Methods

Definitions

We adopted the following pre-specified definitions as the basis for enrollment, study exclusion and treatment decisions. **ITP** was defined by the criteria developed by George, et al.[1] **Chronic ITP** was defined as a platelet count less than normal for 6 months or more after initial diagnosis of ITP. **Severe ITP** consisted of a trough platelet count twice during the preceding 3 months of less than 10,000/mm^3 without bleeding, less than 20,000/mm^3 with bleeding or less than 20,000/mm^3 while on chronic therapy to prevent bleeding. For the purpose of determining eligibility, **refractory ITP** was defined as severe ITP unresponsive to at least 2 standard regimens or in which treatment side effects were intolerable. **Response to standard therapy** consisted of a transient platelet count to > 50,000/mm^3 with steroids, IVIG or anti-D immune globulin or splenectomy. **Evans Syndrome** was defined as ITP with evidence of autoimmune hemolytic anemia and a positive direct antiglobulin test (DAT). ITP with a positive DAT but without a history of overt hemolysis and no other evidence of secondary causes of ITP was considered to be primary ITP. **Secondary ITP** was defined as ITP related to immunodeficiency, systemic lupus erythematosus (SLE) or Evans Syndrome. Patients with Evans syndrome and autoimmune neutropenia (autoimmune pancytopenia) were not grouped separately. Patients with ITP without other evidence of autoimmune disease, SLE, AIHA with neutropenia were classified as primary ITP.

Eligibility

Patients with severe chronic ITP that was responsive to standard therapy were eligible at 12 months from diagnosis while patients with severe, refractory disease were eligible at 6

months. Patients with secondary ITP or Evans Syndrome were eligible for enrollment if not otherwise excluded. Bone marrow evaluation was required prior to enrollment only in patients refractory to all agents or who were never treated.

Exclusion Criteria

Exclusion criteria included seropositivity for HIV; presence of B or T cell neoplasm or any cancer within the previous 5 years; presence of known allergy to murine antibodies; absolute neutrophil count (ANC) less than $1000/mm^3$ (unless diagnosed with Evans Syndrome or autoimmune neutropenia), hemoglobin < 9 gm/dL (<7 gm/dL for patients with Evans Syndrome) unless there was documented bleeding within the previous month; treatment with investigational immunosuppressive medications within the previous 3 months; serum creatinine greater than 1.5x upper limit of normal; and serum alanine aminotransferase (ALT) more than twice the upper limit of normal. Patients were also excluded if they were pregnant or breastfeeding, had life-threatening bleeding within the past three months (unless refractory to single agent standard pharmacologic therapy) or had New York Heart Classification III or IV heart disease.

Monitoring

Screening laboratory evaluation measured in local laboratories included serum pregnancy test for females of childbearing potential within one week of entry; complete blood count with differential; serum chemistries including BUN, creatinine, total and direct bilirubin, LDH and ALT. Immunologic studies were performed by central laboratory Esoterix (Austin, TX) and included B and T cells subsets, IgG, IgA, IgM and IgG subclasses.

Patients had complete blood counts measured weekly for 12 weeks, then monthly. After 12 weeks, patients with minimal or no response were followed for safety measures only. Responders were followed monthly for durability of response.

Adverse Events

Adverse Events were scored by the Common Toxicity Criteria (CTC) from the National Cancer Institute {http://ctep.cancer.gov/reporting/ctc.html} except for thrombocytopenia and bleeding were scored as described here.

Rescue and Supportive Care Regimens

Rescue therapy was allowed for severe thrombocytopenia (<10,000/mm^3 with moderate/severe bleeding, (bleeding score 3-5) or for severe bleeding (bleeding score 4-5) with platelet count < 50,000/mm^3. Four pre-defined rescue regimens were allowed, at the treating physician's discretion. These included oral prednisone or prednisolone 4 mg/kg/day for 4 days; high dose IV methyl prednisolone 5-30 mg/kg/day for 5 doses; IVIG 1 g/kg IV daily for one or two doses (by site preference) and anti-RhD immunoglobulin (WinRho-SDF^{TM}) 50 – 75 mcg/kg for Rh positive patients only.
For patients who had received adrenocortical-suppressive doses of steroids within 30 days of the screening visit, supportive care steroids were permitted during weeks 1 to 6 as follows: either a prednisone "taper" of 0.2mg/kg/day (or less) or "stress dose" hydrocortisone or equivalent, for acute illness only. Patients given ITP treatment regimens other than these listed or for reasons not specified were scored as treatment failures, regardless of platelet count achieved.

Pharmacokinetics

Drug levels were performed on a subset of patients. Trough and 30 minute, 24- and 48-hour post-infusion levels were obtained with doses 1 and 4. A 7-day post level was drawn after dose 1. Pharmacokinetic parameters were obtained separately for each patient at the 1-wk and 4-wk infusions by fitting a two-compartment model (intravascular and extravascular).[2] Two-factor analysis of variance was employed to compare parameters between younger (2 to 9 years) and older (10 to 18 years) subjects and between responders and non-responders at the two infusion times.

References

1. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88:3-40.
2. Feldman HA. A numerical method for fitting compartmental models directly to tracer data. Am J Physiol. 1977;233:R1-7.