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WHEN AND WHY TOO MUCH IRON IS BAD FOR YOU

Patients with chronic forms of myelodysplastic syndrome (MDS) who suffer mainly from severe refractory anemia require frequent blood transfusions in order to maintain a reasonable level of hemoglobin – above 9.0 gm/dL. The demand for blood transfusions can be higher in older patients with co-morbidities affecting the heart and blood vessels. One of the major problems resulting from frequent blood transfusions is accumulation of excess amount of iron in major organs, primarily in the liver, endocrine glands and the heart. When the iron binding proteins in the serum are fully saturated, free iron species have been identified, and they are known to promote biochemical reactions that result in generation of free radicals of oxygen. These radicals are very toxic since they initiate major damage to various components of the cells, such as the lipids in the membrane and also to proteins and to the DNA with the final outcome of premature cell death.

A key question is how to estimate the excess amount of iron? Obviously, one can calculate the amount of iron in each blood transfusion. On that basis there are different recommendations from 4 international groups when to recommend treatment with iron chelators, after receiving from 20 to more than 50 units of blood. Another parameter is the measurement of serum ferritin, which is an iron storage protein synthesized in the liver that binds excess of iron. However, there are differences in the guideline recommendations when to start treatment on the basis of ferritin levels with a range from >1000 to >2500ng/ml. Moreover, factors such as infection can influence serum ferritin levels as an acute phase reactant which can alter the results.

In addition, there are controversial data in the literature about the efficacy of iron chelation therapy on long term survival and quality of life. Some reports present positive results on overall survival, decreased transfusion requirements, a decreased risk to transform to more advanced stages of the disease such as acute leukemia. while others did not find any significant changes of these parameters related to the severity of iron overload. The major

problem with the interpretation of all these studies are their being retrospective. Up to now there are no data on prospective study that will compare survival and quality of life between MDS patients with iron overload with or without treatment with iron chelators.

Until more objective data will be available, what should be the recommended policy for patients with MDS who require frequent blood transfusions and develop iron overload?

Todate, there are 3 available iron chelators. The most commonly used chelator for more than 30 years is Deferioxamine. The main problem is that the way of administration is very uncomfortable since it is given by subcutaneous infusion with a pump for many hours during the night. Obviously, this mode of administration is cumbersume and reduces the compliance. The second chelator is Deferiprone, which at this point has not been approved by the FDA although it has been approved in the rest of the world. This is an oral chelator which has the advantage to remove excess iron from inside iron loaded cells into the circulation. However, one of its major side effects is leukopenia, which is already pre-existing in some patients with MDS. The third chelator is Deferasirox, also an oral chelator, given once a day, which has side effects such as impaired kidney function and gastrointestinal disturbances. One should also be aware of the cost of each one of the chelators.

Therefore, besides the number of transfusions and serum ferritin levels, one should try to use additional parameters of iron overload which will help to decide if and when iron chelation is indicated. For instance, calculating percentage of transferrin saturation, which is an available parameter almost in every laboratory. If the values exceed 75% saturation, it is very likely that there are free iron species in the plasma such as non transferrin bound iron (NTBI) or labile plasma iron (LPI). The free iron species are promoting generation of reactive oxygen species, which are very toxic and cause damage to various components in the cells including DNA, proteins and memrane lipids of major organs such as liver endocrine glands and heart with the final outcome of apoptosis and early cell death. There are available methods to measure NTBI

and LPI, however, at this point they are available only in a few laboratories in the World.

Another non invasive method to measure total body iron in major organs such as liver, heart and pancreas is by T2* magnetic resonance imaging (MRI), which is available in many centers in the US and around the world. Preliminary results did not show evidence for excess iron in the heart or in the pancreas in MDS patients who received less than 100 units of blood, while there was excess iron in the liver.

Taken together, at this point the decision if when and for how long to chelate iron in multitransfused patients with MDS should be made for each individual separately, taking into account the age, comorbidities, compliance, the cost and eventual side effects of the chelators and obviously the number of transfusions, serum ferritin, percent transferrin saturation and T2* MRI. If all of the above criteria will be available, it is hoped that those who really require iron chelation will get the treatment, until more data and more specific parameters to measure ironload will be available in order to recommend more general guidelines.

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