6–42 μg/ml (days 4–6), in synchrony with the T-cell nadirs, and became undetectable by day 13. Antibodies to rabbit ATG appeared after 6–7 days, and their titers increased as ATG was cleared from the circulation. We then evaluated the immunosuppressive effects of ATG using allogeneic skin grafts. Median skin graft survival in 5 dogs given ATG was 14 days, compared to 8 days among 28 controls ($p = 0.0003$). Based on these observations, an HCT protocol was designed; 5 dogs were given ATG (3.5–5 mg/kg) between days –12 and –7 to target a 90–95% depletion of circulating T cells. ATG levels were undetectable by day 0, excluding possible effects on donor T cells. On day 0, dogs were given 1 Gy TBI and marrow from dog leukocyte antigen-identical donors. Median cell doses infused (millions/kg) were: total nucleated cells (TNC) = 263; CD34 = 6.6 and CD3 = 18. Posttransplant immunosuppression was MMF/CSP for 4 and 5 weeks, respectively. All recipients showed initial donor chimerism, with maximal values ranging from 10–75% (median 25%) for granulocytes and 5–40% (median 25%) for mononuclear cells. Four dogs rejected their grafts after a median of 9.5 weeks (range 8–18 weeks), without cytopenias, and they reverted to autologous hematopoiesis. The 5th dog has remained a long-term mixed chimera (>36 weeks). The median times to rejection were 11 weeks (projected) in the study group and 10 weeks in the control group, not given ATG ($p = 0.20$, log-rank test). Analysis of the impact of cell doses suggested that TNC had the highest Spearman correlation coefficient with the duration of donor chimerism, 0.82 ($p = 0.09$). We conclude that ATG reliably depleted circulating T cells by 90–95% and lymph node T cells by approximately 50%. Even so, administering ATG before an otherwise inadequate conditioning dose of 1 Gy TBI failed to lead to uniform stable hematopoietic engraftment.

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THE IMPACT OF PRE-TRANSPLANT ANEMIA ON LONG-TERM SURVIVAL FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANTATION

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Background: Anemia is a common finding in patients with malignancies and is associated with reduced survival times. The impact of anemia on survival during allogeneic bone marrow transplantation (alloBMT) was not known. Recently, we identified that low pre-transplant hemoglobin (PT-Hb) levels were associated with increased mortality during the first 6 months after BMT. However, the impact of the PT-Hb on long-term survival was not known. **Study Design and Methods:** Data from 519 consecutive patients receiving transplants between January 1995 and March 2000 were retrospectively reviewed and survival was evaluated with regard to risk factors, including the PT-Hb until June 2002. Survival was calculated using Kaplan-Meier limit methods. Risk factor subgroups were compared with the log rank test. The PT-Hb levels were determined within 2 weeks of conditioning chemoradiotherapy. **Results:** PT-Hb levels correlated inversely with survival. The percentile 5-year survival of patients with PT-Hb levels of ≤100, 101-110, 111-120, 121-130 and >130 g/L were 35, 29, 46, 62, and 57, respectively, not taking into account any other known transplant-related risk factors. Patients with PT-Hb levels of ≤110 g/L compared to >110 g/L had 5-year survival rates of 33% versus 56% ($p < 0.001$). The effect of the PT-Hb on survival was sustained in subgroups of patients presenting with low or high-risk disease at the time of BMT. The overall 5-year survival rate was 46%. By univariate analyses, the PT-Hb, the use of unrelated donors, BMT in patients with more advanced disease and major ABO mismatch between donor and recipient were found to be significant risk factors for mortality. In a multivariate model, a low PT-Hb level was found to be an independent risk factor ($p < 0.001$; hazard ratio, 1.19 per 10 g/L decrease; 95% CI, 1.10–1.28). **Conclusion:** Pre-transplant anemia is an independent risk factor for increased long-term mortality during alloBMT. It remains to be determined whether decreased survival is the result of direct effects from anemia or, alternatively, a low PT-Hb level may represent surrogate marker for other adverse transplant-related parameters.

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LOW DOSE TOTAL BODY IRRADIATION, FLUDARABINE AND ANTI-THYMOCYTE GLOBULIN CONDITIONING FOR MULTIPLE MYELOMA (MM)

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Seven patients with multiple myeloma underwent non-myeloablative stem cell transplant (NST) with ATG 15 mg/kg/day days -4 to -1, TBI 200 cGy on a single fraction on day -5, and fludarabine 30 mg/m2/day on days -4 to -2. Immunosuppressive therapy was oral mycophenolate mofetil 15 mg/kg every 12 hours and cyclosporine 6 mg/kg every 12 hours started on day -5. Grafts were unmanipulated PBPC mobilized with filgrastim 10 ug/kg/day and collected on day 5. The median age of the recipients was 54 years (range, 38-60). Three patients had 2 prior autologous stem cell transplant (ASCT) and 3 had one prior ASCT. Three patients had refractory MM, 2 had PR to prior therapies, 1 had relapsed disease and 1 was in CR at the time of transplant. Three patients had cytogenetics abnormalities: 2 had del 13q14 and 1 del q20. Three patients had monoclonal IgG kappa, 2 IgA kappa and 2 kappa light chains. Six patients received a full match related graft and one had full match (10/10) unrelated donor graft. Five of seven patients were evaluable for chimerism. Three had >90% and 2 had >80% donor chimerism by day 30. Four patients are alive two of them in CR with a follow up time of 307 and 951 days. One of them had refractory disease at the time of NST. One patient is 61 days post transplant in PR showing continued response. One patient is 93 days post transplant and has a mixed response evidenced by complete disappearance of plasma cells in bone marrow and normal IPEP but a new plasmacytoma in the skull. Three patients died; 2 from infectious complications on days 40 and 57 and one at day 19 with CNS toxicity presumed secondary to fludarabine. One patient developed pulmonary aspergillosis and CMV disease, both resolved with appropriate therapy. Three patients developed acute GvHD, 2 had cutaneous grade I and 1 grade III of liver, gut and skin (unrelated donor graft). All 3 are alive with resolution of the GvHD.The addition of ATG to low dose TBI, fludarabine NST conditioning results in high rate of donor chimerism, preserved graft versus myeloma effect and might help decrease the incidence or severity of GvHD by in vivo T-cell depletion. These results provide an alternative to reduced intensity conditioning with melphalan for allogeneic transplantation in MM.

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IMPROVING DOSING PRECISION IN BUSULFAN (BU)-BASED PREPARATIVE REGIMENS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) USING PARMACOKINETICS DIRECTED THERAPY (PKDT)

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Variation in po Bu absorption and metabolism in patients (Pts) undergoing HSCT contributes to increased relapse rate and excess toxicity. PK studies with ivBu confirm minimal variation in area under the concentrationXtime curve (AUC) in serial doses given to individual Pts and reduction in variation in time to max dose, but little decrease in interpatient variation. These studies suggest that dosing to achieve a precise drug exposure based upon test dose PK