

Azacitidine Low-Dose Schedule In Low-Risk Myelodysplastic Syndromes. Preliminary Results of a Multicenter Phase II Study

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Abstract

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Background: Azacitidine (AZA) at a dose of 75 mg/mq/day subcutaneously for 7 days, every 28 days, induces high hematologic response rates and prolongation of survival in high-risk MDS patients (pts) (*Fenaux, 2009*). However few data are hitherto available concerning the efficacy and safety of Aza in lower risk MDS. A lower dose regimen, AZA 5 (75 mg/mq daily, subcutaneously, for 5 consecutive days every 4 weeks) have shown to induce response rates consistent with the currently approved schedule (*Lyons, 2009*), however in this study pts were not classified according to IPSS risk.

Aim: The use of AZA in the earlier phases of disease could be more effective and useful to control the expansion of MDS clone and disease progression. In our phase II, prospective, multicentric trial, AZA 5 regimen was administered to IPSS low-or-intermediate-1 risk pts, for a total of 8 courses, in order to evaluate its efficacy and safety. Furthermore pharmacogenomic studies (GEP, SNP) cytokine network and PI-PLC-beta1 methylation and gene expression, before and at the end of 4th and 8th course of Aza treatment, were planned to identify new biological markers to predict the response.

Methods: From September 2008 to February 2010, 34 patients (24 males, 10 females), with a median age of 71 (56–84) yrs, with symptomatic transfusion-dependent anemia, previously unresponsive to erythropoietin (EPO) or not expected to respond to EPO, or with severe neutropenia or thrombocytopenia, were enrolled into the study. According to WHO classification, 15 pts had RA, 6 RARS, 7 RCMD and 6 RAEB-1.

Results: At present time 30/34 pts are evaluable: 23/30 pts (77%) completed the treatment plan (8 courses), 3/30 pts (10%) are ongoing and 4/30 (13%) died during the

treatment period. According to the 2006 International Working Group criteria, overall response rate (ORR) was 60,9 % (14/23 pts): 5 pts (21,7%) achieved complete remission (CR), while 9 pts (39,1%) showed an hematologic improvement (HI) (7 erythroid responses, 1 erythroid/platelet response and 1 neutrophil/platelet response). 9/23 pts (39%) maintained a stable disease (SD). Generally the drug was very well tolerated. The most commonly reported hematologic toxicities were neutropenia (55%) and thrombocytopenia (19%). 4 pts (17,4%) died during treatment (2 pts after the 1th cycle and 2 pts after the 4th course) because of septic shock, gastrointestinal hemorrhage, pneumonia, and respiratory distress, respectively. The median duration of response was 3,5 months (range 1–14 months). Surprisingly, 3/14 patients (2 CR and 1 HI erythroid) showed a long duration of response (11, 13 and 14 months, respectively), still ongoing, after discontinuation of AZA. Preliminary data on the lipid signalling pathways suggested a direct correlation between the demethylating effect on PI-PLC- β 1 and responsiveness to treatment.

Conclusion: Our study shows that AZA low-dose schedule may be a feasible and effective treatment for low-risk MDS pts and may induce durable responses. Despite AZA safety, extreme caution is needed in pts with age-related comorbidities and/or with severe neutropenia or thrombocytopenia, especially in low-risk MDS. Furthermore, PI-PLC- β 1 demethylation and gene expression could represent a new biological marker to predict the clinical response to AZA