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In vitro culture of BM cells and CytB polymorphisms can predict the *In-vivo* Hematological response induced by deferasirox

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Background: Many studies showed that iron chelation therapy (ICT) can induce hematological improvement and transfusion independence in a significant percentage of MDS patients. At now we do not have clinical or biological parameters to identify the patients with high probablility of hematological response. The aim of the study was to set up an in vitro assay able to predict in vivo hematological improvement to deferasirox treatment and to identify additional markers of response.

Methods: 22 MDS patients from 9 Italian centres were enrolled in the study. Five were RA, 4 RARS, 8 RCMD, 4 RAEB I , 1 CMML. In 6 of them ICT induced RBC transfusion independence during the first 6 months of therapy, one experienced hematological improvement but he stopped therapy after few months for progression. BM samples were collected from 22 patients before deferasirox treatment and during follow up. BM cells were incubated with deferasirox 50 micromolar for 12 hrs and tested for colony formation in semisolid culture. In addition, different mitochondrial genes were sequenced, including COX1, COX2 and CytB in all the patients enrolled.

Results: In 8 out of 22 patients (3 RA, 2 RARS, 2 RCMD, 1 CMML) the in *vitro* incubation with deferasirox resulted in a significant increase of colonies (BFU-E, CFU-GM and CFUGEMM). (mean value of BFU-E: 9±4 before incubation and 19±11 after incubation). Interestingly, 6 of these 8 patients who showed an "*In vitro*" response experienced transfusion independence after *In vivo* treatment with deferasirox, one showed hematological improvement according to Cheeson's criteria but he died for progression few months after starting therapy and one could not be evaluated because of intolerance to treatment. By contrast patients who did not respond in vitro to deferasirox did not significantly reduce the transfusion requirement. In parallel we analysed mtDNA in BM MNC cells and we found a strict association between two polymorphisms of CytB (14766 and 15326) and the hematological response to deferasirox therapy.

Conclusion: The hematological improvement during deferasirox therapy in MDS patients can be predicted by colony assay after in vitro incubation with deferasirox. In addition, mitochondrial gene polymorphisms can be associated with hematological response. Finally, although not conclusive, the fact that 12 hours of deferasirox incubation can increase the number of BFU-E suggests that deferasirox is probably able to overcome the defect of erytroid progenitors thus pushing the MDS clone towards terminal differentiation rather than to reduce the number of MDS cells thus favoring the normal cells.

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