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# 41th Congress of the Italian Society for Hematology

Bologna, Italy, October 14-17, 2007

## ABSTRACT BOOK

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# ABSTRACT BOOK

## Thrombosis and Hemostasis - Platelets

### CO-057

### LOW DOSE RITUXIMAB SHARES SIMILAR ACTIVITY BUT SLOWER TIMING OF RESPONSE THAN STANDARD DOSE IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

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*Introduction.* Rituximab 375 mg/sqm weekly for 4 weeks has significant activity in patients with immune thrombocytopenia (ITP). In this setting, different biological and clinical evidence suggests the possible use of lower doses of Rituximab. *Methods.* Twenty-one adult patients, median age 44 years (range 16-71 years), with previously treated and symptomatic ITP (18 idiopathic, 3 secondary) were treated prospectively with Rituximab at the fixed dose of 100 mg iv weekly for 4 weeks. Exclusion criteria were positive HIV, HBsAg and pregnancy test, any B-cell lymphoprolipherative disease, other malignancies. Response assessment was evaluated considering the rate of complete and partial responses (CR, PR; platelet level ≥100 and $50\times10^9$/L, respectively and discontinuation of steroid therapy, if present), the time to response (TTR; time necessary to reach a platelet number $\geq50\times10^9$/L), the time to complete response (TCR; time necessary to reach a platelet number $\times10^9$/L) and the duration of response. Peripheral blood immunophenotypic analysis of CD20 was evaluated at baseline and then monthly from the beginning of treatment. B-cell count and pharmacokinetics (PK) were monitored and related with clinical outcome. *Results.* All patients completed the therapeutic program receiving the four infusions of Rituximab as scheduled, none experiencing short term toxicity. All patients achieved B-cell depletion, still maintained at follow-up. Overall, CR and PR rates were 15/21 (71%), 10/21 (47%), 5/21 (24%). Younger age, lower baseline circulating CD20 positive lymphocyte count and shorter diagnosis to Rituximab interval were associated with higher response rate. The median TTR and TCR were 30 and 50 days respectively, significantly longer then those observed with standard dose in patients with similar characteristics (Haematologica 2003;88:538). After a median follow-up of 6 months (range 3-15), 6/15 patients relapsed, and 3 needed further treatments. PK data showed a concentration time-course profile of Rituximab that was super-imposable, once corrected for the difference in the dose, to that observed previously in patients treated with standard dose, diseases with a median value of 4.1 micrograms/milliliter (range 0-11.9), 12 weeks after the start of treatment. *Discussion.* In patients with ITP, low dose Rituximab led to short and mid-term response rates similar to standard dose but with slower timing of response. These results highlight the need for a more specific therapeutic schedule of Rituximab in autoimmune diseases.

### CO-058

### INCIDENCE AND DETERMINANTS OF BLEEDING IN VON WILLEBRAND DISEASE: RESULTS OF THE FIRST PROSPECTIVE MULTICENTER STUDY ON 814 ITALIAN PATIENTS

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*Background.* von Willebrand disease (VWD) is the most frequent inherited bleeding disorder and is due to quantitative and/or qualitative defects of von Willebrand factor (VWF). Despite its improved knowledge among hematologists, no data on the incidence and determinants of bleedings requiring specific treatments are available until now. *Aims and design of the study.* To determine the incidence and determinants of bleedings requiring therapy with DDAVP and/or VWF concentrates in VWD, a national registry was organized by using a database devised to collect detailed retrospective information. Patients included in the registry were followed up for one year and prospective data on number, type and management of bleeding episodes was analyzed. *Methods.* All patients were diagnosed following recommendations of the ISTH-SSC-SC on VWF with bleeding severity score (BSS) calculated at enrollment. Diagnoses of VWD were confirmed by the coordinating center using multimeric analysis in plasma and mutations of VWF gene in types 2 and 3. For different risk categories the incidence of bleeding (mucosal and non-mucosal bleeding) was calculated. Bleeding-free survival was computed with the Kaplan-Meier method and a Cox's proportional hazard model was used to calculate the risk of bleeding in different risk categories. (hazard ratio = HR). *Results.* In the retrospective study, 1,234/1,529 (81%) cases satisfied the inclusion criteria and were enrolled in the registry as types 1 (54%), 2 (40%) and 3 (6%).VWD diagnosis occurs in young adults (83%), mainly in women (57%). Mucosal bleeding (64%) are is more frequent than hematomas or hemarthrosis (15%) but 73% of patients did not require transfusions. In the prospective study based on 814/1,234 (66%) cases of the registry (type 1=47%, 2=47%, 3=6%) 147/815 (18%) were treated in a year for 318 bleeding episodes and 87 minor or major surgeries. BSS >10 ([hazard ratio =6.8, (95%CI 3.8-12.3)], bleeding time <20 min ([BT = 5.5, (3.1-9.8)], VWF:RCo <10 U/dL ([3.2, (1.7-5.9)] and FVIII:C <20 U/dL ([4.1, (2.4-7.0)] were significantly associated with high risk of bleeding. By multivariate model including all the variables, BSS ([5.5, ( 2.8-10.8)] was the most significant determinant of bleeding. The bleeding-free survival at one year was significantly different in type 3 (52%) versus types 1 (96%) and 2 (91%) VWD. On the other hands, patients with VWF.RCo >30 U/dL and FVIII:C > 40 U/dL showed always BSS <5 with the lowest incidence of bleeding (5.0×100 patient-years). A total of 292 DDAVP injections were used to manage bleeding and surgeries in types 1 (65%) and 2 (35%) VWD and 452 injections of VWF concentrates were used to treat bleeding and surgeries in type 3 (75%), type 2 (34%) and type 1 (15%) VWD. *Conclusions.* Based on the results of this prospective study, we can confirm that BSS is an important clue to predict clinical bleeding and the need of therapy with DDAVP and VWF concentrates. In cases with VWF.RCo >30 U/dL and FVIII:C >40 U/dL bleedings occurs very rarely in agreement with their relatively low BSS.

### CO-059

### AME AFFECTS MGAKARYOCYTIC DIFFERENTIATION AND INCREASES PRO-PLATELATS FORMATION *IN VITRO*

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The t(3;21)(q26;q22) resulting in the AML1/MDS1/EVI1 (AME) fusion gene is associated with several hematological disorders often characterized by severe dysmegakaryopoiesis, suggesting that AME alters the megakaryocytic maturation program. We expressed the AME fusion protein in bone marrow lineage negative cells by retroviral infection. The cells were cultured in presence of TPO to induce megakaryocytic differentiation and on day 2 the morphology was analyzed after Wright Giemsa staining. In the AME positive cultures we counted a 5 fold increase (35%) of MKs percentage compared with the control cells (7%). AME positive MKs were smaller in size in comparison to the control. In AME cultures we frequently observed micro-megakaryocytes and other features of dismegakaryopoiesis. During 12 days in liquid culture in presence of TPO, while the control MKs persisted for the entire experiment, the AME positive MKs quickly decreased after 7 days. AME positive MKs produced platelets until day 6. The platelets appeared immature, bigger in size with several features of pro-platelets. The AME platelets were found 10 fold increased as compared to controls and their formation was prolonged for more than 7 days while the control MKs produced platelets for only 2 days. We also expressed AME in the human erythromyeloblastoid cell line K562. PMA was used to induce megakaryocytic differentiation. The cells were collected after 48 and 96 hours and then compared with the control differentiated K562. The DNA content was measured after propidium iodinate (PI) staining by FACS analysis. AME-K562 showed a block in megakaryocytic differentiation. As previously demonstrated in murine cells, also AME-differentiated-K562