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Letters to Editor

Should every Patient with MDS get Iron Chelation – Probably Yes

Keywords: Anemia , MDS, Iron Overload , Chelation.

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Dear Editor,

We read with interest the review article on iron chelation therapy in MDS patients[1] in one of the recent issue of the journal. A recently similar article has also been published suggesting that iron chelation may be helpful in high-risk transfusion dependent MDS patients too.[2] The effect of iron chelation therapy in low-risk MDS patient is reasonably well established as it improves not only the quality of life but also the survival as shown in Dusseldorf MDS registry study.[3] In high-risk MDS iron chelation therapy was usually not considered because of short survival, and, because of some of the complications of chelation, likely in patients with hepatic dysfunction with short survival, it was found to be not worth pursuing. However, since some of the current drugs used for the purpose, e.g., decitabine & azacitidine based therapy, have improved the survival of high-risk MDS patients, so consideration of iron chelation therapy becomes apparent also in these cases. However, this brings us to an important question, i.e., Should all MDS patients even with minor iron overload with serum ferritin above 500 ng/ml. receive iron chelation therapy, particularly when efficient oral iron chelator is now available? To support this idea Angelucci et al.[1] have in the paper under discussion made significant observations. Our knowledge and experience on iron chelation mainly emerge from our therapeutic practice of using the same for transfusion dependent thalassemia patients. Here iron deposition happens in bulk and chelation tends to remove the iron from this bulk relatively inert as well as the extremely active labile and non transfering bound free iron pool generating active, reactive oxygen species (ROS). ROS is capable of mutagenesis by inducing double stranded DNA break.[4] This mutagenesis can theoretically help in the progression of a relatively benign form of MDS to an aggressive one. Though this has not been directly proven it was shown that patients with higher transfusion requirement and iron overload also tend to evolve rapidly into leukemia.[5]

It may be argued that patients with severe prognosis require more red cell transfusions and then develop higher iron overload and having a rapid evolution of MDS to more aggressive form naturally require more transfusions, and thus, the evolution to leukemia has nothing to do with iron overload. On the other hand, it may also be argued that marked iron load, associated with a higher labile iron pool being toxic to red cell progenitors[6,7] and by causing direct red cell membrane damage,[8] induces more frequent red cell transfusion and then more iron overload.

This iron overload brings about genomic instability,[4,8,9] mitochondrial damage and mutation in mitochondrial genome,[10,11] and by producing an unbalanced immune system, leads to rapid progression of MDS[12] to accelerated phase of leukemogenesis. If our second argument and Angelucci et al.[1] argument are correct the iron accumulation even in a minimal amount in crucial cellular compartments without necessarily producing massive iron overload could be damaging and mutagenic. Thus, every patient with MDS and even minimal iron overload should get adequate iron chelation and efforts needs to be

made to see whether such intervention alters the natural history of the disease.

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Replay to: Should every Patient with MDS get Iron Chelation – Probably Yes

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Dear Editor,

We thank Dr. Kanjaksha Ghosh and Dr. Kinjalka Ghosh for their comments on our review paper on iron chelation therapy in myelodysplastic syndrome (MDS).[1] In our article, we tried to summarize how recent improvements in understanding iron pathophysiology and iron toxicity mechanisms could modify our everyday clinical practice. Appropriately dr.s Kanjaksha Ghosh and Kinjalka Ghosh discuss four relevant aspects:

The indication to iron chelation limited to lower risk MDS arises from the notion that iron overload/toxicity requires time to develop significant tissue damage and impact on patients outcome. Higher risk MDS do not have this time. Thus they do not have indication to iron chelation even if transfusion dependent. Estimate of life expectancy of MDS patients come from the pivotal IPSS[2] and revised IPSS[3] papers demonstrating a limited leukemia-free and overall survival for higher risk IPSS groups. However, in these papers survival estimates have been calculated in patients receiving best supportive care and not disease modifying agents. Since that time much time is passed, and new disease modifying agents have become available for MDS patients.[4] Today leukemia free and overall survival cannot be those predicted in IPSS papers. Therefore, the indication to iron chelation in transfusion dependent MDS patients should be revised. The recent retrospective article by Pellegrino Musto[5] supports this evidence. Of course, this extended indication should be confirmed by prospective studies. Nevertheless, the restriction to iron chelating therapy to lower risk MDS patients can be considered overwhelming.

During the last years it has been proved that "iron disease" is not only a "bulky disease" but rather a toxic disease in which the "free iron forms" (i.e. non transferrin bound iron [NTBI], labile plasma iron [LPI] and labile cellular iron [LCI]) play a major role disturbing the delicate intracellular machinery controlling functional iron and storage iron and, at the same time, minimizing reactive oxygen species (ROS) formation. Thus what is important is not only the amount of iron overload but rather duration of tissue exposition to these reactive iron species.[6–8] Following this assumption iron overload should be prevented and not only treated, and treatment should be started as soon as NTBI and LPI appear in plasma. Unfortunately, the specific diagnostic tools are not, so far, available but transferrin saturation is an accurate biomarker of absence of NTBI and LPI.[9]

Drs Kanjaksha Ghosh and Kinjalka Ghosh also discuss the possible interaction between toxic iron species and MDS progression. This is an attractive new issue requiring in deep laboratory and clinical studies[10–15] as for the relationship between iron toxicity and hemopoietic stem cell recovery after hemopoietic cell transplant and transplant outcome.[8,16–19] As Dr. Musto recently reported[5] a surprisingly prolonged progression free and overall survival in higher risk MDS patients receiving iron chelation therapy has been observed. It is generally accepted that ROS levels increase with age; similarly, the methylation pattern also changes during lifetime. Goncalves et al. demonstrated in vivo that in MDS oxidative

stress may contribute to hypermethylation of key tumor suppressor genes. In this scenario, it is reasonable to think that iron chelators and demethylating agents could have a synergistic effect.[20] Of course, even this relationship should be confirmed in prospective and controlled studies.

Finally to understand single factor impact on clinical outcome in MDS patients (transfusion and not transfusion dependent) is a complex and challenging issue. Several competing factors can have an impact on outcome (anemia, the hematologic disease itself, comorbidities, advanced age, etc., etc.) and it is hard to separate one to each other. Well-designed clinical trials should be performed to answer this question. As Researchers and Physicians, we have to recognize that such trial is arduous to be carried out for several reasons: the very limited interest of researchers and industries in supportive care, competition with new drugs development and clinical complexity of MDS patients. We believe that a well-designed, accurate and evidence based transfusion-chelation therapy could be very effective in prolonging survival and quality of life in MDS patients and that optimal transfusion-chelation therapy should not be considered a mere supportive care. Finally, the increasing regulatory difficulties to conduct independent prospective trials make these clinical developments hard and problematic.

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Competing interests: Dr. Angelucci is Chair of the Steering Committee of the Novartis sponsored TELESTO trial and has received honoraria from Novartis Pharmaceuticals
Dr. Pilo: Novartis Advisory board.

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