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Red Blood Cell Transfusion Dependency and Hyperferritinemia Are Associated with Impaired Survival in Patients Diagnosed with Myelodysplastic Syndromes: Results from the First Polish MDS-PALG Registry*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis, cytopenias and a risk of progression to acute myeloid leukemia (AML). Anemia is the most frequent cytopenia diagnosed in patients with MDS. Regular RBC transfusions are the only treatment option for about 40% of patients. Transfusion-dependent patients develop secondary iron overload. The influence of serum ferritin (SF) concentration on survival and acute myeloid leukemia transformation in MDS patients remains controversial. The data for the Central European population is scarce and so far there is no description for Poland.

Objectives. The aim of this study was to perform a retrospective analysis of the relationship of SF concentration with red blood cell transfusion dependency, survival and transformation to acute myeloid leukemia.

Material and Methods. We retrospectively evaluated the data of the 819 MDS patients (58% male; median age 70 years) included in the MDS Registry of the MDS Section of the Polish Adult Leukemia Group (PALG).

Results. Analyses were performed on 190 patients diagnosed with MDS, maximal 6 months before inclusion to the registry in order to avoid selection bias (a shorter survival of higher risk MDS patients). Patients with hyperferritinemia higher than 1000 ng/L vs. patients with SF concentration lower than 1000 ng/L had a median survival of 320 days vs. 568 days, respectively (p log-rank = 0.014). The following factors were found to significantly worsen survival: RBC-transfusion dependence (p = 0.0033; HR 2.67L), platelet transfusion dependence (p = 0.0071; HR 3.321), hemoglobin concentration lower than 10 g/dL (p = 0.0036; HR 2.97), SF concentration higher than 1000 ng/L (p = 0.0023; HR = 2.94), platelet count lower than 10 G/L (p = 0.0081 HR = 5.04), acute leukemia transformation (p = 0.0081; HR 1.968).

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Conclusions. Taking into account the relatively low number of patients in previous studies exploring hyperferritinemia in MDS, the results of the first Polish MDS Registry provide important insights. Hyperferritinemia higher than 1000 ng/L can be an important indicator of poor prognosis in MDS (**Adv Clin Exp Med 2016, 25, 4, 633–641**).

Key words: myelodysplastic syndrome, hyperferritinemia, serum ferritin concentration, red blood cell transfusion dependence, transformation to acute myeloid leukemia.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis, cytopenias and risk of progression to acute myeloid leukemia [1–3]. The natural history of myelodysplastic syndrome is variable, from indolent to aggressive [4, 5]. Another threat is an increased risk of transformation of MDS into acute myeloid leukemia [2]. The French-American-British (FAB) and the World Health Organization (WHO) classifications categorize MDS [6, 7]. The International Prognostic Scoring System (IPSS) [8], the new Revised International Prognostic Scoring System (IPSS-R) [9] and the WHO-based prognostic scoring system (WPSS) [10] are widely used prognostic scores.

Anemia is the most frequent cytopenia diagnosed in patients with MDS. Regular RBC transfusions are the only treatment option for about 40% of patients [2]. Transfusion-dependent patients develop secondary iron overload. Anemia is diagnosed in up to 80% of patients with myelodysplastic syndromes, while neutropenia and thrombocytopenia are found in up to 60% and 40%, respectively [5]. Blood transfusion is important for the survival for some of these patients. RBC-transfusion dependency can be an independent adverse prognostic factor in MDS patients [10].

Multiple red blood cell (RBC) transfusions can lead to a secondary iron overload, as one RBC unit contains about 200 mg of iron [11]. Therefore, elevated SF concentration in an MDS patient can be a result of RBC-transfusions. Surprisingly, it can also be found in non-transfused MDS patients (which can be attributed to ineffective hematopoiesis and increased intake of iron from the intestine). Although iron is an essential bioelement (in oxygen transport and electron transfer) [11], free ionic iron is toxic: Iron overload can lead to heart failure, liver dysfunction and multiorgan damage. Free iron species (non-transferrin bound iron – NTBI) arise in plasma when transferrin approaches saturation [12]. Labile Plasma Iron (LPI) is a chelatable redox-active component of NTBI [13]. These most reactive iron fractions are difficult to measure, but their concentrations were found to correlate with SF concentration in thalassemia major patients [11–13]. Ferritin is the main protein that can store the iron inside the body, thus it can be utilized as a reliable marker of its overload [14]. It is widely used due to its availability and relatively low cost [14]. Liver iron concentration (LIC), based on liver biopsies, showed a close inverse correlation with the respective liver T2-values in magnetic resonance, along with a strong positive correlation with ferritin levels [15].

SF concentration can be influenced by inflammation (it is an acute phase protein), but when infection assessment is performed, this caveat does not hamper its reliability [14].

Despite the numerous studies, the influence of SF concentration on survival and AML transformation in MDS remains controversial [16, 17]. The data for the Central European population is scarce and there was no description for Poland. The first characteristics of Polish MDS patients regarding epidemiological data, toxic exposure and their association with hematological parameters and clinical outcome was first published by our group and this study is the second analysis of the first Polish MDS Registry [18]. The aim of this study was to perform an analysis of RBC-transfusion dependence and SF concentration in patients from the Polish MDS Registry and examine its relationship with red blood cell transfusion dependency and its influence on survival and AML transformation.

Material and Methods

We evaluated the data of the 819 MDS patients (male – 58%, female – 42%, median age 70 years; 18–99 years) included retrospectively in the MDS Registry conducted by the MDS Section of the Polish Adult Leukemia Group (MDS-PALG-002 Study). Twenty-four Polish hematological centers participated in the study (12 university and 12 community hospitals from all over the country). The patients enrolled in the registry had been diagnosed with MDS at any time and they had to be admitted to either an in- or outpatient hematological unit between March 2008 and May 2009. The end of the follow-up was in December 2013. The MDS/AML diagnostic criteria of the World Health Organization (WHO) 2001 Classification of Myeloid Neoplasms were used. All patients had a bone marrow biopsy and complete blood count with microscopic smear performed at diagnosis. Baseline demographic and clinical characteristics (including treatment, toxic exposure and smoking), laboratory parameters, treatment, dependence on red blood cells and platelet transfusions were noted.

Red blood cell transfusion dependency (RBC TD) was defined as having at least 1 RBC transfusion within the last 8 weeks over a period of 4 months, and platelet transfusion dependency (PLT TD) was defined as having at least one transfusion within the last 8 weeks over a period of 4 months.

For a quantitative determination of SF concentration, an immunoturbidimetric assay antigen-antibody was used. SF concentration was measured at the time of referral to the center (at the moment of diagnosis). Patients were divided into lower and higher SF concentration groups. The cut-off point of 1000 ng/mL was chosen for the registry, according to the guidelines for the diagnosis and treatment of iron overload. None of the patients was treated with iron chelators prior to the first ferritin measurement.

The University Bioethics Committee Board approved the registry.

A survival analysis was performed only for patients diagnosed with MDS maximal 6 months before inclusion to the registry in order to avoid selection bias (shorter survival of higher risk MDS patients). Consequently, 190 patients were included in the further analysis.

The overall survival was calculated based on the period between the time of diagnosis of MDS and the end of follow-up or death. The time of transformation to acute myeloid leukemia (AML) was calculated in patients in which transformation was diagnosed, based on the period between the time of diagnosis of MDS and the date of transformation to AML. The significance of differences in survival was determined using a log-rank test. P-value less than 0.05 was considered to be statistically significant. For two-concentration categorical dependent variables, a χ^2 test was used. The independent factors found to be associated with overall survival were tested using the Cox proportional hazard model to obtain a hazard ratio (some continuous data was converted into categorical values consisting of two simple ordinal numbers). A logistic regression analysis was conducted for dichotomous data. The data was processed using the SAS 9.2 System (Statistical Analysis System 9.2) for Windows.

Results

The proportions of patients diagnosed in the time periods between 0, 6, 12, 24, 48 months and longer prior to the entry to our registry were as follows: 28%, 16%, 18%, 21% and 16%. As a result of statistical suitability, we included 190 patients into the further analysis. The most frequent MDS subtypes according to WHO 2001 classification were: Refractory anemia with excess blasts-2 (RAEB-2) (53 patients – 27.9%), refractory cytopenia with multilineage dysplasia (RCMD) (50 patients – 26.3%) and refractory anemia (RA) (24 patients – 18%) (Table 1). There were no statistically significant differences between MDS subtypes regarding SF concentration but we observed a tendency that hyperferritinemia was more often diagnosed in patients with MDS RAEB-2 than in the rest of the analyzed group (31% vs. 14%, $p = 0.06$). There was a statistically insignificant tendency that higher risk MDS patients more often had SF concentration elevated over 1000 ng/mL than lower risk MDS patients (16% vs. 10%, p = NS). For 62 patients (28.5%), it was possible to assess IPSS and classify them to lower or higher risk MDS groups (lower risk MDS (50% of patients) – low and intermediate-1; higher risk MDS (50% of patients) – intermediate-2 and high IPSS).

The median survival of patients was 568 days (Fig. 1). The two-year survival rate was 38% and three-year survival rate was 24%. The median time of follow-up was 816 days.

Information about RBC-transfusion-dependency was available for 180 (94.7%) patients. 104 (58%) patients were red-blood-cell-transfusion dependent, most of them required 1–2 or up to 4 RBC units/8 weeks (45% and 25% of patients). Higher requirements, 6, 8, 10, 12 or more RBC units per 8 weeks, were found in 8.9%, 10.3%, 2.9%, 12.2% and 8.1%, respectively.

Information about platelet transfusion-dependency was available for 182 (95.7%) patients. Twenty nine (16%) patients were platelet transfusion dependent.

Patients diagnosed with MDS RCMD, RA or MDS unclassified vs. patients with other MDS subtypes (5q-, RARS, RAEB-1 or RAEB-2) were less often RBC-transfusion dependent (respectively: 44%, 30%, 38% vs. 58%, $p < 0.05$) and patients diagnosed with MDS RAEB-1 and MDS RAEB-2 were more often RBC-transfusion dependent in comparison to the rest of the group (respectively: 73%, 80% vs. 58%, $p < 0.05$).

Survival was significantly longer for patients not dependent on red blood cell transfusions than for RBC-transfusion dependent patients, diagnosed up to 6 months before inclusion to the registry: Median survival was 930 days vs. 469 days, respectively (Fig. 4; p log rank = 0.035) and two-year survival was 56% vs. 26%, respectively.

Patients dependent on RBC transfusions more often had progression to AML diagnosed than transfusion non-dependent patients (29.8% vs. 19.7%, $p = 0.043$).

For 109 (57%) patients (Fig. 2) (47% male), data about SF concentration was accessible. SF con-

Table 1. Characteristics of patients diagnosed up to 180 day before inclusion to the registry (190 patients)

	N	%
Total	190	
males	111	58
females	79	42
Age	190	
< 50	16	8
50–80	146	77
> 80	28	15
MDS subtype	190	
RA	24	12.6
RARS	7	3.7
RCMD	50	26.3
RCMD-RS	1	0.5
RAEB-1	27	14.2
RAEB-2	53	27.9
5q-	4	2.1
MDS-U	8	4.2
Hb g/dL	190	
≥ 12.0	17	9.0
9–11.9	74	39.0
6–8.9	84	44.0
< 6,0	15	8.0
PLT $\times 10^9$/L	190	
> 100	91	48
51–100	54	28
20–50	25	13
20–10	17	9
< 10	3	2
ANC $\times 10^9$/L	181	
≥ 1.5	77	42.6
0.5–1.4	75	41.4
< 0.5	29	16.0
Cytogenetics	190	
done	62	28.5
not done	128	71.4
IPSS	62	
low risk	10	16
int-1	21	34
int-2	18	29
high risk	13	21
Ferritin serum	109	
≤ 1000 μg/L	89	81.7
> 1000 μg/L	20	18.3
RBC TD	180	
yes	104	58
no	76	42
PLT TD	182	
yes	153	84
no	29	16

centration was lower or equal to 1000 ng/mL for 89 patients while for 20 patients it was higher. There was no significant difference between these groups regarding age (p = 0.39). We observed that hyperferritinemia was more often diagnosed in women than in men (75% vs. 48%, p = 0.019). Hemoglobin concentration did not differ between patients with SF concentration equal to or lower than 1000 ng/L vs. patients with higher values (mean hemoglobin concentration 9.3 g/dL vs. 7.9 g/dL, respectively, p = 0.13). Neutrophil count was statistically significantly different between the subgroups: 2.1 g/L vs. 1.2 g/L, respectively, p = 0.0022. The patients with SF concentration higher than 1000 ng/mL were more often RBC transfusion-dependent than patients with lower concentrations (84% vs. 54%; p = 0.01).

Survival was significantly longer for patients with lower SF concentration as compared to the group with higher concentration. Patients diagnosed up to 6 months before inclusion to the registry with SF concentration lower than 1000 ng/L had a median survival of 568 days vs. 320 days for patients with higher values (log-rank = 0.014) (Fig. 3). Of note, there were no statistically significant differences in IPSS between the two groups with different SF concentrations and the percentage of missing data was also comparable for both groups [IPSS low and intermediate-1 15 patients (20% of patients with SF concentration lower than 1000 ng/L) vs. 3 patients (15% of patients with SF concentration higher than 1000 ng/L), respectively (p = ns.), IPSS intermediate-2 and higher: 13 patients (17% of patients with SF concentration lower than 1000 ng/L) vs. 5 patients (25% of patients with SF concentration higher than 1000 ng/L), respectively (p = ns.), lack of data 49 patients (63% of patients with SF concentration lower than 1000 ng/L) vs. 12 (60% of patients with SF concentration higher than 1000 ng/L), respectively (p = ns.)].

There was no significant difference in the frequency of AML transformation in MDS patients from both SF concentration groups (higher vs. lower: 23.6% vs. 25%, p > 0.05). We did not find a significant difference in median time to transformation to acute leukemia between patients with higher and lower SF concentration. Median time to transformation was 211 days vs. 318 days, respectively, p = 0.35. The transformation of MDS to AML was observed in 47/190 patients (25%). The transformation to AML was diagnosed more fre-

Hb – hemoglobin; ANC – absolute neutrophil count; PLT – platelets; RBC TD – red blood cell transfusion dependency; PLT TD – platelets transfusion dependency; IPSS – international prognostic scoring system; RA – refractory anemia; RARS – refractory anemia with ringed sideroblasts; RCMD – refractory anemia with multilineage dysplasia; RCMD-RS – refractory anemia with multilineage dysplasia with ringed sideroblasts; RAEB-1 – refractory anemia with excess blasts-1; RAEB-2 – refractory anemia with excess blasts-2; 5q(-) – MDS associated with isolated del(5q); MDS-U – MDS unclassified.

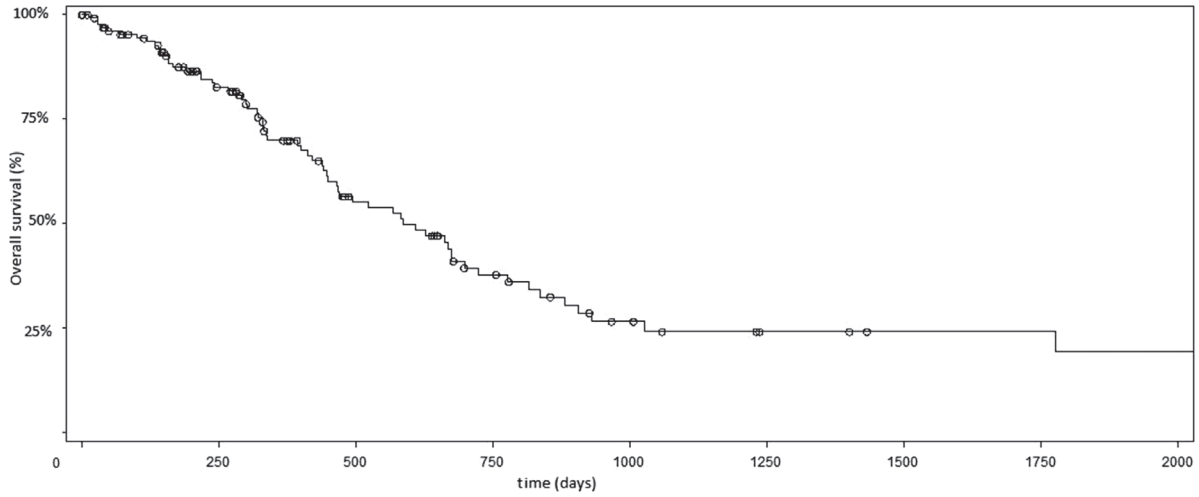

Fig. 1. Survival for patients diagnosed up to 6 months from diagnosis to inclusion to the registry

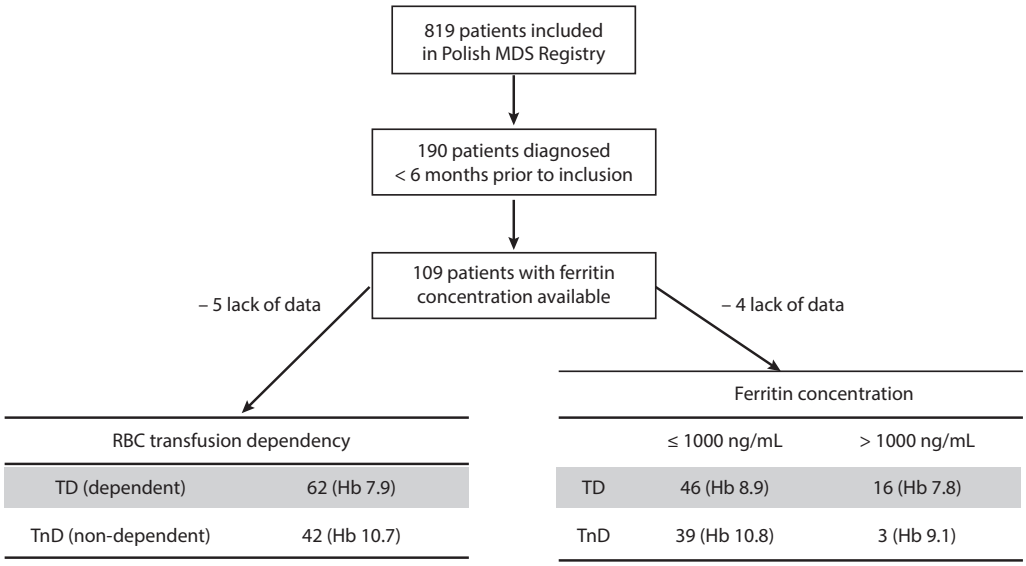

Fig. 2. Patients analyzed in the study (with hyperferritinemia and transfusion dependency groups)

TD – transfusion dependent; TnD – transfusion non-dependent; Hb – hemoglobin concentration in g/dL

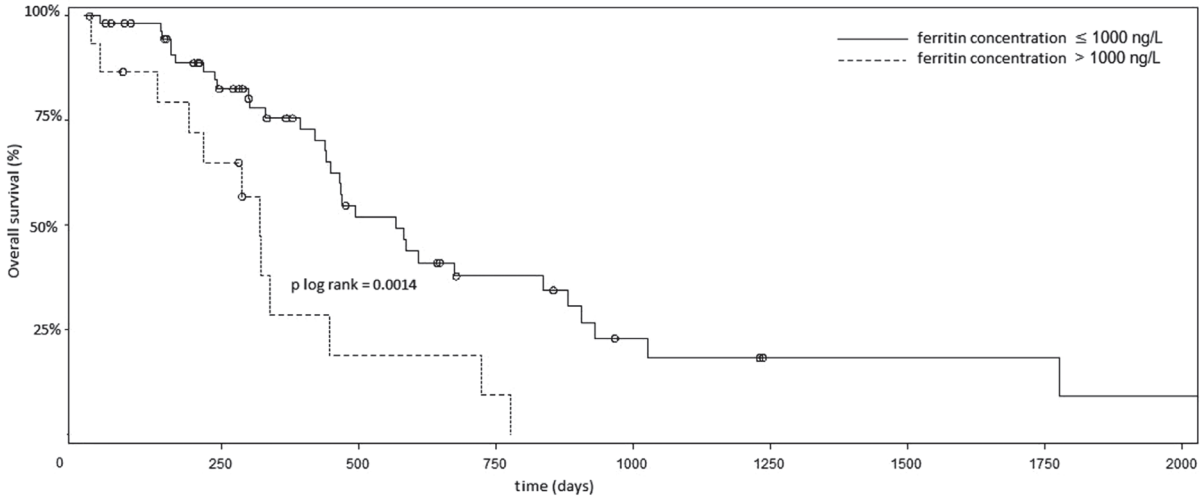

Fig. 3. Survival for patients diagnosed up to 6 months from diagnosis to inclusion to the registry according to concentration of ferritin (p log-rank = 0.0014)

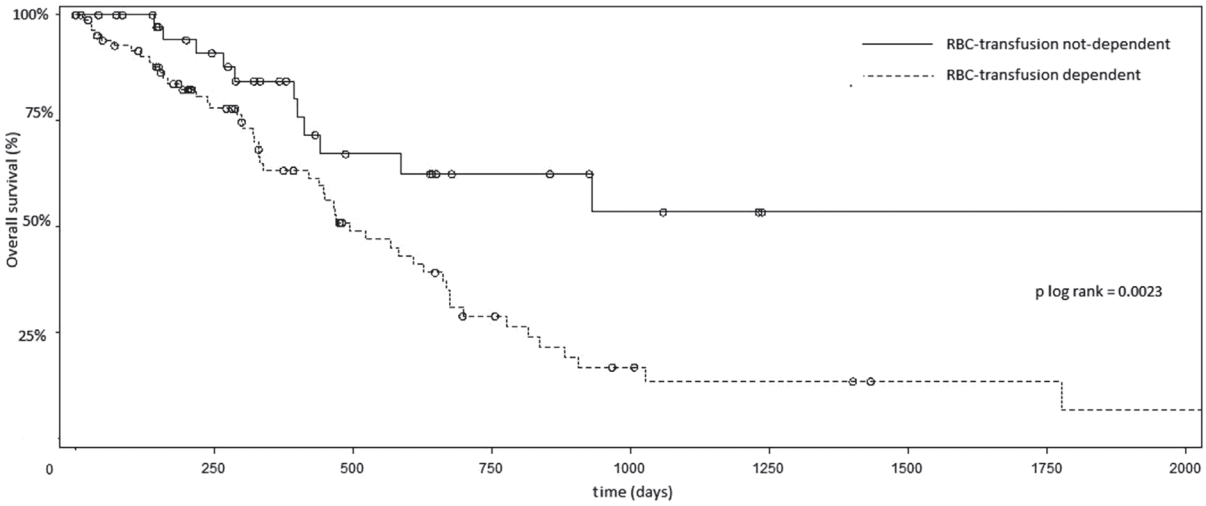

Fig. 4. Survival for patients diagnosed up to 6 months from diagnosis to inclusion to the registry according to RBC transfusion-dependency (p log-rank = 0.0023).

RBC-transfusion non-dependent – red blood cell transfusion non-dependent;
RBC-transfusion dependent – red blood cell transfusion dependent.

quently in patients with MDS RAEB-2 and MDS RAEB-1 than in the rest of the group (51% and 33%, respectively, vs. 25%, $p < 0.0001$).

The data regarding SF concentration was available for 109 patients (57%) (Fig. 2). Mean hemoglobin concentration was 10.7 g/dL for non-RBC-transfusion dependent patients (N = 62) and 7.9 g/dL for RBC-transfusion dependent patients (N = 42; $p < 0.05$), with a lack of data about transfusion-dependency for 4 patients (Fig. 3). For the 109 patients for whom the data regarding SF concentration was available, 89 patients (82%) had SF concentration less than or equal to 1000 ng/L and 20 patients (18%) had SF concentration higher than 1000 ng/L. In the subgroup with higher SF concentration, 3 patients were not RBC-transfusion dependent (median hemoglobin concentration 9.1 g/dL) and 16 patients were RBC-transfusion dependent (mean hemoglobin concentration 7.8 g/dL; p = ns.), and there was no data regarding transfusion dependence accessible for one patient. In the subgroup with lower ferritin concentration, 39 patients were not RBC-transfusion dependent (median hemoglobin concentration 10.6 g/dL) and 46 patients were RBC-transfusion dependent (median hemoglobin concentration was 8 g/dL; p = ns.). It is worth noting that hemoglobin concentration in the subgroup of RBC-transfusion non-dependent patients with SF concentration higher than 1000 ng/L was 9.1 g/dL (near the transfusion threshold), statistically insignificantly lower in comparison to the transfusion non-dependent group with lower SF concentration, probably because of the low number of patients in the first subgroup.

The univariate Cox proportional hazard analysis showed that the following factors significantly worsened survival: RBC-transfusion dependence ($p = 0.0033$; HR 2.67), hemoglobin concentration lower than 10 g/dL ($p = 0.0036$; HR 2.97), SF concentration higher than 1000 ng/L ($p = 0.0023$; HR = 2.94), platelet transfusion dependence ($p = 0.0071$; HR 3.321), platelet count lower than 10 G/L ($p = 0.008$; HR = 5.04), and acute leukemia transformation ($p = 0.0081$; HR 1.97). We found that RBC-transfusion dependency and SF concentration higher than 1000 ng/L were also found to be independent prognostic risk factors of death in the univariate proportional hazard risk analysis.

There was no multivariate analysis possible because of the quite small number of patients having all data accessible and being recognized 6 months before the inclusion to our registry.

Discussion

Most of the patients diagnosed with MDS are red-blood-cell-transfusion dependent and this is the main reason of iron overload [19]. But not only RBC-transfusions but also ineffective hematopoiesis can lead to iron overload due to higher absorption of iron from the gut [20]. It is also hypothesized that iron can be involved in the pathogenesis of MDS [17]. In the analyzed group, the hemoglobin concentration in the high SF group tended to be lower than in the low SF group and such a relationship was also confirmed by Park et al. [16].

In this study we provide the results of red blood cell transfusion dependency and SF concentration in the Polish MDS population. A correlation of RBC-transfusion dependency and hyper-

ferritinemia with worse survival was confirmed. In patients with myelodysplastic syndromes, hematopoiesis, mainly erythropoiesis, is ineffective [1, 19].

Our conclusion that the requirement for RBC--transfusions significantly worsens the survival of patients with MDS is in concordance with the literature [2].

Anemia and its severity are recognized as being among the most important factors affecting patients with MDS [2].

In our group, women prevailed in the higher SF concentration group, but Kikuchi et al. found that males more often had hyperferritinemia, and the SF in males was significantly higher [17]. Kikuchi et al. [17] also found the difference that men more often had iron overload, probably because menstruation in females affected ferritin concentration. The reason could be the more advanced women's average age and their postmenopausal status, but also the low number of analyzed patients. Park et al. [16] observed a correlation of higher ferritin concentration with MDS RARS, which was not confirmed in the present study due to the low number of patients with this MDS subtype.

The negative influence of iron overload on survival observed in our registry was in agreement with previous reports of Kikuchi et al. [17], Takatoku et al. [21] and Cakar et al. [22]. Malcovati et al. [10], Gattermann et al. [19] and Garcia-Manero et al. [23] also underlined a negative influence of transfusion-related iron overload on survival in MDS patients. Park et al. [16] found no correlation of ferritin concentration with survival, but only with dependency of RBC-transfusions. Chee et al. [24] showed no correlation between ferritin concentration, the number of red blood cell transfusions and their influence on overall survival in patients diagnosed with refractory anemia with ringed sideroblasts. Patients with indolent MDS that are transfusion-dependent can also have long survival. But the effect of iron overload in lower risk MDS patients can be more apparent because these patients live long enough to experience iron toxicity [25].

Cakar et al. [22] failed to confirm any impact of SF levels on overall survival, which might also be attributed to the small sample size and inadequate follow-up period.

In the present study we showed that a higher SF level at diagnosis was an important factor for overall survival in MDS patients. Iron is a catalyst of free radical production, and a high SF level or iron overload could accelerate generation of ROS or other oxidative compounds [17]. But it is controversial in the literature whether high SF concentration could affect the progression of MDS to AML [26]. In our group we did not observe more frequent transformation to AML in patients with higher SF concentration. Kikuchi et al. [17] and Malcovati et al. [26] underlined that with growing concentration of SF, the risk of transformation to acute leukemia increases. In our study the transformation of MDS to AML was observed significantly more often in RBC transfusion-dependent patients, which was also one of the negative prognostic factors of life expectancy in the previous reports [2, 10]. Park et al. [16] did not find a statistical difference in the risk of transformation to AML between groups with lower and higher SF concentration (300 ng/m) but the trend was shown (6.7% vs. 12%; p = ns.). In the study group of Park et al. [16], most of the patients were at low risk of MDS. Sanz et al. [27] found that hyperferritinemia had a negative influence on survival and risk of transformation of MDS to AML.

In our group, we have shown that the following factors significantly worsened survival: RBC-transfusion dependence, platelet-transfusion dependence, ferritin concentration higher than 1000 ng/dL, hemoglobin concentration lower than 10 g/dL, platelet count lower than 10 g/L, and acute leukemia transformation. Kikuchi et al. [17] also showed that a neutrophil count lower than 1.5 g/L, higher cytogenetic risk and high risk IPSS were important risk factors, which was not confirmed in this study possibly because of the low number of patients in the subgroups.

Our results suggest that red blood cell transfusion, hyperferritinemia and iron overload could aggravate the prognosis of MDS and were also negative prognostic factors. It is important to note that the distribution of hyperferritinemia and lack of data regarding IPSS was similar in the 2 groups of ferritin concentration, higher and lower than 1000 ng/mL, and hyperferritinemia was found as negative independent risk factor. It is not unusual that the data regarding MDS is underestimated [28, 29]. It has been reported in several studies that administration of an iron chelator could prolong the overall survival of MDS patients [30]. However, the impact of iron overload on morbidity and mortality is often difficult to precisely evaluate in MDS [1] due to the frequency of confounding factors such as co-morbidities [26], ageing, evolution of the disease and its complications [30].

The limitations to our results include the following: (1) it was not possible to obtain data for all the patients diagnosed with MDS in Poland in this time, but we were able to avoid bias by calculating survival only among patients diagnosed 6 months before inclusion to the registry, because the median survival time of higher risk MDS patients is about 4 months; (2) lack of data regarding mainly ferritin concentration and cytogenetics in both groups (higher and lower ferritin concentrations), but it is important that the IPSS distribution in both groups

was similar. The percentage of patients with cytogenetic data, although fairly low, is comparable to other studies, especially the registry based ones [28]. In some of the reported studies on MDS patients, the period of patient inclusion was short and the follow-up period was also limited [29].

Red-blood-cell-transfusion dependence and SF concentration higher than 1000 ng/mL were found to be independent prognostic risk factors of death in univariate proportional hazard risk analysis. Hyperferritinemia was not associated with higher risk of transformation to AML. Taking into account the relatively low number of patients in previous studies exploring this topic (35–126 patients) [17, 22, 24] and underestimation of the prevalence and data regarding patients diagnosed with MDS in other registries [29] too, the presented study provides important insights.

Although the percentage of patients with available results of cytogenetic examination was fairly low (28.6%), in the Prospective Registry of Polish MDS Patients (initiated in 2010 by the MDS Section of PALG and still in progress) this proportion is much higher and reaches the satisfactory value of 60.7% (unpublished data). Owing to this, we will be able to evaluate the risk (IPSS, IPSS-R, WPSS) in a higher percentage of the patients.

To prevent iron overload, symptomatic anemia is a major criterion for estimating the severity of anemia in MDS patients, we should consider if the patient needs to be transfused [30]. It is important that the decision about transfusion should be carefully considered and not taken only based on hemoglobin value. Patients with chronic anemia, including MDS patients, constitute an important and significant part of the orders of RBC units to blood banks. Blood transfusion should only be considered when the anemia is likely to cause or has caused a reduction in oxygen supply that is inadequate for the patient's needs.

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