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PERSONAL VIEW

IRON OVERLOAD IN PATIENTS WITH TRANSFUSION DEPENDENT MYELODISPLASTIC SYNDROME

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A b s t r a c t: The myelodisplastic syndrome is a heterogeneous group of diseases, characterised by ineffective and dysplastic haematopoesis and pancytopenia in the peripheral blood, followed by progressive disturbance of differentiation of the haematopoetic stem cell, resulting in evolution of the disease towards acute leukaemia. According to the latest WHO classification, the term myelodisplastic syndrome includes diseases with an indolent course, as well as diseases with a fast evolution towards acute leukaemia. Because of this diversity, haematologists base their therapeutic decisions on prognostic scoring systems which incorporate all the significant factors with an influence on survival in this group of patients with myelodisplastic syndrome. Bearing in mind that anaemia is the most frequent form of cytopenia in patients with myelodisplastic syndrome, it is common that at some point of the disease almost every patient with myelodisplastic syndrome is transfusion-dependent.

Frequently applied transfusions secure the correction of anaemia in these patients, giving them a good quality of life, but at the same time endangering them with the potential threat of iron overload, when the physiological mechanisms of iron excretion from the organism become insufficient. There is a clear correlation between transfusion dependence and the overall survival in patients with myelodisplastic syndrome. Chelators secure the lowering of the iron surfeit and are indicated in transfusion-dependant patients with myelodisplastic syndrome (need for two blood units monthly, during one year), when the ferritin level increases over 1000, in patients who are candidates for

transplantation as well as in patients from good prognostic groups with median survival over one year. The therapy with chelators lasts as long as the patient is transfusion-dependant.

Key words: myelodisplastic syndrome, chelators, iron overload.

Myelodisplastic syndromes (MDS) are a group of haematologic disorders that occur in elderly people with a median age at diagnosis ranging between 60–75 years. The incidence of MDS appears to be rising in industrialised countries in tandem with the ageing of the population. They are a clonal haematopoetic stem cell disorder characterized by ineffective and dysplastic haematopoesis, peripheral cytopenias and an increasing risk of progression into acute myeloid leukaemia (AML). Patients with MDS have widely variable cellular haematopoetic (morphologic) features, chromosomal abnormalities, clinical manifestations and prognoses. The disease course may be indolent or aggressive. This is the reason for a risk adapted treatment strategy as mandatory for disorders that range from indolent conditions lasting years to forms approaching acute myeloid leukaemia [5, 20, 21].

According to the French-American British (FAB) Classification published in 1982, MDS was based on morphological criteria and this classification was used in all investigational studies for MDS for the following twenty years. The rising need for a prognostic system with greater power to predict survival resulted in creating the most useful proposal for the classification of MDS, which was given in 2002 by the WHO. (Table 1) This proposal is very important because it is based on the parameters and factors which have been evaluated as significant ones that influence survival and leukaemic progression in patients with MDS. Variables that have been included are uni- or multilinage haematopoetic dysplasia, narrower blast count intervals and specific cytogenetic abnormalities. The retrospective studies that followed confirmed the prognostic relevance of this classification and proved that the WHO classification can guide clinical decision-making regarding therapeutic choices [9, 10, 16].

Nowadays, prognosis of a subset of patients with MDS has substantially improved with novel therapeutic optionals such as epigenetic treatment, farnesyltransferase inhibitors, and immunomodulatory drugs. The selection of therapy for MDS is based on patient risk score including WPSS risk category, age, and performance status. Treatment goals are different in different cases and they range from managing cytopenias and improving quality of life to altering the natural history of the disease in high-risk patients. New therapeutic strategies have emerged so that today patients with MDS can be treated with different

Table 1

WHO Classification of myeloid neoplasm (23)

Disease	Blood findings	Bone marrow findings
Refractory anaemia (RA)	**Anaemia No or rare blasts < 1 × 10^9/L monocytes**	**Erythroid dysplasia only < 10% grans or megas dysplastic < 5% blasts, < 15% ringed sideroblasts**
Refractory anaemia with ringed sideroblasts (RARS)	**Anaemia No blasts**	**Erythroid dysplasia only < 10% grans or megas dysplastic ≥ 15% ringed sideroblasts, < 5% blasts**
Refractory cytopenia with multilineage dysplasia (RCMD)	**Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods, < 1 × 10^9/L monocytes**	**Dysplasia in ≥ 10% of cells in two or more myeloid cell lines < 5% blasts in marrow, no Auer rods, < 15% ringed sideroblasts**
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	**Cytopenias (bicytopenia or pancytopenia) No or rare blasts No Auer rods, < 1 × 10^9/L monocytes**	**Dysplasia in ≥ 10% of cells in two or more myeloid cell lines ≥ 15% ringed sideroblasts, < 5% blasts, no Auer rods**
Refractory anaemia with excess blasts-1 (RAEB-1)	**Cytopenias <5%blasts No Auer rods, < 1 × 10^9/L monocytes**	**Unilineage or multilineage dysplasia 5–9% blasts, no Auer rods**
Refractory anaemia with excess blasts-2 (RAEB-2)	**Cytopenias 5–19% blasts Auer rods ±, < 1 × 10^9/L monocytes**	**Unilineage or multilineage dysplasia 10–19% blasts, Auer rods ±**
Myelodysplastic syndrome, unclassified (MDS-U)	**Cytopenias No or rare blasts, no Auer rods**	**Unilineage gran or mega dysplasia < 5% blasts, no Auer rods**
MDS associated with isolated del(5q)	**Anaemia < 5% blasts Platelets normal or increased**	**Normal to increased megakaryocytes with hypolobulated nuclei < 5% blasts, no Auer rods, isolated del(5q)**

therapeutic optionals such as: "Best supportive care", including iron chelation, haemopoietic growth factors, Immunosuppressive treatment, differentiation induction, immunomodulatory drugs, arsenic trioxide, low-dose chemotherapy, epigenetic treatment, farnesyltransferase inhibitors, intensive chemotherapy, and allogeneic stem cell transplantation [1, 22].

Red cell transfusions are the mainstays of therapy in patients with MDS and symptomatic anaemia. Anaemia is the most frequently observed cytopenia in MDS and is present among the majority of the patients. About 60% of patients will have severe anaemia and will require red cell transfusion. Red blood transfusion as a sole therapeutic option will be offered to 40% of MDS patients with anemia. In fact almost every patient with myelodisplastic syndrome will be transfusion-dependent in some period of evolution of the disease. Doctors treating patients with MDS and anaemia evaluate anaemia-related symptoms and existence of comorbidities. This clinical evaluation guides doctors in the need for transfusion therapy. They will give transfusion to any MDS patients because it is well known that red blood cell transfusions are a vital, life saving treatment for many patients with MDS and anaemia and it is necessary to preserve the patient's quality of life. At the same time doctors are aware that every unit of transfused blood contains 200–250mg of iron and the human body has no mechanism to actively excrete excess iron. This situation often results in cumulative iron overload as an inevitable consequence of chronic transfusion therapy [14, 15, 17].

Cazzola and Malcovati showed that patients with established transfusion dependency had a significantly reduced probability of survival (survival hazard 1.58; $P = 0.005$). One of the possible explanations for decreased survival with transfusion dependency may be due to more severe bone marrow inefficiency and inadequate chelation therapy [5].

Table 2

WHO classification-based Prognostic Scoring System (WPSS)

Variable	**0**	**1**	**2**	**3**
WHO category	RA, RARS, isolation 5q−	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	–
Transfusion requirement†	No	Regular	–	–

Good: normal, −Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; and intermediate: other abnormalities. †At least 1 RBC transfusion every 8 weeks over a period of 4 months

Transfusion dependency is associated with shorter survival and increased risk of leukaemic evolution and can be used as an indicator of disease severity in MDS. This important observation incorporated transfusion dependency into WPSS which is a dynamic prognostic scoring system for predicting survival and leukaemic evolution in MDS patients. This is more noticeable in low-risk, intermediate-1 MDS patients, and patients with RA [7, 19, 20].

On the one hand iron is vital for survival, but on the other hand an excess of iron is potentially lethal. Use of red cell transfusions for anaemia in patients with MDS is the main cause of iron overload in MDS. But there is also an underrecognized cause of iron overload in some patients with MDS such as increased absorption iron from the gut due to ineffective erythropoesis. Iron export into plasma from duodenal entereocytes occurs as a result of elevated protein ferroportin which is negatively regulated by hepcidin. Hepcidin is a key hormone that regulates iron metabolism by inducing internalization and degradation of ferroportin [18].

During normal iron homeostasis, circulating iron is bound to transferin. Transferin is a dedicated iron-binding protein with a high affinity for ferric iron and is one of the adaptive defenses against excess iron. The reticuloendothelial system as a storage for iron has a capacity of about 10–15 grams, corresponding to about 50 red blood cell units. When these capacities are exceeded parenchymal deposition and tissue damage occurs. For example, if the patient has been receiving two red blood cell units per month, this situation would be expected in just two years [13].

Red cell transfusion is the main cause of iron overload in the group of patients with MDS and this leads to accumulation of macrophage iron and its export into plasma when there is no more capacity of transferin to bind it. Non-Transferin bound iron (NTBI) or "free" iron is formed when a state of iron overload occurs, and there is no more capacity for transferin to bind iron. Lable plasma iron (LPI), one form of NTBI is a toxic, cell-penetrating, redox-active that is directly chelatable and can be taken up by liver, cardiac and endocrine cells through uptake mechanisms that are independent of the transferin receptor. Ineffective erythropoiesis accompanied with decreased iron use by the bone marrow in patients with suppressed erythropoiesis and in patients undergoing myeloablation for HSCT is another mechanism that increases NTBI. Elevated values of NTBI and LBI lead to increased risk of bacterial and fungal bloodstream infection and induce genomic instability in haematopoetic progenitors. Cardiac dysfunction results from myocardial iron deposition.

Pullarkat clearly emphasized that the benefit from iron chelation in MDS is not only from the reduction in cardiac and other end organ damage due to tissue iron overload, but from a potential favourable impact on three other outcomes: reduction of infections, improvement in survival after allogeneic haematopoetic stem cell transplantation (HCT), and delayed leukaemic progres-

sion. Bearing this in mind, this study clarifies that chelation therapy should be appropriate for higher grades of MDS [18].

Patients benefit from iron therapy in two ways. Iron therapy binds and removes iron from the body at a rate that is either equal to the rate of transfusional iron input, known as maintenance therapy, or greater than iron input, known as reduction therapy [7, 8, 11, 24].

Table 3

Comparison of Basic Properties of the Three Chelators Available in Clinical Use (4)

Property	Chelators			
	Ideal	Deferoxamine	Deferiprone	Deferasirox
Route	Oral	s.c.; i.v.	Oral	Oral
Molar Fe chelating eff.	High	1 : 1	3 : 1	2 : 1
Usual dose mg/kg/d	–	20–50	75	20–30
Half life	Long	20–30min	3–4 hrs	12–16 hrs
Excretion	easy	Urine/Fecal	Urine	Fecal
Full day LPI Coverage	Yes	No	No	No
Penetration to tissue	+++	+	++/+++	++/+++
Lowering liver Fe	+++	+++	+	+++
Lowering heart Fe	+++	++ (high doses)	++/+++	++
Compliance	+++	+/++	++/+++	++/+++

Medications that can fulfil those criteria are helators. an ideal chelator for the future iron chelation era should allow individualizing and tailoring of the treatment in order to attain a high compliance rate, achievement of a negative iron balance and limitation of side-effects [8, 11].

Iron overload is an important adverse prognostic factor for patients with haematologic malignancies undergoing haematopoetic stem cell transplantation (HSCT). HSCT is the only curative therapeutic approach in patients with MDS and is highly recommended for high risk patients, especially younger ones. An elevated pretransplant serum ferritin level is strongly associated with lower overall, disease-free survival and transplant-related mortality. Patients with a high ferritin level have an increased risk of veno-occlusive disease [2]. There is a statistically significant absolute difference of 37% in 5-years overall survival for patients with MDS between the highest and lowest ferritin quartilies. Chelation therapy should be considered as an option for significant improvement in transplantation outcomes for patients of MDS undergoing haematopoetic stem cell transplantation.

The American Society of Hematology established precise recomendations for initialing and moniotoring iron chelator therapy in myelodisplastic syndromes, according to the consensus statement on iron overload in myelodis-

plastic syndromes published by the MDS Foundation's Working Group on Transfusional Iron Overload [3, 13].

MDS patients who would benefit most from treatment of iron overload are those who require transfusion of more than 2 red blood cell units per month for more than a year; patients with a ferritin level more than 1000ng/mL; patients with low risk MDS (according to IPSS low or intermediate –1, according to WHO –RA, RARS, and 5q-); patients with life expectancy of more than a year; patients who do not have comorbidities that would limit prognosis, those patients who are candidates for allograft; patients in whom preservation of organ function is needed and patients without response or ineligible for primary therapy such as immunomodulatory or hypomethylating agents [13].

For monitoring iron overload the following tests are recommended: serum ferritin, transferin saturation. There are cases when monitoring of organ function is indicated (cardiac, hepatic, endocrine). The recommended test should be repeated every three months. In additional test such as MRI, or investigational parameters like NTBI (nontransferin binding iron), LPI (lable plasma iron) can be performed.

There is a consensus regarding the duration of iron chelation therapy. Patients with MDS should be on iron chelation therapy as long as they are transfusion-dependent and transfusion therapy continues.

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Р е з и м е

ПРЕОПТОВАРУВАЊЕ СО ЖЕЛЕЗО КАЈ ПАЦИЕНТИТЕ СО ТРАНСФУЗИОНО ЗАВИСЕН МИЕЛОДИСПЛАСТИЧЕН СИНДРОМ

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А п с т р а к т: Миелодиспластичниот синдром опфаќа хеторегена група на заболувања кои се карактеризираат со нарушување на хематопоезата, панцитопенија во периферната крв следена со прогресивно нарушување во диференцијацијата на хематопоетската стем-клетка кое резултира во еволуција кон акутна леукемија. Според најновата класификација на Светската здравствена организација, поимот миелодиспластичен синдром во себе опфаќа, од една страна, заболувања со индолетен тек, но, исто така, и заболувања со брза еволуција кон акутна леукемија. Поради тоа, хематолозите терапевтската одлука ја базираат на прогностичките скоринг системи кои во себе ги синтетизираат сите сигнификантни фактори кои значајно влијаат на преживувањето во групата на пациенти со миелодиспластичен синдром.

Тргнувајќи од фактот дека анемијата е најфреквентната цитопенија која се јавува кај пациентите со миелодиспластичен синдром, разбирливо е дека во одреден период од заболувањето речиси секој пациент со миелодиспластичен синдром (80–90%) е трансфузионо зависен. Честите трансфузии им обезбедуваат на пациентите корекција на анемијата, а со самото тоа и добар квалитет на живот, но истовремено и потенцијална опасност од преоптоварување со железо кога ќе се засистат и надминат физиолошките механизми на отстранување на вишокот на железото од организмот. Постои јасна корелација на трансфузивната зависност и вкупното преживување кај пациентите со миелодиспластичен синдром. Хелаторите обезбедуваат намалување на вишокот на железо и се индицирани кај пациентите со миело-

диспластичен синдром кои се трансфузионо зависни (потреба од две еденици крв месечно во текот на една година), покачено ниво на феритин над 1000, пациенти кандидати за трансплантација, и пациенти кои припаѓаат на добри прогностички групи со средно преживување над една година. Терапијата со хелатори трае сè додека пациентот е трансфузио зависен.

Клучни зборови: миелодиспластичен синдром, хелатори, преоптоварување со железо.

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