COMPLEX PATHOGENETIC APPROACH IN CORRECTION OF IRON DEFICIENCY CONDITION IN PATIENTS WITH LOW RISK MYELODYSPLASTIC SYNDROME (a literature review)

S.V. Gritsaev
FSBI Russian Research Institute of Hematology and Transfusiology of the Federal Medical and Biological Agency, ndm2@mail.ru

Z.D. Yunusova
Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan

N.A. Baymatova
Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan

Sh.D. Babadzhanova
Tashkent Medical Academy

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a literature review


1FSBI Russian Research Institute of Hematology and Transfusiology of the Federal Medical and Biological Agency;
2Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan;
3Tashkent Medical Academy

Abstract

Background. Patients with low-risk MDS remain dependent on regular transfusions, acquiring a secondary, post-transfusion excess of iron, which accordingly is an indication for the appointment of chelation therapy (CT). All over the world this problem continues to be studied, confirmation that this article cites about 40 sources of literature review.

Methods. Three online medical databases were searched to identify studies reporting the data on the complex methods of treatment for the correction of iron deficiency condition in patients with low risk myelodysplastic syndrome. The primary outcome was to learn the worldwide tendency on this matter and to compare the results of different authors.

Results. Several primary and secondary studies have been published that demonstrate improved survival of low-risk MDS patients who received chemotherapy. Overall, we identified 842 items as a result of search. Then we found 156 studies as similar among the databases that were deleted afterwards. Then, remaining 686 records were screened excluding 512 findings owing to different reasons. Further, the titles of 174 studies were read, 51 articles found as potentially eligible, which obtained in full text. All full text articles were learnt by the authors of the review. Finally, we included 26 studies to our review.

Conclusion. Chelator therapy is a component of the treatment for low-risk MDS patients with post-transfusion overload with iron. Its appointment as part of a complex-pathogenetical therapy should not be formal. The description of iron chelators can reduce transfusion dependence and increase survival in patients with MDS.

Key words: myelodysplastic syndrome (MDS), acute leukemia, low-risk MDS patients, anemia, ferritin, erythropoiesis-stimulating drugs, chelator therapy, exjade.
BACKGROUND

Myelodysplastic syndrome (MDS) is a group of heterogeneous clonal diseases characterized by the presence of cytopenia in peripheral blood (PB), bone marrow (BM) dysplasia and the risk of transformation into acute leukemia (AL). MDS is one of the most severe issues in hematology today. MDS is more specific pathology for the older age group. 80% of cases with MDS occur in people over 60. Childhood MDS is extremely rare. It is known that the choice of therapeutic tactics is largely determined by the patient's age, somatic condition, risk level by IPSS and WPSS scale, as well as the availability of a suitable donor.

The choice of treatment for patients with MDS is a rather complicated process, and, first of all, this is characteristic for patients from the low-risk group. An excess of blast cells in the bone marrow, especially in combination with an unfavorable variant of the karyotype, involves treatment aimed at preventing further progression of the disease and/or preparing for transplantation of allogeneic hematopoietic stem cells. Those the hematologist, based mainly on data on age, somatic status and comorbidity, selects one of three possible options. These are protocols for the treatment of acute myeloid leukemia, hypomethylating drugs in monotherapy mode or in combination with other drugs and restraint therapy, which presupposes the appointment of predominantly cytostatic tablets.

The task of treating low-risk MDS patients is the correction of cytopenia and, above all, anemia (Abrashkina, 2008; and Klimkovich, 2005). For this category of patients, the problem is not so much in the choice of erythropoiesis-stimulating, immunosuppressive, immunomodulating or hypomethylating drugs. The analysis of predictors associated with efficacy allows correct selection of patients, to reduce the frequency of transfusion of donor red blood cells or even completely reject them. The problem is that not all patients manage to achieve the answer. Moreover, in most cases the answer is transient in nature. Thus, if a patient with low-risk MDS is not a candidate for transplantation, then he remains dependent on regular transfusions with different intensity, as a result, acquires a secondary, post-transfusion, excess of iron and, accordingly, there are indications for the appointment of chelator therapy (CT) (Rat, 2013).

The effectiveness of iron chelators is assessed by the level of serum ferritin and the iron content in the liver and myocardium, determined by magnetic resonance imaging. However, taking into account the negative effect of excess iron on vital internal organs mediated by damage to cell structures by products of free radical oxidation, it is not so much the reduction of ferritin indices (Suleymanova, 2017; Greenberg et al, 1997; and Bennett, 2008), but the problem of a possible reduction in mortality that is not associated with the progression of MDS and improving overall survival (OS) (Kokhno, 2009; Malcovati et al, 2015; Steensma & Bennett, 2006; Mitchell et al, 2013). Considering the fact
that the damaging effect of excess iron on bone marrow hematopoiesis is not ruled out, it is possible that the appointment of chemotherapy can also improve blood counts. This position is of fundamental importance, since chronic anemia, as you know, is an independent factor in the deterioration of the survival of patients with MDS (Mitchell et al, 2013).

It is known that the maintenance of iron homeostasis is ensured by a balance between the absorption and recycling of a trace element in the body in the absence of mechanisms to remove its excess. In this case, the intake of iron from the intestine into the blood, carried out with the participation of ferropoietin, is controlled by hepsidin (Gattermann et al, 2012; List et al, 2012). A genetically mediated decrease in the expression and, accordingly, hepcidin production, observed in particular in patients with congenital hemochromatosis, is accompanied by an increase in the level of serum iron. Reduced hepcidin expression may also be a consequence of ineffective erythropoiesis, as, for example, in patients with thalassemia who do not need transfusions (Greenberg et al, 2010).

Another reason for the excess iron is transfusion of donor red blood cells with accumulation of iron mainly in the cells of the reticuloendothelial system (Remacha et al, 2010). Transfusion of 4-5 doses of donor red blood cells adds approximately 1 gram of iron to the 4 grams contained in the body. Under these conditions, the depletion of the binding ability of ferritin is accompanied by the appearance of iron unbound with ferritin, including its aggressive form - the labile iron of plasma. The accumulation of excess iron, the formation of labile iron in plasma and products of free radical oxidation results in damage to the cells of the myocardium, liver, pancreas and a number of other organs with impaired functional activity, which may ultimately lead to death of the patient (Rose et al, 2010). It is possible that an excess of iron may be associated with the risk of transformation into acute myeloid leukemia (AML) (Malcovati et al, 2007).

The actuality of studying iron excess and treatment in patients with low-risk MDS is not so much the decrease in ferritin, as the problem of a possible reduction in mortality, not associated with the progression of MDS, and improve the overall survival of this contingent. In Uzbekistan, such studies were conducted only in patients with thalassemia. In this connection, it became necessary to study this problem in patients with MDS.

**PURPOSE OF THE STUDY**

To study the recent data in the literature related to the iron excess and treatment in patients with low-risk MDS and the problem of a possible reduction in mortality associated with the progression of MDS. To analyze improvement in the overall survival of this contingent.

**METHODS**

**PROTOCOL AND REGISTRATION**

The literature review was conducted following the guidelines set by the Preferred Reporting Items for Systematic Reviews and
Meta-Analysis (PRISMA) (Moher et al, 2009).

ELIGIBILITY AND EXCLUSION CRITERIA

Both primary and secondary studies were included for this review. We did not apply any restrictions regarding the period of the publication for studies. Only English papers were included. The review covered both prospective as well as retrospective data analyses. We did not used filters for the country of publication.

SEARCH STRATEGY

Three medical electronic databases (MEDLINE, EMBASE and Cochrane) were searched to find the studies reporting the complex pathogenetic therapeutic tactics for the correction of iron deficiency condition in patients with low risk myelodysplastic syndrome. In the search strategy techniques on the web sites mentioned above, we used the following key words:

myelodysplastic syndrome (MDS), acute leukemia, low-risk MDS patients, anemia, ferritin, erythropoiesis-stimulating drugs, chelator therapy, exjade.

STUDY SELECTION

Titles and abstracts of the articles reviewed by the authors of the study applying the search methods outlined above in order to identify the studies that match the inclusion criteria. Found items were searched and compared for duplicate articles, similar studies were deleted. Eligible studies were checked to find any more interesting sources for our review. When we found any interesting paper that suitable for our criteria of eligibility, full texts the study were obtained and read till the end. Any disagreements between reviewers, resolved by discussion.

RESULTS

STUDY SELECTION.

Overall, 842 items found as a result of search through databases mentioned above. Next, we identified 156 identical studies that were deleted afterwards. Then, remaining 686 records were screened excluding 512 findings owing to different reasons. Further, the titles of 174 studies were read, 51 articles found as potentially eligible, which obtained in full text. All full text articles were learnt by the authors of the review. Finally, we included 26 studies to our review. Owing to the different style, methods and outcomes of the studies (heterogeneity), we did not perform meta-analysis.

STUDY CHARACTERISTICS

Today, several papers have been published that demonstrate improved survival of low-risk MDS patients who received chemotherapy. R. Lyons et al. (2017) reported the results of a 5-year prospective, non-intervention study that included 599 low-risk MDS patients over the age of 18 from 118 US centers. The diagnosis was established according to the classification of WHO or FAB, a variant of the forecast on the IPSS scale. Post-
transfusion iron overload was verified if 20 or more doses of donated red blood cells were transfused or transfusions continued at a frequency of ≥6 doses every 12 weeks, and/or the level of serum ferritin was more than 1000 ng/ml. The period from the diagnosis of MDS to inclusion in the study ranged from 0 to 429.9 months. Vascular diseases were detected in 54.4% of patients: arterial hypertension in 50.8% and coronary heart disease in 25.2%. Diabetes mellitus and thyroid disease occurred in 24.5% and 21.0% of patients, respectively. Patients were divided into three groups: without chemotherapy, chemotherapy and chemotherapy for a duration of ≥6 months.

The authors found that the appointment of iron chelators and, above all, long-term chemotherapy was accompanied by a significant improvement in survival: 86.3 and 98.7 months, respectively, compared to 47.8 months in the group of patients without chemotherapy; p<0.0001. One reason is the significantly higher frequency of deaths among patients who were not prescribed chelators: 73.3% versus 62.2% in the CT group and 59.6% in the CT group for ≥6 months. At the same time, improvement without progressive survival was demonstrated. The median time from diagnosis of MDS to transformation into AML in the groups was 46.7, 86.3 and 97.8 months, respectively; p<0.0001.

H. Leitch et al. (2017) analyzed data from 239 MDS patients with low and intermediate-1 IPSS risk, of which 83 received (Deferazirox, Deferoxamine, or both drugs sequentially) and 156 did not receive chemotherapy. In the CT group there were more young patients and MDS patients with ring sideroblasts, with a later development of transfusion dependence and higher serum ferritin levels. Before or during chemotherapy, patients received one of the treatment options commonly used to treat MDS. The duration of chemotherapy was from 1.2 to 123.5 months, the median was 12.4 months. As in the previous work, a significant improvement in the survival of patients with the appointment of iron chelators was found: 5.2 years versus 2.1 years without chemotherapy; p<0.0001.

Given the heterogeneous composition of patients, the authors evaluated the OM in groups with comparable clinical and hematological parameters (age, IPSS-R variant, transfusion frequency per month, duration of the period from diagnosis of MDS to the start of transfusions) and again revealed significantly worse survival of patients who did not receive chemotherapy. At the same time, there were no differences in the causes of death and without leukemic survival in comparable groups.

The results of 8 observational studies published over the period 2008–2014 were used by A. Mainous et al. (2014) for meta-analysis. And again, a significant improvement in the survival of low-risk MDS patients who received chemotherapy was demonstrated. The difference in median OM was 61.2 months, i.e. the appointment of iron chelators increased survival by 5 years. Since interim data were presented in 3 publications, in 2017 I. Abraham et al. (2017) presented the results of a new meta-
analysis of the results of 7 observational studies due to an increase in the observation time (Kohgo et al, 2008). The result was a repeat of the conclusion about the direct dependence of OM of low-risk MDS patients on the appointment of iron chelators. Moreover, the difference in median survival has already reached 74 months, i.e. with the appointment of chemotherapy, an increase in life expectancy of 6.2 years is possible.

The mechanisms responsible for improving the survival of low-risk MDS patients with the appointment of chelators are not known. The most attractive explanation seems to be a decrease in iron reserves. However, a short monitoring of serum ferritin and liver iron levels is insufficient to substantiate this assumption (Greenberg et al, 2008; Bennett, 2008; and Gattermann, 2018). Moreover, individual researchers failed to demonstrate a significant decrease in ferritin levels even with prolonged chemotherapy, which casts doubt on the feasibility of using this indicator as a marker for assessing the effectiveness of iron chelators(Kohgo et al, 2008). As possible mechanisms for improving OM, a decrease in the need for transfusions of donor red blood cells and a decrease in the risk of progression in AML are also considered (Andrews, 2012; Lyons et al, 2017). But the biological effect of chelators in the form of a decrease in the level of iron not associated with ferritin, labile iron of plasma and products of free radical oxidation, which helps prevent damage to vital organs, seems more likely to occur (Gattermann, 2018; Leitch et al, 2017). An indirect confirmation may be a decrease in the risk of death with prolonged use of Deferasirox in an adequate dose (Andrews, 2012; Mainous et al, 2014; and Abraham et al, 2017). Zeidan et al. (2015) found that each additional week of chelator administration is associated with a reduced risk of death, especially in the case of chronic chemotherapy for more than 53 weeks (HR: 0.395; 95% CI: 0.197–0.792; p = 0.009).

The appointment of iron chelators is attractive to clinicians not only for the ability to improve OM. No less important is the chance to reduce the dependence of MDS patients on transfusions. On this issue in the literature one can find a description of both individual observations and an analysis of a significant number of cases. The largest number of MDS patients in the case histories that were analyzed for the frequency of achievement of the hematological response (HR) was included in the EPIC study - prospective, 1-year, multicenter, open, stage III to study the effectiveness of Deferasirox in patients with excess iron (Lyons et al, 2017). Inclusion criteria were post-transfusion iron overload, defined as a ferritin level of ≥1000 ng/ml or transfusion of more than 20 doses of donor red blood cells (if the ferritin level was <1000 ng / ml), or iron concentration in the liver >2 mg Fe/g dry weight (method MRI T2), as well as the projected life expectancy of at least 1 year and the absence of another type of specific therapy. Patients who took at least one dose of Deferasirox were
selected for post-hoc analysis. Of the 341 MDS patients included in the study, erythrocyte, platelet, and neutrophil responses were evaluated in 247, 100, and 50 patients, respectively. The erythrocyte response was recorded in 21.5% of patients with a median time to response of 109 days. At the same time, in 11.3% of patients there was only a decrease in dependence on transfusions, in 8.9% only an increase in hemoglobin concentration, and in 1.2%, both responses were simultaneous. Platelet response occurred in 13.0% of patients with a median time to response of 169 days. A neutrophilic response was observed in 22.0% of patients with a median time to response of 226 days. The response was accompanied by a decrease in ferritin levels.

A decrease in ferritin was also revealed by other authors (Gattermann et al, 2012), which suggests that the response is dependent on a decrease in iron stores. For a more correct identification of the possible reasons for improving blood counts and reducing the need for transfusions with the appointment of Deferasirox M. Breccia et al. (2015) analyzed 9 publications describing individual cases with HR, 4 with the results of clinical trials and 3 with indicators from real clinical practice. Aggregate analysis allowed the authors to admit the role of the following mechanisms. The direct effect of chelators on the pathological clone and cells of the hematopoietic microenvironment. Stimulation of mechanisms for removing iron from storage sites with its subsequent utilization by hematopoietic tissue. Decreased plasma labile iron and oxygen free radicals. Suppression of the function of the transcription factor NF-kb. Suppression of the intracellular signaling pathway mTOR. It should be assumed that the hematological response is the result of the joint or sequential functioning of several of the above mechanisms initiated by the use of iron chelators. This, in part, can explain the absence of HR in other MDS patients.

DISCUSSIONS

The review of the recent literature on the topic of complex treatment of iron deficiency condition in patients with low risk myelodysplastic syndrome showed that there are some shortcomings in studies evaluating the effectiveness of chelators. Moreover, this includes the lack of randomization and the possible selection of patients with a more favorable prognosis in the CT group, yet, the available data allow us to expect improved survival and reduced transfusion dependence when prescribing iron chelators.

For this, as follows from the already mentioned studies (Kohgo et al, 2008; and Mainous et al, 2014) and the study of M. Delforge et al. (2014), compliance with 2 fundamental conditions is necessary: dose adequacy and duration of therapy. Given the possible toxic complications when taking Deferasirox, the next important condition is clinical and laboratory monitoring with timely dose adjustment. The most common complications of prescribing Deferasirox (exjad) include gastrointestinal upsets and an increase in creatinine levels (Zeidan et al, 2015), which are reversible in compliance
with the recommendations prescribed in the instructions, i.e. timely dose reduction, interruption or withdrawal. Taking exjade half an hour before dinner and gradually increasing the dosage under the control of serum ferritin levels can prevent the development of adverse events (Rose et al, 2010). Exjade, which is available in the form of coated tablets, the patient takes 30 mg / kg per day (Rose et al, 2010; Breccia et al, 2015; Delforge et al, 2014; Cermak et al, 201; Nolte et al, 2015).

CONCLUSION

Chelator therapy is a component of the algorithm of treatment for low-risk MDS patients with post-transfusion overload with iron. Its appointment as part of a complex-pathogenetical therapy should not be formal due to only the identification of criteria for excess iron in the body. The description of iron chelators can reduce transfusion dependence and increase survival in patients with MDS. The conditions for a complex-pathogenetically substantiated manifestation of the clinical effectiveness of chelator therapy are careful selection of candidates, timely dose adjustment and long-term use of chelators. In Uzbekistan, chelator therapy with the use of exjade in patients with thalassemia is successfully used, only the complex pathogenetically substantiated prescription of therapeutic drugs is provided at the expense of state funds.

STUDY LIMITATIONS

The review did not include the quality assessment and risk of bias within included studies. This might affect the general outcomes as well as conclusion of this review. Thus, further literature review and meta-analyses on this topic can be conducted with the quality assessment.

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ETHICAL APPROVAL

The ethical approval for the study was granted by the Committee of Ethical Approval for Researches under the Ministry of Health of the Republic of Uzbekistan.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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REFERENCES:

publication”. Hematology and transfusiology. 2. pp. 3-8.


15. Remacha AF, Arrizabalaga B, Del Canizo C et al. (2010). “Iron overload and


deferasedirox therapy in transfusion-dependent patients with myelodysplasticsyndromes”. Haematologica; 97 (9): pp. 1364-1371.


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