Evaluation of Azacitidine in transfusion-dependent, Epo-refractory patients with lower-risk MDS

Magnus Tobiasson, Lena Brandefors, Ingunn Dybedahl, Hege Garelius, Michael Grövdal, Inge Högh-Dufva, Lars Kjeldsen, Claus Marcher, Lars Nilsson, Astrid Olsnes Kittang, Anna Porwit, Leonie Saft, Mette Skov Holm, Lars Möllgård, Eva Hellström-Lindberg

Background: Transfusion-dependency (TD) in patients with low- and int-1-risk MDS is associated with increased morbidity and mortality (Malcovati, JCO 2007). Around 30% of such patients respond to Epo +/- G-CSF with a median duration of two years (Jadersten, Blood 2005). Azacitidine (Aza) has been reported to induce transfusion-independence (TI) in patients with lower-risk MDS (Silverman, JCO 2002; Lyons, JCO 2009; Musto, Cancer 2010). However, this treatment has not been systematically evaluated in patients resistant to Epo +/- G-CSF, neither has the benefit of the combination of Aza and Epo been assessed in a prospective study.

Methods: This prospective open-label, non-randomized phase II study included 30 consecutive patients with IPSS low- or int-1 risk MDS and a RBC transfusion need of ≥4 units q 8 weeks. Patients were either refractory to full-dose Epo + G-CSF for >8 weeks, or considered ineligible for such treatment according to a previously published predictive model (Hellstrom-Lindberg, Br J Hem 2003). Enrolled patients were treated with Aza 75 mg/m^2/d for five days q 28 days for six cycles. Patients remaining TD after six cycles were treated with another three Aza cycles, with the addition of Erythropoietin 60,000 units/week. Primary endpoint was number of patients achieving TI after six cycles and secondary endpoints were number of patients achieving TI after Aza+Epo, effect on bone marrow morphology, peripheral blood parameters, and safety profile.

Results: Thirty patients were enrolled from January 2010 until September 2011. See table 1 for patient characteristics. Eighteen patients were previously treated with Epo+G-CSF whereas remaining patients scored “low” in the predictive model and were thus considered refractory upfront. Median number of transfusion units needed was 7 (4-14) q 8 weeks preceding inclusion. Median platelet and ANC count pre-treatment was 220x10^9 (22-1468) and 2.1 x10^9 (0.3-15.1), respectively. Severe thrombocytopenia (<30) and neutropenia (<0.5) was observed in 3 and 3 patients, respectively.

Ten patients pre-terminated the study; five due to sustained cytopenia; two due to death (one sudden death and one neutropenic septicemia); two due to patient’s wish and one due to investigators choice. Twenty-nine serious adverse events were reported in 16 patients with infection (n=19) being most common. Nadir values after each cycle of Aza were seen at week 3 for thrombocytes (median 130x10^9) and at week 4 for neutrophils (median 1.2x10^9), respectively.

Twenty-four patients were evaluable for treatment with Aza alone and 14 patients for Aza+Epo. TI was achieved in 5 patients (21%) after Aza alone and in one more patient after Aza+Epo. Three of 6 responding patients had a karyotype including trisomy 8. In a multivariate analysis, trisomy 8 was significantly (p=0.01) associated with response.

Discussion: Aza can induce TI in patients with TD lower-risk MDS, but response rate is lower in this cohort of documented EPO-G-CSF-refractory patients compared to previous reports of less well-controlled cohorts. Since toxicity is substantial, candidate patients for this treatment must be selected carefully. Patients with trisomy 8 show a significantly higher response rate. The combination of Aza and Epo can be effective in rare cases.

Table 1: Patient characteristics

Median (range) Age	69y (55-80)	Significant fibrosis (grade ≥ 2), n	4
Gender (M/F)	21/9	Median (range) cell percentage	70% (20-100)
Median duration of disease	2y (0-20)	Median (range) blast count	2% (0-9)
Medianctransfusion units needed q 8 weeks	7 units (4-14)	IPSS, Low / INT-1, n	6/24
WHO classification, n		WPSS, Low / Int / High, n	3 / 14 / 13
RA / RARS / RCUD	1 / 2 / 2	IPSS Cytogenetics, n Favorable / Int / Adverse	20 / 10 / 0
RCMD / RCMD-RS	13 / 5	Karyotype including trisomi 8, n	4
RAEB-I / MDS 5q-	3 / 1	Median S-erythropoietin	443 u/L (25-2313)
MDS / MPD	3	Median S-ferritin	1891 µg/L (220-6230)