Azacitidine (AZA) improves long-term outcomes of higher-risk MDS patients and is now the reference frontline therapy of higher-risk MDS not eligible for allogeneic stem cell transplant. Anaemia is the most common symptom of MDS and most patients become transfusion-dependent with the risk of iron overload. Deferasirox is an orally available iron chelator administered once-daily in transfusion-dependent patients with iron overload. We report our experience on using the azacitidine in patients with high-risk MDS, evaluating the efficacy and safety. Concomitant treatment with deferasirox was performed in a routine clinical setting following Consensus Guidelines on Iron Chelation Therapy. In our Institution from October 2009 to December 2014 we have treated 29 elderly patients (19 male and 10 female, median age 76 years, r. 72-88) affected by HIGH-RISK MDS (IPSS INT-2/HIGH). Patients received subcutaneous azacitidine at 75mg/m(2) daily for 7 days every 4 weeks. All patients completed at least 6 cycles of therapy. 11/29 (38%) patients underwent more than 8 cycles of therapy. 17/29 patients underwent as well iron chelation therapy with deferasirox receiving a starting dosage of 10 mg/kg/day, subsequently titrated according to serum ferritin (SF) measured monthly. Complete response (CR), partial response (PR), and hematologic improvement (HI) were observed in 2 (7%), 5 (21%), and 11 (38%) patients, respectively. The median number of cycles to clinical response was 4 (range 4-8). The 2-year rate of acute myeloid leukemia-free survival was 48%. Five serious adverse events occurred in five patients with one fatal outcome. 15 out of 18 patients who showed any hematologic response (CR+PR+HI) meeting International Working Group 2006 criteria had also performed deferasirox therapy. No increased toxicity was noted when deferasirox was used concomitantly with azacitidine. Our results confirm the effectiveness of the therapy with azacitidine in HIGH-RISK MDS elderly patients with acceptable toxicity profile. Peripheral cytopenias were the most commonly occurring adverse event, with gastrointestinal adverse events and injection-site reactions among the most commonly occurring non-haematological adverse events. In conclusion, azacitidine is an important agent for use in the treatment of elderly patients with MDS. Furthermore concurrent use of deferasirox in patients with iron overload seems to significantly improve the hematologic response by reducing transfusion requirement.

P124

DOES G6PD-DEFICIENCY RELATED OXYDATIVE STRESS AND HEMOLYSIS AFFECT ERYTHROID RESPONSE TO ERYTHROPOIETIN STIMULATING AGENTS IN MYELODYSPLASTIC PATIENTS?

F. Pilo, A.A. Di Tucci, I. Tandurella, E. Angelucci

UO Ematologia e CTMO Ospedale Oncologico "A. Businco" Cagliari, Italy

Background: Anemia is the most frequent cytopenia in Myelodysplastic Syndrome (MDS). Epoetin α, Epoetin β and Darbepoetin α (ESA) have been investigated in several studies as useful to treat anemia in this category of patients.Available pre-clinical data support oxidative stress and hemolysis contributing to ESA resistance but not clinical data is today available. G6PD deficiency is an X-linked condition characterized by a markedly reduced capability to protect red blood cells from oxidative stresses. In the island of Sardinia the prevalence is reported to be as high as 12%. *Patients and Methods:* We retrospectively analyzed all MDS patients who had received ESA in our centre. Diagnosis of MDS was made according to WHO criteria. Patients were stratified based on International Prognostic Scoring System (IPSS). At diagnosis baseline EPO level and G6PD quantitative estimation were detected. Red blood cell (RBC) transfusions requirement before starting treatment was evaluated. Erythroid hematologic improvement (HI-E) was evaluated according to the International Working Group (IWG) response criteria (Cheson *et al.* JCO 2006). *Results:* Thirty patients met the above specified criteria. Of them 7 were G6PD-defiecient and 23 had normal G6PD level values. Seventeen were male and 13 female, median age was 71 years (range 51-96). Twenty patients presented with refractory anemia (RA), 8 refractory anemia with ringed sideroblasts (RARS), 2 refractory cytopenias with multilineage dysplasia (RMCD). Twenty-four patients were IPSS low- risk and 6 Intermediate I. At baseline serum EPO level was less then 200 IU/L in all patients. Forty percent required RBC transfusion before starting ESA treatments. Twenty patients (80%) achieved an HI-E (14 major and 10 minor). In the G6PD-deficient group HI-E was observed in 7 over 7 patients (major in 4 and minor in 3). In the control group HI-E was observed in 17 over 23 patients (major in 10 minor in 7). (P=0.29). *Conclusions:* We evaluated 30 MDS low- risk and Int I IPSS patients who received ESA in the last 20 years in our centre. Despite the common belief that oxidative stress and hemolysis may contribute to ESA resistance, no statistically significant difference to potentially resistance to ESA treatment in G6PD deficiency have been observed. We conclude that G6PD-deficiency does not contraindicate the use of ESA in this setting of patients.

Table 1. Patients' characteristics.

	G6PD deficient patients	G6PD normal patients
Number	7	23
Sex	2 F 5 M	11 F 12M
Age (years)	70 (62-93)	70,5 (51-96)
Diagnosis	3 AR, 3 RARS, 1 RCMD	17AR, 5 RARS, 1 RCMD
G6PD level (UI/g Hb)	Median 0,4 (range 0,04-0,89)	Median 1,19 (range 1,02-1,44)
ESA type	5α-epo, 1β-epo, 1 DAR	19α-epo, 3β-epo, 1 DAR
Serum EPO level < 200 UI/L	7	23
RBC requirement before treatment	7 no, 0 yes	11 no, 12 yes

Abbreviation:
F = female; M = male; G6PD = glucose-6-phosphate dehydrogenase; ESA=erythropoietin stimulating agent; Hi= Hematologic improvement ; MDS= myelodysplastic syndrome; RA= Refractory Anemia; RARS = Refractory Anemia with ringed sideroblasts : RCMD =refractory cytopenias with multilineage dysplasia; RBC = red blood cell

P125

TFR2 AND EpoR EXPRESSION AT DIAGNOSIS AS POSSIBLE PREDICTORS OF ERYTHROPOIETIN TREATMENT RESPONSE IN MDS PATIENTS

A. Di Savino, U. Familiari, A. Palmieri, F. Crasto, A. Volpengo, P. Scaravaglio, V. Gaidano, P. Nicoli, E. Gottardi, M. Papotti, A. Roetto, G. Saglio, D. Cilloni, M. De Gobbi

Università di Torino, Dipartimento di Scienze Cliniche e Biologiche, Orbassano, TO, Italy

The myelodysplastic syndromes (MDS) are heterogeneous hematopoietic diseases associated with bone marrow failure, peripheral cytopenias, and a tendency to progress to acute myeloid leukemia. Anemia and transfusion dependency constitute major problems for MDS patients. Treatment with erythropoiesis stimulating agents is a first-line treatment for the anemia of most patients with MDS. However not all MDS respond and a majority of patients eventually relapse with transfusion dependent anemia. Erythropoietin (Epo) is the principal regulator of red blood cell production. Upon Epo binding to its cognate receptor (R), the Epo-R promote the activation of JAK2 and Lyn, which in turn phosphorylate the signal transducer and activator of transcription 5 (STAT5). Dimerization of phospho (P)-STAT5 enables its translocation to the nucleus and binding to target gene promoters, ultimately promoting the expansion, differentiation, and survival of red blood cell precursors. Transferrin receptor 2 (TFR2) is a second transferrin (Tf) receptor that binds to Tf with a 25-fold lower affinity but acts as an iron sensor regulating hepatic hepcidin production. At least 2 alternatively spliced forms of transcripts, α and β, are transcribed from the TFR2 gene. Several recent findings (Forejtnikova *et al.*, Blood 2010; Wallace *et al.*, Br J Haematol. 2015; Nai *et al.*, Blood 2015) highlight the interconnection between the hepatic and erythroid functions of TFR2 in regulating iron metabolism and erythropoiesis. Our monocentric and retrospective study aimed to identify the possible impact of TFR2 and EpoR mRNA expression at diagnosis in MDS patients. We report the expression pattern of TFR2 α, β and EpoR in various subtype of MDS in comparison to normal controls and we found heterogeneous expression with a tendency of TFR2 being less expressed in RAEB-2. Moreover a positive and significant correlation between TFR2 and EpoR expression was seen. Finally, to further assess the clinical implication of the correlation observed, we analysed the erythroid response in the cohort of patients that underwent to Epo treatment and we noticed that only patients with TFR2 and EpoR levels comparable to normal controls reached an increase in hemoglobin level of ≥1.5 g/dl after 12 weeks of treatment. Taken together, our results provide evidence suggesting TFR2 and EpoR as potential molecular markers in predicting at diagnosis the response of Epo treatment in MDS patients.