

dependent diabetes was more common in patients < 65 (42.0% vs. 65.9%, $p < 0.0001$), all other co-morbidities that could also contribute to anemia and/or limit response to epoetin alfa (CHF, cancer) were significantly more common in the elderly. Mean Hb change from BL to final assessment was similar for both age groups (≥ 65 , 2.4 ± 1.5 g/dL; < 65 , 2.4 ± 1.5 g/dL). The number of patients responding to epoetin alfa (increase in Hb ≥ 1 g/dL from BL) was 637 (88.8%) in ≥ 65 and 564 (90.8%) in < 65 . Similar responses were seen by Weeks 4 and 8 for both groups (≥ 65 , 54.3% and 90.0%; < 65 , 57.6% and 91.7%) as were responses of ≥ 2 g/dL (≥ 65 , 52.2%; < 65 , 56.8%). The % of patients transfused at BL (≥ 65 , 11.3% vs. < 65 , 11.0%) and during study was similar for each age group. Although fixed epoetin alfa doses were similar between the two groups (mean doses: ≥ 65 , $11,306 \pm 3374$ U/wk; < 65 , $11,514 \pm 3538$ U/wk), body weight dosing in the elderly was higher (mean dose: ≥ 65 , 155.4 ± 56.0 U/kg/wk; < 65 , 139.7 ± 56.9 U/kg/wk, $p < 0.0001$). Once weekly epoetin alfa was well tolerated in both groups and reported adverse events were consistent with those expected for these patients. **Conclusions:** Although elderly patients with anemia due to pre-dialysis CKD have poorer renal function, more co-morbidities and presumably less marrow reserve, their response to fixed doses of once weekly epoetin alfa is similar to younger patients. In the elderly, comparable Hb responses may relate to increased epoetin alfa dosing per unit body weight.

Abstract# 3763

Successful Use of Rituximab with Prednisone, Cyclosporine, Immunoglobulin and Erythropoietin in a Jehovah's Witness Patient with Pure Red Cell Aplasia Associated with CLL. Meghna R. Desai*, Laura Donahue. *Don monti division of Oncology /hematology, North Shore University Hospital, Manhasset, NY, USA.*

A 68 year old female Jehovah's Witness with CLL diagnosed in 2000 was treated with Fludarabine x 6 cycles. In February of 2003 she developed massive adenopathy, B symptoms and was started on Fludarabine and Rituximab. She developed rapidly progressive anemia after 2 cycles of treatment. Work up ruled out hemolytic anemia, and a bone marrow biopsy showed myeloid predominance with a M: E ratio of 5:1. Laboratories revealed reticulocytopenia and parvovirus IgM titers were negative. The evaluation was consistent with pure red cell aplasia. As patient does not accept pRBC transfusion and hemoglobin decreased to 5.1 g/dL, she was started on prednisone, cyclosporine, immunoglobulin with erythropoietin, iron and folate concurrently, with a small increment in hemoglobin. She was then started on rituximab with normalization of hemoglobin after 4 cycles. Pure red cell aplasia is a type of anemia characterized by absence of red cell precursors in the bone marrow and reticulocytopenia with normal white cell and platelet count. It is a known complication of CLL (6%). Corticosteroids are the first line treatment with addition of cyclosporine if response not obtained. Responses to high dose IVIG have also been reported. Recently rituximab, an anti CD-20 monoclonal antibody, has been used to treat several autoimmune diseases refractory to conventional immunosuppressives. There are rare case reports of its usefulness in treating pure red cell aplasia. We report a case of pure red cell aplasia complicating CLL successfully treated with rituximab, cyclosporine, prednisone, immunoglobulin and erythropoietin without transfusional support.

	hemoglobin response to treatment over 3 months						
	pre-treatment	after 2 cycles of FR	day 8 of immuno-suppressive therapy	day 30 of immuno-suppressive therapy	s/p cycle #1 of rituximab	s/p cycle #3 of rituximab	s/p cycle #4, day 19 of rituximab
hemoglobin g/dL	11.7	5.8	6.3	6.1	9.2	11.0	12.6
treatment	prednisone, cyclosporine, IVIG, erythropoietin		prednisone, cyclosporine, erythropoietin	prednisone, IVIG, cyclosporine, erythropoietin	prednisone, cyclosporine, erythropoietin, rituximab #2	prednisone, cyclosporine, erythropoietin, rituximab #4	cyclosporin, erythropoietin, off prednisone.

date (2003)	hemoglobin g/dL	reticulocyte %	Hemoglobin recovery with treatment.				erythropoietin sq	rituximab
			prednisone	cyclosporine	IVIG			
3/17	11.7							
5/19	7.5	0.2				60,000u biw		
5/28	5.1	0.1	80 mg po qd	500 mg po bid	75 mg IV x 2 days	10000 u qd		
6/2	5.3	3.1	60 mg po qd	400 mg po bid		10000 u qd		
6/4	6.3	2.2	60 mg po qd	400 mg po bid		10000 u qd		
6/9	7.7	3.1	30 mg po qd	400 mg po bid		60,000u BIW		
6/13	6.5	2.3	20 mg po qd	400 mg po bid		60,000u BIW		
6/19	7.2	0.1	20 mg po qd	400 mg po bid		60,000u BIW		
6/26	6.1		20 mg po qd	400 mg po bid	80 mg IV	10000 u qd		
6/30	6.7		20 mg po qd	400 mg po bid		10000 u qd		
7/1			20 mg po qd	400 mg po bid		10000 u qd		
7/3	7.6		20 mg po qd	400 mg po bid		10000 u qd	375 mg /m2	
7/11	9.2		20 mg po qd	400 mg po bid		10000 u qd	375 mg /m2	
7/18	10.3		20 mg po qd	400 mg po bid		10000 u qd	375 mg /m2	
7/25	11.0		5mg po qd	400 mg po bid		10000 u qd	375 mg /m2	
8/12	12.6		discontinued	300 mg po qam, 200 mg po qhs		10000u q6days/week		

Abstract# 3764

In Vivo Effects of Recombinant Human Erythropoietin on Late-Stage Erythroid Precursors in Murine Bone Marrow. Peter J. Bugelski*, Thomas Nessor*, Joanne O'Brien*, Dorie Makropoulos*, Amy Volk*, Kim Shamberger*, Renold Capocasale*. (Intr. by Emmanuel C. Besa) *Experimental Pathology, Centocor, Malvern, PA, USA.*

Recombinant human erythropoietin (EPO) is widely used for the treatment of anemia. Although the effects of EPO on early erythroid precursors (BFU-e and CFU-e) have been studied extensively in vitro, detailed knowledge of its effects on late-stage bone marrow

precursors is not currently available. Recently, a two-color flow cytometric technique using quantitative analysis of ter-119 and CD71 has been described which enables enumeration of the proerythroblast through orthochromic erythroblast stages of erythropoiesis (Sokolovsky M et al. Blood 98:3261, 2001). We have coupled this technique with pulse labeling with bromodeoxyuridine (BrdU), annexin V binding and staining with 7-aminoadriamycin to study the effects of a single dose of EPO on cell cycle and apoptosis in femoral bone marrow as a function of dose and time. In addition, we used an ADVIA 120 hematology analyzer to evaluate reticulocytosis and the erythron in peripheral blood. A single subcutaneous dose of EPO caused a dose and time dependent increase in cell number and DNA synthesis in pro- and basophilic erythroblasts. EPO also caused a dose and time dependent decrease in apoptosis in these populations. In contrast, the number of polychromatic and orthochromic erythroblasts was decreased. This decrease was commensurate with an increase in reticulocytes, and increases in mean cell volume and red cell distribution width (RDW) in the peripheral blood. In keeping with previous in vitro work, our in vivo data suggest that EPO expresses three distinct effects on late stage erythroid precursors in murine bone marrow; enhancing cell division, decreasing apoptosis, and accelerating differentiation.

Abstract# 3765

Individualized Risk of Adverse Events in Fanconi's Anemia (FA). Blanche P. Alter,¹ Yi Huang*,² Philip S. Rosenberg*,¹ ¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; ²Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

The objective was to estimate the risks of bone marrow failure (BMF) leading to death or transplant, leukemia (AML), and solid tumors (ST) specific to each patient, using readily-diagnosed congenital abnormalities that manifest early in life. The data were from the follow-up to BMF, AML, or ST in the North American Survey cohort (n=144). A score of 1 or 0 was given for the presence or absence of: developmental delay; short stature; abnormal head, hearing, heart-lung, kidney, lower limbs, thumbs, radii, or other skeletal abnormalities. The main outcome measures were the cumulative incidence of BMF, AML, and ST, by age, modeled as competing risks. Six risk factors were significantly associated with the hazard of BMF: radii, developmental delay, heart-lung, kidney, hearing, and head. Abnormal radii (RAD) was the strongest single risk factor for BMF; the other five candidate risk factors were not individually significant after adjusting for RAD. We defined a congenital abnormality (CAB) score equal to the number of abnormalities in this set of five; it is distinct from the Auerbach score that predicts chromosome breakage. CAB score was significantly associated with BMF after adjusting for RAD (P = 0.05). No risk factor was associated with the hazards of ST or AML. By competing risks, the cumulative incidence of each endpoint depends on both RAD and CAB scores that define 2 x 6 = 12 prognostic groups (since RAD can be normal, 0, or abnormal, 1). The cumulative incidence of BMF by age 5 ranged from 6% for the lowest BMF risk group (RAD 0, CAB 0) to 46% for the highest BMF risk group (RAD 1, CAB 5). By age 10, it ranged from 18% to 83%, and by age 20 it ranged from 37% to 92%. Patients at lower risk of BMF were more likely to live long enough to develop ST or AML. The cumulative incidence of ST by age 40 ranged from 0.6% in the highest BMF risk group to 29% in the lowest BMF risk group. We conclude that abnormal radii is the strongest correlate of risk of early BMF. The CAB score additionally separates the large majority of FA patients with normal radii into prognostically distinct groups. However, we do not recommend this model for routine clinical use until the association of CAB score and BMF risk has been replicated in a larger dataset.

Abstract# 3766

Dyskeratosis Congenita (DC): Molecular Diagnosis in a Patient with No DC Phenotype. Implications for Future Management. Blanche P. Alter,¹ June Peters*,¹ Ann Carr*,² Peter M. Lansdorf,³ Gabriela M. Baerlocher,⁴ Judith P. Willner*,⁵ Babette B. Weksler*,⁶ ¹Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; ²Westat, Rockville, MD, USA; ³Terry Fox Laboratory, BC Cancer Agency and Department of Medicine, University of British Columbia, Vancouver, BC, Canada; ⁴Department of Hematology, Inselspital, Bern, Switzerland; ⁵Department of Human Genetics, Mount Sinai School of Medicine, New York, NY, USA; ⁶Department of Medicine, Weill Cornell Medical College, New York, NY, USA.

Molecular testing for inherited hematologic diseases may open Pandora's box, by identifying as "affected" individuals who have no physical or laboratory evidence of the disease. We studied a family in which autosomal dominant DC was identified. A 42 year old woman had grey hair since the age of 13, with thrombocytopenia and macrocytic anemia since age 18. As an adult, she has had extremely dry, brittle skin and nails, ulceration of her oral mucosa, recurrent painful cystitis and anal fissures, basal cell and squamous cell carcinomas of the skin, and a hypocellular bone marrow without dysplastic morphology but with an abnormal cytogenetic clone (46,XX,-6,+der(16)t(1;16)(q21;q23) noted at age 33. At age 37, she underwent bilateral hip arthroplasty for osteonecrosis of the femoral heads. Laboratory studies revealed thrombophilia, homozygosity for PAI-1 4G/4G, and heterozygosity for the MTHFR polymorphism associated with hyper-homocysteinemia. The patient's mother had similar early greying, nail dystrophy, and pancytopenia with a myelodysplastic syndrome (MDS). She also had cervical cancer and T-cell LGL. She developed interstitial pulmonary fibrosis, and died at age 62 of sepsis. The proband was found to have a germline mutation in the hTERT gene (the RNA subunit of telomerase), as does one of her 3 children. This 11-year-old son was physically normal, including his nails. His blood count was normal: Hb 13.5 g/dL, MCV 90.4 fL (normal <92), WBC 4950 and absolute neutrophils 2252/mm³, as was Hb F (0.4%), and his bone marrow was morphologically and cytogenetically normal. Both the proband and her son, and not her