Could haemochromatosis (HFE) gene mutations affect response to iron chelation in myelodysplastic syndrome?

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Dear Editor,

We have read the paper by Fabiani et al. (Fabiani*, et al* 2018) investigating potential molecular mechanisms behind haematological improvement (HI) during iron chelation therapy (ICT) in patients with lower risk myelodysplastic syndrome (MDS) with great interest. Authors reported that neither patients' characteristics (including baseline and follow-up ferritin concentrations), nor mutations in any of the specific genes frequently mutated in myeloid malignancies showed significant associations with the occurrence of HI during ICT. We would like to point out that haemochromatosis (*HFE*) gene mutations which are affecting significant proportion of MDS patients and increase the risk of iron accumulation in this context (De Souza*, et al* 2015, Lucijanic*, et al* 2016) were not assessed by the authors in the current study.

Heterozygosity for *HFE* gene mutations is an equally common feature in both MDS patients and healthy population. Mutations show variable geographic distribution and affect up to one third of MDS patients when considering two most frequent mutations (C282Y, H63D) (Lucijanic*, et al* 2016). Although considered not to be directly implicated in the pathobiology of MDS and not to significantly affect iron accumulation in the general population (Burt*, et al* 1998, Jackson*, et al* 2001, Rossi*, et al* 2001), heterozygosity for *HFE* gene mutations was shown to intensify iron overload in transfusion-dependent (De Souza*, et al* 2015) and accelerate iron accumulation in transfusion-independent MDS patients (Lucijanic*, et al* 2016). Most interestingly, *HFE* mutated patients seem to experience significantly shorter overall and leukaemia free survival (Lucijanic*, et al* 2016). Therefore, question emerges whether *HFE* mutated MDS patients might require lower thresholds to start chelation therapy and/or more intensive chelation to achieve response, but these issues have not been sufficiently investigated at the moment.

We congratulate the authors of the current work (Fabiani*, et al* 2018) on the valuable insight into the biology of MDS. However, mechanisms behind amelioration of iron overload and improvement in haematopoietic function still remain elusive. Since *HFE* gene mutations seem to significantly modulate iron metabolism in MDS, it would be very interesting to see whether they affect the odds of acquiring HI during ICT and how do they distribute among investigated somatic mutations. We hope that authors could provide such analysis.

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