroger et al. 0.5862 (95% CI 0.4391-0.7333), Armand et al. 0.5339 (95% CI 0.3850-0.6828), IPSS 0.5534 (95% CI 0.4121-0.6948), WPSS 0.5672 (95% CI 0.4354-0.6991), IPSS-R 0.5885 (0.4430-0.7340), DRI 0.5747 (0.4429-0.7065), EBMT 0.5230 (0.3758-0.6702), serum ferritin 0.4500 (0.2861-0.6139), PAM index 0.5584 (0.4037-0.7131), CRP before conditioning 0.4845 (0.3234-0.6456).

p=0.003). The disease-specific prognostic indexes (IPSS, WPSS, IPSS-R), and transplant comorbidity indexes (PAM, EBMT, HCT-CI) did not predict OS . However, differences in OS rates between the risk groups according to disease-related prognostic systems such as Disease-Related Index, DRI (p=0.049), and risk score by Kroeger et al. (p=0.071) have shown a trend towards statistical significance (Supplement, Fig. 1-7. The supplemental files could be found in electronic version of this paper at www.cttjournal.com). The 5-year OS in low risk group, according to transplant risk score proposed by Kroeger et al. was 61%, thus being significantly higher compared to intermediate and high/very high risk – 26% (p=0.041). Surprisingly, we found no difference in OS between intermediate and high/very high risk groups (28% and 22%, respectively). This might be a reason for the failure of the index used by Kroeger et al. to achieve statistical significance. Interestingly, that the causes of death were nearly the same in both risk groups, i.e., ca. 50% of patients died due to transplant related factors.

ROC analysis shows influence of different prognostic systems and factors upon OS in the MDS patients. Amount of transplanted CD34+ donor cells proved to be the only factor which significantly affected transplant outcome (p=0.006) in this analysis (Fig. 2).

However, only presence of aGVHD grade 1-2 (p=0.013), absence of septic episodes (p=0.006), and DRI (p=0.037) retained their statistical significance in the multivariate analysis (Fig. 3). Other prognostic scores, except of DRI, did not show a statistical significance.

Discussion

The major question in every MDS patient with currently existing treatments is whether he will benefit from allo-HSCT. Despite the fact that all existing treatments in most cases lead to only temporary responses, the results of allo-HSCT in MDS unfortunately are also one of the most disappointing compared to other diseases [15]. According to our 5-year observation data, the OS level in allotransplanted MDS patients is 34%. The other studies are showing nearly the same results: from 45% to 37% [1, 16]. This is due to relatively high NRM [3], but also due to high relapse rate [2, 17]. Currently used indexes of the natural course of the disease such as IPSS, WPSS, IPSS-R are established to evaluate risk of death and transformation to acute myeloid leukemia in untreated MDS patients [3, 4, 5]. All of these indexes are well validated in large patient cohorts [17]. However, their role in predicting the outcome after allo-HSCT is not so well defined.

Lee et al. [18] evaluated prognostic impact of IPSS before allo-HSCT. The authors showed significant differences in OS after allo-HSCT between low/intermediate and intermediate/high groups. Further it was shown that WPSS has a relevant prognostic value in posttransplant outcome of patients with MDS [19]. Modified prognostic model IPSS-R was assessed pre-transplant as a predictor of transplant outcome by C. Scheid et al. [20]. In that study, IPSS-R significantly influenced OS after allo-HSCT, but OS in high and intermediate groups were comparable: 47% and 44%, respectively. This was due to high and comparable NRM in these groups.

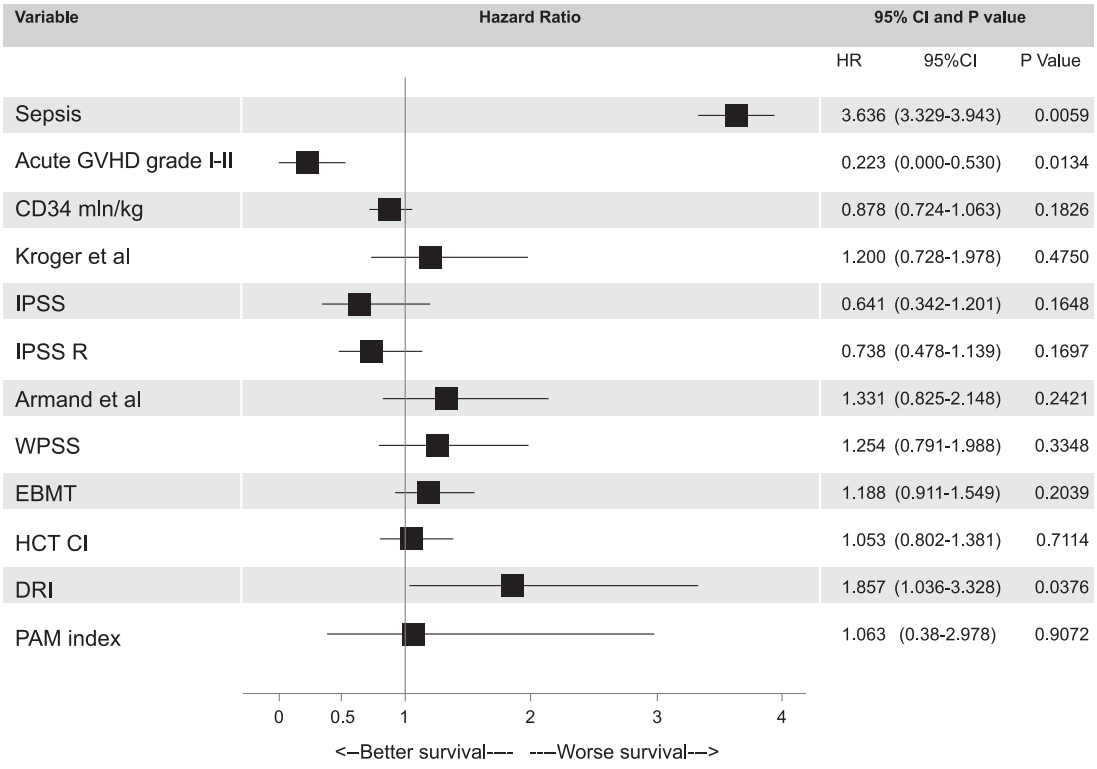

Figure 3. Analysis of the prognostic value of risk indexes in the multivariate model

Note: Multivariate analysis of overall survival. Acute GVHD, graft CD34+ cells and sepsis in aplasia were included based on univariate selection of the most predictive variables. The indexes were added as the fourth co-variable separately in a series of tests. The cumulative confidence intervals for the clinical variables were produced with fixed effect model from the individual hazards in the series.

In our study we have also observed high NRM in the favorable prognostic groups based on IPSS or IPSS-R.

The potential causes for early mortality in this group are relatively well discussed in the literature. They include primary graft failure [21], iron overload which results in higher incidence of liver veno-occlusive disease [22] and infectious complications [23]. It should be noted that, according to our data, the rate of primary graft failure is 10% being considered relatively high. The incidence of graft failure varies from 2 to 13% [2, 16, 24]. We didn't find any correlation between rate of graft failure and type of stem cell source or rate of CD34+ cells in the graft, as reported in previous studies [21]. According to the results of large study by Olsson et al. [21], MDS diagnosis itself is associated with increased risk of graft failure, along with other hematologic malignancies, e.g., myeloproliferative disorders and chronic lymphocytic leukemia. Poor graft function may be another documented cause of NRM that leads to increased incidence of opportunistic infections and hemorrhagic complications [25]. Thus, high NRM rate was the main reason of non-significant predictive value of classical indexes after allo-HSCT found in our study.

A number of indexes accounting for NRM based on previous treatment burden, like as duration of the disease in EBMT index, or comorbidity burden, like in HCT-CI, or prediction of viral reactivations based on serological markers, like in PAM. However, there are conflicting results about influence of the comorbidity indexes on OS in MDS patients. Guilfoyle et al. did not find associations between HCT-CI and OS in MDS patients [26]. On the other hand, a large retrospective study showed that EBMT score accurately predicted OS and NRM [27]. In the present study, we have not observed any predictive impact of these indexes on the disease outcome. The published data and results of our study indicate that biological mechanisms behind NRM might be in certain cases different in MDS compared to the other diseases [28].

Several new prognostic indexes have been recently developed aiming for precise evaluation of transplant outcome in MDS patients. Kroeger et al. have combined the disease-related factors (cytogenetics, blood blasts, and platelets) and patient-related factors (performance status and age) into a common prognostic system [8]. Armand et al. added ferritin level and type of a conditioning regimen to the disease-related risk factors [9]. The disease risk index was another prognostic system evaluated in our study. It includes cytogenetics and remission status of MDS patients at transplant [7]. These indexes, except of DRI, were assessed in large data sets to specifically account for the risk of relapse and the risk of NRM. There is only a limited number of studies validating these indexes [29]. Interestingly, about half of IPSS-R high/very high risk patients were reclassified as more favorable category, the intermediate-1, according to risk score by Kroeger et al. and Armand et al. [8, 9]. Thereby, the disease- and transplant-specific scoring systems determine the transplant outcome in different ways. According to our data, only DRI significantly influenced OS values among all the mentioned prognostic scores. In our study, these transplant-specific indexes were shown to define well the group with good prognosis and adverse prognosis. However, we observed that clinical prognosis for the intermediate group proved to be as adverse as for the high-risk patients.

Thus, our study indicates that current prognostic indexes do not well define the intermediate prognosis. It is likely that most of the heterogeneity of the disease fall into this category, including patients with stromal and miRNA signaling deficiency [30], pyroptosis of hematopoietic stem cells [31], certain mutations without cytogenetic abnormalities [32]. Any of these pathogenetic variants might manifest in different mechanisms of NRM and relapse risk. Pooling the patients into large cohorts alleviate these differences by creation of risk indexes. However, small-group or individual prediction might not be so accurate, due to the causes mentioned above. Thus, future development of indexes and predictive systems for allo-HSCT should incorporate molecular data, at least, for the intermediate risk groups in MDS.

Conclusion

In our relatively small single-center study, we have observed little predictive value of currently existing scoring systems, particularly due to adverse results in the intermediate risk patients. Further characterization of this "intermediate" patents is required to broaden the clinical application of the scoring systems for individual treatment planning.

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Disclosure statement

Authors confirm the absence of any conflicts of interests.

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Применение стандартных и новых прогностических систем у больных с миелодиспластическим синдромом, подлежащих аллогенной трансплантации гемопоэтических стволовых клеток

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Резюме

Разработан ряд предиктивных индексов для прогнозирования исхода у пациентов с миелодиспластическим синдромом (МДС). Целью нашего исследования была оценка прогностического вклада показателей заболевания и трансплантации в результаты аллогенной трансплантации гемопоэтических клеток (ТГСК) пациентам с МДС.

Пациенты и методы

В ретроспективное исследование была включена группа из 53 пациентов с МДС (за исключением вторичного острого миелобластного лейкоза), леченных с применением алло-ТГСК. Целью работы была оценка предиктивной значимости следующих прогностических индексов: IPSS, IPSS-R, WPSS, Disease Risk Index (DRI), а также прогностической системы, предложенной Kroeger et al., Armand et al., индекса претрансплантационной оценки смертности (PAM), оценки риска по EBMT и ТГСК-специфичного индекса коморбидности (HCT-CI).

Результаты

В результате работы показана достоверная разница в оценке риска при сравнении отдельных индексов (p <0,001). Были отмечены следующие клинические факторы, значимые для общей выживаемости (ОВ) в одно- и многофакторном анализе: острая реакция «трансплантат против хозяина» (ОРТПХ) I-II степени (HR 0,.223; 95% CI 0.059-0,721; p=0,0134) и возникновение сепсиса в период аплазии (HR 3,636; 95% CI 1,438-8,673; p=0,0059). Несмотря на значительный вклад числа CD34+ клеток в трансплантате, (p=0,006), выявленного посредством ROC-анализа, только индекс DRI являлся существенным средством прогноза 5-летней выживаемости в многофакторной модели (HR 1,857; 95% CI 1,036-3,328; p=0,037). Более низкая эффективность других МДС-специфичных индексов в прогнозировании исходов алло-ТГСК связана, по-видимому, с неблагоприятными исходами в группе промежуточного риска. В заключение мы должны отметить необходимость дальнейшей характеризации пациентов промежуточной группы риска при прогнозировании исхода лечения.

Ключевые слова

Миелодиспластический синдром, аллогенная трансплантация гемопоэтических стволовых клеток, прогностические индексы, оценка риска.