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Efficacy of azacitidine in acute myeloid leukemia: A retrospective study

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Background: Treatment for acute myeloid leukemia (AML) in patients unfit for intensive chemotherapy is challenging.
Introduction: Given its activity in myelodysplastic syndrome, azacitidine is thought to be a potential therapeutical alternative to low-dose Cytarabin in this patient population.
Purpose: To assess the efficacy of azacitidine in patients with AML unfit for intensive chemotherapy
Materials and Methods: We retrospectively analyzed all patients with AML treated with azacitidine at the University Hospital Zurich or the Kantonsspital Münsterlingen. Treatment schedule: azacitidine 100 mg/m^2 subcutaneously on days 1 to 5 of a 28 day cycle or azacitidine 75 mg/m^2 subcutaneously on days 1 to 7 of a 28 day cycle. Observation period: September 2004 to February 2012. End of follow-up: 31st of May 2012. Primary end-point: Overall-survival. Secondary end points: Hospitalization days and transfusion independency.
Results: Forty patients were included in the analysis of whom 22 (55%) had de novo AML, 15 (38%) AML relapse, and 3 (7%) underwent a bridging therapy prior to allogeneic stem cell transplantation. The median age was 67 years, 21 (52%) patients were female, 19 (48%) patients were transfusion dependent and the median bone marrow blast count was 43% (interquartile range 26-80). According to the HOVON/SAKK 102 risk stratification patients were classified in a good-risk, intermediate-risk, poor-risk or very-poor risk group in 6 (15%), 8 (20%), 18 (45%) and 6 (15%), respectively. For two (5%) patients these data are lacking. Median overall-survival was 591 (337-824) days in the whole treatment group and 403 (232-683) days in patients with de-novo AML. After censoring for the hospitalization days during the first treatment cycle, patients had to be hospitalized for a median of 6 (0-21) days (whole treatment group) and 5 (0-15) days (de novo AML), respectively. Transfusion independency occurred in 3 (16%) patients. No serious adverse events related to azacitidine were noted.
Conclusions: Treatment with azacitidine is safe for AML patients unfit for intensive chemotherapy. Once the outpatient treatment was established, only few hospitalization days were needed. However, only a minor effect on transfusion dependency was seen. Large randomized trials (e.g. NCT01074047) will have to address the question whether azacitidine is superior to the standard of care in this patient population.

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Treatment outcome of 5'-azacitidine for myelodysplastic syndrome

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Background: Myelodysplastic syndrome (MDS) is characterized by ineffective hematopoiesis associated with multilineage cytopenias leading to serious morbidity or mortality, and the additional risk of leukemic transformation. 5-azacitidine, a DNA hypomethylating agent, provides important clinical benefits for patients with MDS.
Introduction: There has been several reports about the treatment effect of 5'-azacitine. However, the long-term follow-up data for patients who are not candidate for stem cell transplantation has been rarely reported.
Purpose: We report here the treatment outcome of 5-azacitidine in MDS patients who are not candidate for stem cell transplantation compared to patients with best supportive care.
Materials and Methods: Forty-three MDS patients treated with 5-azacitidine were evaluated. They received 5-azacitidne 75mg/m^2/day subcutaneously for 7 days every 28 days. Follow-up bone marrow aspiration and section biopsy was performed to measure the response per four cycles and hematologic responses were measured before the start of every cycles of 5-azacitidine. The control group was 44 patients treated with conservative management.
Results: Of total forty-three patients, twenty-two (51.2%) showed the clinical responses to 5-azacitidine treatment. Three (7.0%) and one (2.3%) patient showed complete response and partial response, retrospectively. Marrow complete response was found in one patient (2.3%) and seventeen patients (39.5%) showed hematologic improvement. In 5-azacitidine responders, the one year progression-free survival was 46.7%. The one year event-free survival of 5-azacitidine treatment group and control group was 75.2% and 61.1%, respectively (P=0.15). Infection-related treatment toxicity was reported in fifteen patients (34.9%), but there was no significant increment compared with control group at adverse event per patient-year of exposure.
Conclusions: 5-azacitidine was found to be clinically effective in patients with MDS and showed tolerable toxicities.

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Successful azacitidine based treatment of therapy related myelodysplastic syndrome with normal karyotype occurred after acute myeloid leukemia

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Background: Therapy-related myelodysplasia (t-MDS) occurs as a complication of cytotoxic treatment given for cancer.
Introduction: Typically at presentation chromosomes abnormalities and/or complex karyotype are present. Standard chemotherapy is often not effective with very low complete remission rates so prognosis remains poor. Azacitidine is an hypomethylating drug that showed to be effective in MDS.
Purpose: We describe here 3 patients with t-MDS secondary to chemotherapy for de novo acute myeloid leukemia (AML), successfully treated with Azacitidine.
Materials and Methods: Between April 2011 and November 2012 we observed in our centre 2 women and one man previously successfully treated for AML (M2,M2 NPM+, and M5) who were then diagnosed with MDS, defined by blast count <20% and typical cytological morphology in bone marrow aspirate.
Patient 1 was a 48 years-old lady diagnosed in March 2011 with RAEB-1, not transfusion dependent and with 2 cytopenias. Patient 2 was a 74 years-old lady diagnosed in February 2012 with RAEB-1 but with a mild anemia; patient 3 was a 64 years-old man presented in February 2012 with RCMD transfusion dependent for Red blood Cells and Platelets. All patients were Intermediate-1 and Intermediate according to IPSS and WPSS scores respectively. Karyotype was evaluable in all patients and was normal.
t-MDS occurred after 44 months of complete remission (CR) for patient 1, after 22 months from 2nd CR for patient 2 and after a 8 months CR for patient 3.
Azacitidine was started at a median of 1 month from t-MDS diagnosis at the dose of 75 mg/sqm daily for 7 days every 4 weeks. A median of 9 courses were administered (range 7–15). Response was assessed according to the International Working Group criteria.
Results: Patient 1 received 15 courses of azacitidine and after obtaining complete remission underwent allogenic stem cell transplantation. Patient 2 received 9 courses of azacitidine achieving complete

remission and she is still on treatment. Patient 3 achieved stable disease with persisting severe thrombocytopenia and anemia after 7 courses of azacitidine but died because of hemorraghic stroke.
Therapy was generally well tolerated except for patient 3 who experienced several grade 2- 3 infective episodes. Median overall survival of t-MDS patients was 12 months (range 6–22).
Conclusions: Currently there is no standard treatment for patients wit t-MDS. In our small experience, azacitidine given upfront showed to be effective improving overall survival with an accetable toxicity profile. Further studies are needed to confirm these results.

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Delayed response to lenalidomide in International Prognostic Scoring System (IPSS) low-risk myelodysplastic syndrome (MDS)

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Background: Lenalidomide has immunomodulatory, anti-angiogenic and anti-neoplastic properties interacting in receptor/ligand signaling of cellular responses [1]. Notably, the treatment of MDS with 5q- with lenalidomide produces a 67% rate of transfusion independence and improves erythropoesis with manageable side effects in 3 months of therapy in those with low-risk and IPSS-1 [2].
Introduction: Although natural history studies have not yet been performed, a major disease-modifying activity is possible with lenalidomide representing a major advance for patients with 5q-. However, problems with myelosuppression, cost of treatment and consequences of the long term effect of continuous immunomodulation with lenalidomide remain unkonwn.
Purpose: We report three cases of IPSS Low risk MDS with a delayed response to lenalidomide.
Materials and Methods: All patients were participating in clinical trial for lenalidomide in Low and INT-1 MDS patients with or without 5q- abnormality. Key characteristics are outlined in Table 1.
Results: Lenalidomide withdrawal time after TI is not clearly established. However we observed up to 24 months of freedom from transfusion and all patients eventually relapsed and required other therapy including demethylating agents. Reasons for discontinuation were based on an attempt to reduce long time drug exposure and minimize side effects after achieving a satisfactory hematological response. After a 6 to 11 month trial of Lenalidomide in IPSS Low risk MDS, delayed TI can occur 1-4 months after discontinuation of therapy. Delayed TI was not associated with a cytogenetic response.
Conclusions: TI was achieved after discontinuation of lenalidomide with no apparent suppression of the 5q-clone. Interestingly, one patient had lymphoid aggregates of B and T cells throughout treatment, raising the possibility that the immune stimulatory effects of lenalidomide may be a variable against the 5q- clone. Transient response may be due to immunomodulatory effects but persistence of the 5q-clone can be responsible for relapses after the immune response has waned. Continuing lenalidomide may prolong or re-induce another response.
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Postsplenectomy evolution in one case of hypoplastic myelodysplastic syndrome

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Background: Aplastic anemia (AA) is a clonal hematopoietic stem cell disease characterized by pancytopenia and various degrees of bone marrow hypocellularity. The PNH clone is present at diagnosis in over 50% of AA patients. The exact mechanism of the PNH clone expansion is unclear. 2 of the late clonal complications of immunosuppresion treated AA may actually coexist with AA (the AA/PNH syndrome and hypoplastic mielodisplastic syndrom (h MDS).
Introduction: We are showing the clinical observation of the patient having a severe aplastic anemia wich evolution after immunosuppresion (IS) went towards PNH and h MDS.
Purpose: Despite all the therapeutical approach, the patient went worse and splenectomy was our only choice.
Materials and Methods: The patient G.O.37 years old had diagnosis in 2006 with Aplastic anemia based on pancytopenia and bone marrow trephine biopsy showing reduction in all haemopoietic tissue replaced by fat spaces. After immunosuppression with Cyclosporin and prednisone the patient had obtained complete remission sustained, until April 2009, when became pancytopenic with bone marrow aspirate showing hipercellularity. The further treatment is based on transfusions of erithocytary mass, cyclosporine and prednisone with increased dose. In October 2009 the patient develops a superficial femoral thrombosis with urinary haemosiderin positive. Examinations done at Hematology Department of the Emergency Universitary Hospital – Dr. Horia Bumbea, Bucharest: Cellular immunophenotype – have confirmed the PNH diagnostic. The further treatment is based on enoxaparinum s.c., followed by oral Acenocumarolum, transfusions of erithocytary mass, danazol and prednisone. The treatment of late clonal complications of AA is often difficult. Allo-SCT and the recent introduction of anticomplement monoclonal antibodies are the only effective current treatments. The bone marrow aspiration showed persistence hypoplastic myelodysplastic syndrome (hMDS) – refractory cytopenia with multilineage dysplasia. The patient received transfusion of eritrocites and platelets, methylprednisolon and dexamethason but no persistent improvement and even

Abstract P-195 – Table 1

Pts characteristics and prior tx IPSS: 0–Low	Transfusion requirement (RBC)	Duration of lenalidomide trial without TI	Karyotype	Time to TI after discontinuation of lenalidomide	Duration of TI	Remarks on BMb
64 yo Female Danazole, arsenic, EPO	2 units/3-4 weeks	6 months	del5q	1 month	24 months	Persistent abnormal karyotype; lymphoid aggregates of B and T cells
58 yo Female Low dose cytarabine, all trans-retinoic acid	2 units/ 4 weeks	11 months	del5q	4 months	14 months	Persistent abnormal karyotype
82 yo Male EPO	2 units/4 weeks	6 months	45 X, -Y	1 month	16 months	Persistent dysplasia

BMb, Bone marrow biopsy; EPO, erythropoetin; TI, transfusion independance; RBC, red blood cells.