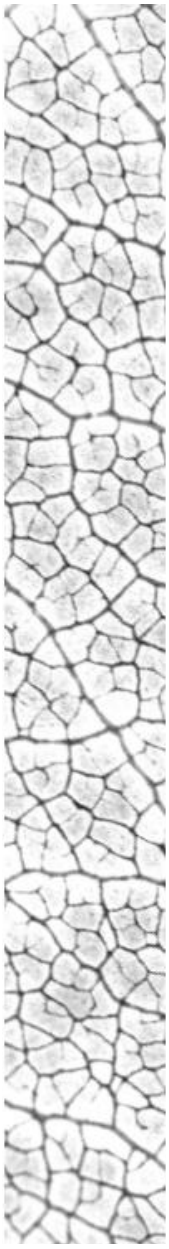

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Retrospective evaluation of hyperferritinemia and iron overload in patients with myelodysplastic syndrome

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Abstract

Introduction: The myelodysplastic syndromes (MDS) are a group of myeloid clonal disorders characterized by morphologic features, including hyper cellular bone marrow, unilineage or multilineage dysplasia and peripheral blood cytopenic. Anemia is the most commonly diagnosed cytopenic symptom in MDS patients. Regular red blood cell (RBC) transfusion is the often needed for the patients' symptomatic anemia. Transfusion-dependent patient's undergone tissue iron overload that may frequently be a prominent clinical feature. The purpose of this study was to determine the serum ferritin and iron levels in MDS patients and evaluation the outcome of the treatments received. **Methods**: In a retrospective study, the clinical and laboratory data were obtained of all patients with MDS referred to the clinic of Namazi hospital in Shiraz during 2017-2018 and analyzed by SPSS software. **Results**: Of 76 patients who entered the study 48 (62.66%) were males with a mean age of 68.48 ± 9.33 years and 28 (37.34%) were women with a mean age of 70.42 ± 10.97 years. The mean of ferritin serum level among all patients was 601.13 ± 828.29 mg / l which 16 men and 6 women had > 500 mg / l ferritin concentration, and a direct and significant correlation found between male and serum ferritin level. 17.33% of patients received iron chelator. In addition 15 (19.7%) and 6 (8.00%) of patients intake erythropoietin alone or with GM-SCF growth factor, respectively. **Conclusion**: Considering the relatively low number of studies are employed the hyperferritinemia in MDS patients, the obtained data define the hyperferritinemia incidence in MDS depended transfusion and serum ferritin higher than 1000 mg/dl can help to good prognosis for patient survival.

Keywords: myelodysplastic syndrome, ferritin, increased iron load

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INTRODUCTION

Myelodysplastic syndromes (MDS) present a heterogeneous group of hematopoietic stem cell malignancy which characteristized with the production of ineffective and dysplastic RBC and related with transformation to acute myeloid leukemia (Jemal et al. 2011, Schottenfeld and Fraumeni Jr 2006). Reduced quantities and qualities of RBC, platelets and mature granulocytes are observed in MDS patients which lead to systemic complications, such as anemia, bleeding and infection (Vardiman 2012).

Anemia is the most common cytopenia manifestation in patients with MDS. It has been reported that, an approximately 80% of patients develop anemia and are refractory to iron, folate, and vitamin B12 supplements in the early stages of MDS (Cazzola and Malcovati 2005). So it is an inevitable to intake whole blood or pack cell in several times for these patients. More than 40% of MDS patients are requiring RBC transfusion at various stages of the disease, and some of at risk patients are dependence to RBC transfusion (Greenberg et al. 2011). Therefore, chronic blood transfusion and the ineffectiveness of erythropoiesis, led to elevated serum ferritin concentration in an MDS patients. Although iron is a vital bioelement tissue, iron overload can damage and disable some organs, such as the heart and liver (Porter 2001).

Ferritin is a main iron storage protein found in all cell types thus it can be used as a reliable indicator of its overload (Park et al. 2011). Hence, the continuous screening and serum ferritin and iron levels assessment associated with other clinical and laboratory indicators can provide a substantial insights of diagnosis and treatment in MDS patients.

The aim of this study was to investigate the relationship between RBC-transfusion dependence and

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serum iron, ferritin and transferrin concentration in patients with MDS of Shiraz, Iran. The results of present study can help to identify prognostic potential effects of ferritin and iron loading in these patients.

MATERIAL AND METHODS

The present study was a retrospective. Patients affiliated to MDS referring to clinics and the Department of Hematology and Oncology of Namazi Hospital, Shiraz University of Medical Sciences during the 2017-2018 were included in this study.

Assuming a purpose-based samples all individuals are counted within the selection units. Thus a 76 total number patients with MDS were enrolled and followed up by the end of 2018.

The inclusion criteria was confirmation of MDS diagnosis by bone marrow sampling and exclusion criteria included patients with acute and chronic infection during serum ferritin measurement, positive CRP (1+ to 3+) before infectious disease or absolute neutrophil counts less than 1500.

Procedure

Considering that in MDS patients, in many cases, there are no clear clinical symptoms or non-specific manifestations, a definite diagnosis of the disease was obtained by bone marrow specimens.

Then, the primary and common tests for MDS patients who had undergone supportive interventions, such as chemotherapy or blood transfusion during clinical care were recorded and analyzed. Laboratory reports included peripheral blood cells counts as well as serum iron, ferritin, transferrin and TIBC parameters were recorded.

Serum ferritin levels were then subtracted from the cut-off point of 500 mg / l or 1000 mg / l and compared to the clinical outcome.

Patient Monitoring

Duration of the patient's treatment from the beginning of the study until to one year, patients were asked to visited and presented their laboratory and medical records to the blood and oncology clinic.

Moreover, if the patients who were monitored over time to compensate of anemia had received iron supplements or chelators, erythropoietin and growth factors such as GM-CSF more were recorded and the number of blood transfusions determined.

Statistical Analysis

To analyze the data, SPSS software ver22 was used. Descriptive statistics is presented by Mean and standard deviation. Furthermore independent-samples t-test, Mann-Whitney test, Chi-square test are employed as inferential analyses.

Table 1. Mean and median levels of ferritin, iron, transferrin and TIBC in patients with MDS

Gender		Male	Female	Sig*
Ferritin (mg/dl)	Mean±SD	601.13±828.29	685.35±1427.19	0.589
	Median	319.00	198.00	
Iron (U/l)	Mean±SD	86.07±30.29	77.20±45.33	0.007
	Median	77.00	60.00	
Transferrin (U/l)	Mean±SD	37.38±62.35	34.76±10.65	0.116
	Median	215.00	34.000	
TIBC (U/l)	Mean±SD	224.21±62.35	219.16±66.45	0.579
	Median	215.00	207.00	

*=P<0.05 was statistically significant

Table 2. Ferritin statue in cut of point 500 and 1000 mg/dl in MDS patients

Gender	Serum Ferritin		Serum Ferritin	
	≤1000 mg/dl	>1000 mg/dl	≤500 mg/dl	>500 mg/dl
Male	39(%52.7)	7(%9.5)	30(%40.5)	16(%21.6)
Female	22(%29.7)	6(%8.1)	22(%29.7)	6(%8.1)
Total	61(82.43%)	13(17.56)	52(70.27%)	22(29.72%)
P-value	0.352		0.170	

RESULTS

A total of 76 patients with MDS included 48 males (62.66%) with a mean age of 68.48 ± 9.33 years and 28 women (37.33%) with a mean age of 70.42±10.97 years which comparisons of sex had statistically difference, However mean age was not significant (P = 0.022 P = 0.434, respectively).

The mean and median serum concentrations of ferritin, iron, and transferrin and total iron binding capacity (TIBC) are presented in **Table 1**. Results of Kolmogorov Smirnoff showed all variables were P<0.05 so they considered as abnormal variables. Mann-Whitney test indicated the comparison of serum free iron was significantly different between genders. However comparison of ferritin, transferrin, and TIBC serum level were not significant between males and females (P>0.05).

Serum ferritin concentration was higher or equal to 1000 mg/dl and 500 mg/dl for 13 and 16 patients, respectively whereas for 61 and 55 patients they were lower, respectively. There were no significant differences between these groups regarding 500 and 1000 cut off mg/dl point (p = 0.352 and P=0.170 respectively). We observed that hyperferritinemia was more often diagnosed in Men than Women (9.5% vs. 8.1 %) (**Table 2**).

Frequency of various treatment received by MDS patients are presented in **Table 3**. We did not find any significant difference in frequency of therapeutic agents received by MDS patients between male and females (P>0.05). We found higher frequency of Males received pack cell-transfusion, erythropoietin, chelator and iron complement against women (11.8%,14.5%,11.8%,3.9% vs 3.9%,5.3%,5.3%,0% respectively). However 63.15% of MDS patients intook GM-SCF whom 57.89% were female.

Table 3. Comparison of therapeutic agents received by MDS patients between genders

	Receive	Male	Female	Total	Sig
GM-SCF	Yes	4(5.26%)	44(57.89%)	48(63.15%)	0.762
	No	2(2.63%)	26(34.21%)	28(36.84%)	
Pack cell	Yes	9(11.8%)	3(3.9%)	12(15.78%)	0.518
	No	39(51.3%)	25(32.9%)	64(84.21%)	
Erythropoietin	Yes	11(14.5%)	4(5.3%)	15(19.73%)	0.551
	No	37(48.7%)	24(31.6%)	61(80.26%)	
Chelator	Yes	9(11.8%)	4(5.3%)	13(17.56%)	0.757
	No	39(51.3%)	24(31.6%)	61(82.43%)	
Iron complement	Yes	3(3.9%)	0(0.0%)	3(3.94%)	0.293
	No	45(59.2%)	28(36.8%)	73(96.05%)	

DISCUSSION AND CONCLUSION

In this study, ferritin levels and iron overload in patients with MDS patients were studied. The results showed that 48 patients were males (62.66%) and 28 were females (37.3%). These results were consistent with Noemi et al study. (2011) who showed that 59.5% of MDS patients were male and the 41.5% were female (Roy et al. 2011).

The results of this study showed that 16% of the patients received the pack cell whom the majority of them (11.8%) were male. Moreover up to 17.6% of patients had ferritin levels >1000 mg / l and correlation analysis between the number of packed cells intake and the ferritin level was statistically significant. In this section, our results were in line with the Waszczuk-Gajda et al. (2016) who reported 18.3% of patients had ferritin levels > 1000 mg / l, which was a negative predictor of survival (Waszczuk-Gajda et al. 2016).

The results of present study demonstrated that the mean of ferritin serum level among all patients was 601.13 ± 82.89 mg / l. Additionally, 16 men and 6 women had mean serum ferritin levels > 500 mg / l, and a direct and significant correlation found between male and serum ferritin levels. Moreover, 13 patients (17.6%) had serum ferritin levels > 1000 mg / l. This study was in agreement with the Park et al study (2011), who showed that overloaded ferritin levels more than 300 mg / l was correlated with male sex, RARS diagnosis, hemoglobin < 8 mg / dl and MCV> 100, Circular sideroblasts > 15% in bone marrow of 318 MDSs identified based on International Prognostic Scoring System (IPSS) and Int criteria (Park et al. 2011).

Kikuchi et al(2012) found that most patients with high ferritin levels were male (Kikuchi et al. 2012). while Waszczuk-Gajda et al. (2016) showed that the majority of patients with ferritin levels were female (Waszczuk-Gajda et al. 2016).

In a study by Noemi et al. (2011), the mean value of serum ferritin in MDS patients was 2140 µg / l (Roy et al. 2011).In another study by Li et al (2013), on 191 newly diagnosed MDS patients ferritin greater than 500 mg / l independently had an adverse affect on the survival of patients (Li et al. 2013). Moreover Kikuchi et al. (2012) stated patients with low and high IPSS scores had the mean ferritin of 277±372 and 467±354 mg / L, respectively, which was significantly higher in high-risk MDS subjects (Kikuchi et al. 2012).

RBC transfusion is an integral part of the management of MDS syndromes, however when iron loading in the serum of patients is more than transferrin capacity , iron will combine with the oxygen and could generate hydroxyl radicals (Porter 2001, Chee et al. 2008). These toxic products can promote lipid peroxidation, DNA, protein and cell membrane damage. BCL2 Family members are antitumor proteins that inhibit of this pathway, although in some clinical conditions, the BCL2 level of the intracellular might reduce, thereby increasing apoptosis in hematopoietic progenitor cells (Greenberg). Chronic transfusion also increase the iron load and can cause significant damage to the heart, liver and endocrine glands (Andrews 1999).

According to the results of the previous studies, it has been determined that evaluating the history of iron overload in MDS patients undergoing blood transfusion therapy independently affects their survival (15-17). As Alessandrino et al (2010) reported, the survival rate was low in patients with a history of receiving more than 20 units of blood transfusion. Meanwhile, repeated transfusion was associated with the incidence of GVHD (Alessandrino et al. 2010). Another study on 467 MDS patients revealed that survival rates in RBC transfusion dependence patients were lower rather than those without blood transfusion. This effect was obvious among patients with refractory to anemia and thus was susceptible to prolonged toxicity of iron overload (Malcovati et al. 2005). In present study it was not possible to estimate survival rate of all patients due to lack of access to them, however we found that only 2 patients with ferritin levels greater than 1000 mg / L and mean age >70 died during the period of study. In the study of Ge et al (2015) which was in line of present study demonstrated the serum ferritin level with a cutoff point of 623 mg / l with a 77.5% sensitivity and 75% specificity was able to predict mortality in MDS patients. Therefore in addition of age and, IPSS scores other factors such as cytogenetic disorder, serum ferritin can also be used as a predictive index of these patients (Glauser et al. 2013).

Iron chelators are one of the preferred therapies for the iron overloading in MDS patients (Greenberg 2006). The results of studies conducted in thalassemia patients are widely recommending the use of chelators, while there is not enough data about MDS. Perhaps one of the reasons is the limitation in the classification of patients in priority of receiving chelating agents, also according to clinical manifestation these managements are different. Significant cytopenia indices, IPSS scores, age, and functional status are effective in determining the therapeutic algorithm (Greenberg, Popova 2019, Abdussalam-Mohammed, 2020).

As the results of this study showed, 17.33% of patients received iron chelator that 11.8% of them were men. In this regard, in Noemi et al. (2011) revealed 30% of patients received iron chelator, which deferoxamine was the most important chelator (Roy et al. 2011).

Ramacha et al (2014) found that 36.5% of patients received deferasirox. The use of this chelator significantly improved the survival rate compared to those who did not receive (Kacimi et al. 2020, Remacha et al. 2015).

It is important to assign effective chelators to low-risk patients instead of high-risk patients. Because iron chelators are less likely to succeed due to clinical problems such as hematopoietic impairment and the potential to progress to AML (Greenberg et al. 2011). Because clinical problems rather than tissue siderosis are overall more prominent, for example, hematopoietic failure, potential progression to AML thus Iron chelation is less likely to succeed in higher-risk patients.

There are several of effective anemia treatment options, which could help to prevent iron overload and other transmission-related side effects in MDS patients. A direct approach is the use of hematopoietic growth factors such as erythropoietin with or without G-CSF. Other treatments are like using immunosuppressive drugs. We found 15 (19.7%) patients received erythropoietin and 6 (8.00%) of them received GM-SCF growth factor. It has been shown that erythropoietin treatment is able to increase erythroid responses up to 20-25%. Similarly, response of erythrocytes elevated to 50% when this cytokine administrated with GM-SCF or G-SCF (Harvey 2010). However, other studies have reported that MDS patients did not completely respond to growth factors (Rose et al. 1995, Malcovati et al. 2013). These treatments vary according to individual characteristics and blood transfusion status. Erythropoietin is helpful at low risk MDS patients specially depended to blood transfusions. Therefore, cytokine therapy usually begins in the early phase of the disease. Although very early intervention, such as before a blood transfusion, is contraventional because some patients may be unstable condition and they potentially threated by risk of mutagen factor. Furthermore, other side effects may be emerged so taking this medicine early before the blood transfusion should be taken with caution.

CONCLUSION

Since the high incidence of anemia in patients with MDS, supportive care with long-term RBC transfusion therapy is recommended, especially in patients with low risk and longer life expectancy. Development of effective factors in reducing blood transfusion dependence is an important approach in MDS management. However, many patients still insist on long-term RBC infusion, and since endogenous mechanisms for iron removal are limited, starting to use iron chelators is essential. Standard recommendations for the initiation and maintenance of iron chelators should be a good standard for the care of patients with MDS-dependent transfusion.

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