mean onset of response in all patients was 2.9 cycles (range = 1–14), with a mean response duration of 12.1 cycles (range = 2–112). Onset of response and response duration did not differ between any groups. For patients with abnormal cytogenetics, 10 of 25 evaluable patients (40%) demonstrated a normal karyotype on follow-up marrow testing. An IWG response was seen in 7 of these 10 patients (70%). Treatment was well tolerated in all groups. The most common side effects were nausea, vomiting, diarrhea, and cytopenia.

Conclusion: Results of this study demonstrate similar response rates, duration of response and tolerability in MDS patients irrespective of karyotype. There does not appear to be a material difference in response to AZA between MDS patients with and without cytogenetic abnormalities or in those with simple versus complex karyotype. Moreover, complete cytogenetic responses can be seen with this agent.

P151 Azacitidine in combination with EPO + G-CSF and valproic acid rapidly determines hematological improvement in pretreated non responsive IPSS INT-1 MDS patients

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The DNMTinhibitor azacitidine has been approved by FDA for treatment of patients with myelodysplastic syndromes (MDS) of all IPSS risk scores. In Europe approval will be subject to results obtained in the ongoing phase III study involving only INT-2 and high risk MDS patients. In fact, a large number of MDS patients with lower IPSS score could be advantageously treated with azacitidine alone or combined with other agents, but data focused on this specific subset of patients are lacking. We evaluated whether azacitidine, in combination with growth factors and the histone deacetylase (HDAC) inhibitor valproic acid (VPA) could determine hematological response in pretreated, refractory MDS patients with IPSS score INT-1. We treated 6 patients with azacitidine 50 mg/m^2/day for five days every 28 days, plus erythropoietin (hrEPO) 40.000 U twice weekly, granulocyte colony stimulating factor (hrG-CSF) 300 ug, once weekly and VPA 600–1200 mg/day. These patients were not eligible for treatment with DNMTinhibitors in any of the ongoing trials and all of them had undergone previous treatment with EPO plus G-CSF for more than 24 weeks, without any hematological response. Five out of six had been treated also with thalidomide 100mg/day, but no response was observed, due to intolerance to treatment and subsequent early drop out. All patients were RBC transfusion dependent, 3/6 both for RBC and platelets. Mean age was 60.8 (35–78). None of the patients had more than 6% bone marrow blasts and only 1/6 had a complex karyotype. Because of the heavy burden of transfusions and deteriorating general conditions, we started treatment. Courses were very well tolerated, with only nausea grade 1–2; in particular, the slow escalation in VPA doses prevented CNS side effect. VPA blood concentrations were kept within neurological therapeutic range. At present, patients received 3–6 courses of therapy, and all showed hematological improvement after only 2 courses. In particular, RBC and platelet transfusion independence was achieved for 5/6 patients, with also general reversal of neutropenia. In one patient, starting with platelets counts below 10×10^9/L and regularly transfused weekly, platelet number was within normal range after 2 cycles of therapy. Hemoglobin levels were in all patients above 9 g/dL, but in none achieved normalization. Only one patient after 4 courses is still transfusion dependent, although with a significantly lower requirement. In conclusion, combination treatment with low dose-azacitidine, growth factors and HDACi VPA was safe and well tolerated, and was extremely effective in inducing rapid hematological improvement in the entire small cohort of pretreated, resistant INT-1 risk MDS patients analyzed.

P152 G-CSF increases hematological response and survival among patients with myelodysplasia treated with azacitidine

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Introduction: In a previous publication we demonstrated that the addition of G-CSF to azacitidine (AZA) improved overall hematological response rate (OHR), as well as erythroid and platelet response in patients with myelodysplastic syndrome (MDS). Here we report further analysis of response onset, response duration, and overall survival (OS).

Methods: We identified 86 MDS patients treated at our institution who received an average of 10.8 cycles of AZA. Forty-nine (49) of these patients also received either erythropoietin (Epo), G-CSF or both during the course of their AZA treatment, while 37 did not receive hematopoietic growth factors. These 2 groups did not differ significantly either in number of cycles of AZA received ($p = 0.500$), FAB MDS subtype ($p = 0.347$) or IPSS score ($p = 0.970$). In the groups receiving growth factors, G-CSF was given for an average of 3.5 cycles and Epo for an average of 6 cycles. Hematological responses were tabulated by International Working Group criteria and compared using chi-square statistics. Survival was calculated from first treatment with AZA and compared using Mann-Whitney U tests as data was not normally distributed.

Results: Patients who received G-CSF +/− Epo had an 84% (31/37) OHR versus 51% (25/49) in patients who did not receive G-CSF (p = 0.003). Moreover, patients who received G-CSF or G-CSF + Epo had a similar OHR of 84% and 83%, respectively. In contrast, patients treated with Epo had an OHR (50%) similar to those treated with AZA alone (51%). These data suggest that the addition of G-CSF is responsible for the improved OHR. Further, patients who received G-CSF +/− Epo had a median OS of 17 months versus 13 months in patients who did not receive G-CSF (AZA+/−Epo) (p = 0.047) and 12.5 months in the AZA only group (p = 0.031). Despite the apparent survival benefit in patients who received G-CSF, number of cycles to onset and duration of response did not differ between groups.
Conclusion: In patients with MDS treated with AZA the addition of G-CSF significantly improved OHR, erythroid and platelet response, and OS. We postulate that G-CSF may have an anti-apoptotic effect as has been previously demonstrated when used in combination with Epo. The survival benefit of G-CSF might be improved if further study identifies the optimal dosing regimen.

P153 Clinical effects of 5-azacitidine five days/monthly schedule in three symptomatic low-risk (IPSS: 0−1) myelodysplastic patients

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Promising results have been reported by the use of nucleoside 5-azacitidine (5-Aza) in the treatment of myelodysplastic syndrome (MDS). When 5-Aza was administered at a dose of 75mg/mq/day subcutaneously for 7 days, every 28 days, it showed to be superior to supportive care, with higher response rates and reduced risk of progression to acute myeloid leukaemia (AML), mainly in the high risk MDS patients. We attempted to use an alternative schedule, 75 mg/mq subcutaneous daily for 5 consecutive days every 28 days, to evaluate its efficacy and tolerability in low risk MDS patients. Between May and December 2006 we treated five patients affected by refractory anemia (RA) with Low Risk IPSS (score 0–1). Age at diagnosis ranged between 66 and 73 years. All patients failed EPO therapy and were in chronic red blood cell (RBC) supportive care with a median transfusions requirement of 4 units/monthly. The 5-Aza five days/monthly schedule was administered for a total of 8 courses. The response treatment criteria was according to International Working Group (IWG) as reported by Cheson et al. Two months after the end of therapy (8 courses) the evaluation of response was completed in 3 out of 5 patients. An hematologic improvement (HI) was observed in two patients, both reaching a major erythroid response (major HI-E), with no longer needed transfusions and RBC transfusion independence of 20 and 16 weeks respectively. The third patient obtained a transitory major HI-E after the 2th course of treatment, maintaining a transfusion independent time for 16 weeks and increasing haemoglobin greater than 2 g/dl; he failed after the 7th course of therapy. Quality of life (QOL) measured by the FACT-An score improved in all patients. Extrahematologic toxicity was mild and consisted in nausea and vomiting (WHO grade I) in two patients and flu-like syndrome with fever (WHO grade I) in one patient. Hematologic toxicity consisted in neutropenia (WHO grade III) and thrombocytopenia (WHO grade II) in one patient; it was transitory and no delay of treatment was necessary.
Our preliminary results show that the 5-Aza five days/monthly schedule is very well tolerated and it appears to have an efficacy similar to the seven days/monthly schedule, at least in low-risk MDS setting. Considering that the optimal schedule and duration for demethylating agents has not yet been established, further MDS patients recruitment is warranted to confirm the efficacy of this alternative 5-Aza low dose regimen.

P154 Combination of fludarabine and cytarabine as induction treatment of poor prognosis myelodysplastic syndrome (MDS) and secondary acute myeloid leukaemia (sAML): a single centre experience

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Background: response rate of poor prognosis MDS and sAML to conventional chemotherapy (cytarabine + an anthracyclin with or without a third drug) is unsatisfactory, namely about 35–50%, compared to 75–80% of de novo AML. Fludarabine and cytarabine containing regimens (FLA) have shown promising results in complete remission (CR) induction of poor prognosis MDS/sAML. Fludarabine has no direct activity on MDS/sAML but improve cytotoxicity of cytarabine increasing intracellular concentration in leukaemic blasts of its toxic metabolite, ara-CTP.
Aim: to retrospectively evaluate the efficacy of FLA regimens as induction treatment of poor prognosis MDS/sAML pts.
Methods: period January 1999-January 2007, 72 patients (pts), median age 58 (22–74), 31 pts >60 yrs; first diagnosis (WHO): AMLMD 34, RAEB2 10, RAEB1 4, RCMD 2, MS 1, t-AML/MDS 21. Cytogenetic risk (66 pts): high 26,