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(*Unless otherwise noted)

INNOVATIVE RESEARCH ADVANCES STEM CELL AND BONE MARROW TRANSPLANTATION

-- Studies identify special considerations among children and adults over 55 in need of stem cell transplants --

(ATLANTA, December 10, 2007) – New data being presented at the 49th Annual Meeting of the American Society of Hematology in Atlanta, GA, suggest innovative strategies to improve the success of stem cell and bone marrow transplantation. These studies demonstrate improved outcomes using a new treatment regimen for children with a specific form of leukemia; new ways to increase the number of specialized stem cells harvested from the bone marrow prior to transplantation; efforts to effectively expand stem cell transplantation among patients older than 55; and preclinical research that re-examines the way physicians prepare a patient's immune system to accept a stem cell transplant. A press conference revealing this new research will take place Monday, December 10, from 8:00 to 9:00 a.m.

"The data and discussion highlighted today give a glimpse into the great strides and promises of stem cell transplantation," said Armand Keating, MD, Princess Margaret Hospital, Toronto, Canada, and moderator of the transplantation press conference. "Stem cell transplantation is certainly not new, but advanced techniques and new ways of applying older technologies have the potential to change clinical practice and dramatically improve survival rates and quality of life for our patients whether young, old, or in the prime of their lives."

Stem cells are the body's "parent" cells and can produce specialized cells that differentiate and become various tissues in the body, such as those found in the blood, immune system, heart, brain, and liver. Treatments used to fight cancer cells in the body often also devastate healthy cells and

tissues, including stem cells, and the ability to extract, purify, and then reintroduce – or transplant – stem cells to patients following cell-destroying cancer treatments can help "rescue" a patient's compromised immune and hematologic system and speed his or her recovery.

- **Children with a certain type of acute lymphoblastic leukemia who receive imatinib along with high-dose chemotherapy experienced improvements in survival [Abstract #4]***

  *Kirk R. Schultz, MD**,** Child and Family Research Institute and the University of British Columbia, Vancouver, British Columbia, Canada*

  **Abstract 4 is being presented on Sunday, December 9, at 2:30 p.m. during the Plenary Scientific Session (1:30 – 4:00 p.m..). The embargo will lift at that time.*

  A Children's Oncology Group study examined whether increasing the number of days of imatinib (Gleevec®) therapy in combination with high-dose maintenance chemotherapy would improve early event-free survival in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. A total of 93 children were enrolled in one of five cohorts, receiving imatinib for 42 days, 63 days, 84 days, 126 days, or 280 days, respectively, prior to maintenance chemotherapy. A bone marrow transplant was performed after two cycles of imatinib therapy only if a sibling donor was available; otherwise chemotherapy was continued. Patients who received a bone marrow transplant started imatinib four to six months following the transplant for six months.

  Increasing imatinib exposure resulted in improved early event-free survival at one year of 70.6 percent for the first and second cohorts, 90.9 percent for the third and fourth cohorts, and 95.3 percent for the fifth cohort. The one-year event-free survival in cohort five, 65.7 percent, was significantly higher than had been seen in previous Children's Oncology Group studies.

  In conclusion, the study found that imatinib given in combination with intensive chemotherapy resulted in a significant improvement in early event-free survival. Imatinib given following a bone marrow transplant also improved early outcomes in related-donor bone marrow transplants. Intensive imatinib with intensive chemotherapy results in equivalent early event-free survival among patients treated with allogeneic-related or alternative-donor bone marrow transplants. Longer observation will be needed to see if these results produce a clinically significant difference in long-term event-free survival.

- **Umbilical cord blood may be good source of stem cells for cancer patients older than 55 [Abstract #331]**
  Navneet S. Majhail, MD, University of Minnesota, Minneapolis, MN

  The aging of the Baby Boomer generation – every hour another 330 Americans turn 60 – will have a tremendous impact on the prevalence of blood cancers and other disorders of the hematologic system in the years to come. Many older people with blood disorders may not be candidates for life-saving stem cell transplants because they cannot tolerate the steps needed to transplant stem cells harvested from their own bone marrow or cannot find donors who share their same genetic make-up. For these patients, stem cells from umbilical cord blood (UCB) may be a good alternative stem cell source.

  This study of 90 patients found that UCB was a viable source for stem cells for older patients who needed a transplant but did not have a matched related donor. The use of UCB and reduced-intensity immune system conditioning extended the availability of transplant therapy to older people previously excluded on the basis of age and lack of a suitable matched donor.

- **Production of specialized stem cells increases when new compound is added to standard pre-transplantation routine for multiple myeloma patients [Abstract #445]**
  John DiPersio, MD, PhD, Washington University School of Medicine, St. Louis, MO

  In order for a stem cell transplant to be successful, physicians must be able to extract – or harvest – an adequate number of specialized cells called CD34+ cells via a procedure known as apheresis. The CD34+ cells are purified following their extraction and re-introduced, or transplanted, back into the body following high-dose radiation or chemotherapies designed to kill the cancer cells in the body. Various medicines are given to patients to accelerate the production of CD34+ cells, and physicians continue to look for new ways to improve how quickly and how many of these cells can be produced.

  Interim results of a phase III, randomized, placebo-controlled trial concluded that the addition of the drug plerixafor to G-CSF therapy in patients with multiple myeloma results in a statistically significant increase in number of harvested CD34+ cells, and that transplants using these cells were durable at three months of follow-up. Patients receiving plerixafor +G-CSF were more than twice as likely to achieve target CD34+ cell apheresis amounts compared with patients receiving G-CSF alone (72 percent vs. 34 percent). These gains were seen without additional side effects for patients receiving the add-on drug treatment.

- **Targeting a new antibody may lead to more tolerable transplantation procedures, according to early animal research [Late-Breaking Abstract #LB2]**
  Agnieszka Czechowicz, Stanford University School of Medicine, Stanford, CA

  While stem cell transplants use the body's own immune system to repair the damage done by cancers or blood disorders and their treatments, the body's own remaining stem and immune cells often fight against a transplant and limit its effectiveness in helping a patient recover. In this animal study, a new model eliminated the myeloablative – or cell-killing – conditioning regimens used in traditional stem cell transplants by targeting a special protein on the surface of cells – the C-kit antigen.

  To achieve these positive results, the researchers cultivated stem cells with a special antibody called ACK2, administering the antibody to mice. The ACK2-treated animals saw the rapid removal of more than 98 percent of their own stem cells, and subsequent stem cell transplants in the mice were highly successful. This study could eventually define a new way of approaching bone marrow transplantation/hematopoietic stem cell transplantation (BMT/HSCT). Extrapolation of these methods to humans may enable efficient conditioning regimens for transplantation, thus expanding the potential applications of BMT/HSCT to include treatment of many non-malignant hematologic disorders and a wide variety of autoimmune disorders, such as diabetes and multiple sclerosis, as well as the facilitation of organ transplantation.

The study authors and press program moderator will be available for interviews after the press program or by telephone. In addition to the press conference on transplantation, four additional press briefings will take place at the annual meeting focusing on blood clotting and bleeding disorders, leukemias, sickle cell disease and thalassemia, and hematologic malignancies. For the complete annual meeting schedule and additional information, please visit *www.hematology.org/meetings/2007*.

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The American Society of Hematology (www.hematology.org) is the world's largest professional society concerned with the causes and treatment of blood disorders. Its mission is to further the understanding, diagnosis, treatment, and prevention of disorders affecting blood, bone marrow, and the immunologic, hemostatic, and vascular systems, by promoting research, clinical care, education, training, and advocacy in hematology.

[4] Improved Early Event Free Survival (EFS) in Children with Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) with Intensive Imatinib in Combination with High Dose Chemotherapy: Children's Oncology Group (COG) Study AALL0031. Session Type: Plenary Session

Kirk R. Schultz, W. Paul Bowman, William Slayton, Alex Aledo, Meenakshi Devidas, Harland Sather, Michael J. Borowitz, Stella M. Davies, Michael Trigg, Bernice Pasut, Dean Jorstad, Tammie Eslinger, Laura E. Burden, Chenguang Wang, Robert Rutledge, Paul S. Gaynon, Andrew J. Carroll, Nyla A. Heerema, Naomi Winick, Stephen Hunger, William L. Carroll, Bruce Camitta Children's Oncology Group, Arcadia, CA, USA

Ph+ ALL remains one of the highest risk subsets of childhood ALL. The COG AALL0031 protocol (open 2002 - 2006) gave imatinib at 340 mg/m2 for an increasing number of days in combination with an intensive chemotherapy backbone. Cohorts received 42 days of imatinib exposure (Cohort 1 N= 8), 63 days (Cohort 2 N=12), 84 days (Cohort 3 N=11), 126 days (Cohort 4 N=12) and 280 continuous days (Cohort 5 N=50) prior to maintenance therapy. If an HLA-identical sibling donor was available, a BMT was performed after the first two cycles of therapy post induction otherwise chemotherapy was continued. BMT patients received imatinib starting 4 - 6 months post BMT for a 6 month duration. Ninety-three patients were treated, 10 of whom had failed induction (induction failures were removed from the following analyses). We observed that MRD positivity (<0.01%) was significantly lower (p = 0.0002) after consolidation block 1 and after consolidation block 2 (p = 0.007) in Cohorts 3 - 5 (imatinib in consolidation blocks 1& 2) versus Cohorts 1/2 combined (no imatinib in consolidation blocks 1&2). Early EFS improved with increasing imatinib exposure with a 1 year EFS of 70.6±11.1% for Cohorts 1 & 2, 90.9±6.4% for Cohorts 3&4, and 95.3±3.6% for Cohort 5 (p = 0.02). The 1 year EFS for Cohort 5 was significantly higher than for historical controls from previous COG studies (N=56; 1 year EFS 65.7±6,4%; p = 0.006). Twenty-one patients had matched sibling transplants (8 of 43 in Cohorts 1 - 4 and 13 of 44 in Cohort 5). Eleven of 83 (13%) patients were removed from protocol by treating institutions for alternative donor BMT. Intent-to-treat analysis does not show a statistically significant difference in early outcome between those patients in Cohort 5 treated without sibling donor BMT compared to patients who received a matched sibling donor BMT (p = 0.26). The related donor BMT group treated with 6 months of Imatinib post BMT had a higher 1 year EFS compared to a comparable historical BMT group receiving no Imatinib on prior pediatric cooperative group protocol with a 1 year EFS 78%. Cohort 5 chemotherapy treatment group outcomes were not significantly affected after removal of patients receiving off protocol BMT. We conclude that imatinib given in combination with intensive chemotherapy resulted in a significant improvement in early EFS and reduction in early MRD. Post BMT imatinib also improved early outcome in related donor BMT. Intensive imatinib with intensive chemotherapy gives equivalent early EFS to patients treated with allogeniec related or alternative donor BMT. Longer observation will be required to see if this results in a difference in long term EFS.

Outcome in patients on COG protocol, AALL0031

Therapy given	N	1 year EFS	SE
Intent-to-treat analysis - Cohort 5 Chemotherapy with continuous dosing imatinib (includes 6 patients removed from study for alternative donor BMT)	31	96.7%	3.5%
Intent-to-treat analysis - Sibling BMT (all Cohorts)	21	95.0%	5.3%
Cohort 5 (with removal of alternative donor BMT patients)	25	95.8%	4.3%
Off protocol alternative donor BMT (all cohorts)	11	81.8%	12.3%

Abstract #4 appears in Blood, Volume 110, issue 11, November 16, 2007
Keywords: Bone Marrow Transplant|MRD|BCR-ABL

Sunday, December 9, 2007 1:30 PM

Session Info: Plenary Scientific Session (1:30 p.m.-4:00 p.m.)

[331] Reduced Intensity Allogeneic Transplant in Patients Older Than 55 Years: Unrelated Umbilical Cord Blood Is Safe and Effective for Patients without a Matched Related Donor. Session Type: Oral Session

Navneet S. Majhail, Claudio Brunstein, John E. Wagner, Marcie Tomblyn, Avis Thomas, Jeffrey S. Miller, Mukta Arora, Dan S. Kaufman, Linda J. Burns, Arne Slungaard, Philip B. McGlave, Daniel J. Weisdorf Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN, USA

The lower morbidity and mortality of reduced-intensity conditioning (RIC) regimens has allowed allogeneic hematopoietic cell transplantation (HCT) in older patients. Unrelated umbilical cord blood (UCB) has been investigated as an alternative stem cell source because of insufficient availability of suitably HLA matched related (MRD) and adult volunteer unrelated donors. We hypothesized that RIC HCT using UCB would be safe and efficacious in older patients and compared the transplant related mortality (TRM) and overall survival (OS) after RIC HCT in patients older than 55 years using either MRD (n=47) or, in patients with no 5/6 or 6/6 HLA compatible related donors, UCB (n=43). RIC regimen consisted of total-body irradiation (200 cGy) and either cyclophosphamide and fludarabine (n=69), or busulfan and fludarabine (n=16) or busulfan and cladribine (n=5). The median age of MRD and UCB cohorts was 58 (range, 55-70) and 59 (range, 55-69) years, respectively. AML/MDS (50%) was the most common diagnosis. All MRD grafts were 6 of 6 HLA matched to the recipient. Among patients undergoing UCB HCT, 38 (88%) received two UCB units to optimize cell dose and 40 (93%) received 1-2 HLA mismatched grafts. The median total nucleated cell dose was 9.2×10^8/kg (range, 3.0-21.2) for MRD grafts and 0.4×10^8/kg (range, 0.2-0.8) for UCB grafts. The median followup for survivors was 27 (range, 12-61) months. The probability of progression-free survival (PFS) at 3-years for recipients of MRD and UCB was 30% (95% confidence intervals [CI], 16-44%) and 34% (95% CI, 19-48%)(p=0.98) and OS was 43% (95% CI, 29-58%) and 34% (95% CI, 17-50%)(p=0.57), respectively. The cumulative incidence of sustained donor engraftment at 6 weeks was 100% for MRD and 89% (95% CI, 80-99%) for UCB recipients (p=0.05). The cumulative incidence of grade 2-4 acute graft-versus-host disease (GVHD, 42% vs. 49%, p=0.20) and TRM at 180-days (23% vs. 28%, p=0.36) was comparable between the MRD and UCB groups; however, UCB recipients had a lower incidence of chronic GVHD at 1-year (40% vs. 17%, p=0.02). On multivariate analysis, graft type (MRD vs. UCB) had no impact on TRM, PFS or OS; only HCT comorbidity index score was independently predictive for these endpoints. For the whole cohort, 180-day TRM for patients with HCT comorbidity index scores of 0, 1-2 and $\geq$ 3 was 14% (95% CI, 0-28%), 19% (95% CI, 5-32%) and 44% (95% CI, 26-62%), respectively. Compared to patients with a higher score, patients with a score of 0-2 had lower TRM (hazard ratio [HR] 0.3 [95% CI, 0.1-0.7]) as well as better PFS (HR 0.5 [95% CI, 0.3-0.9]) and OS (HR 0.5 [95% CI, 0.2-0.9]). Our study supports the use of HLA mismatched UCB as an alternative graft source for older patients who need a transplant but do not have a MRD. The use of RIC and UCB extends the availability of transplant therapy to older patients previously excluded on the basis of age and lack of a suitable MRD. Older HCT candidates with limited comorbidity have a low and acceptable risk of TRM and a careful review of existing comorbidities is necessary when considering older patients for HCT.
Abstract #331 appears in Blood, Volume 110, issue 11, November 16, 2007
Keywords: UCB Transplant|Transplant-Related Mortality|Survival

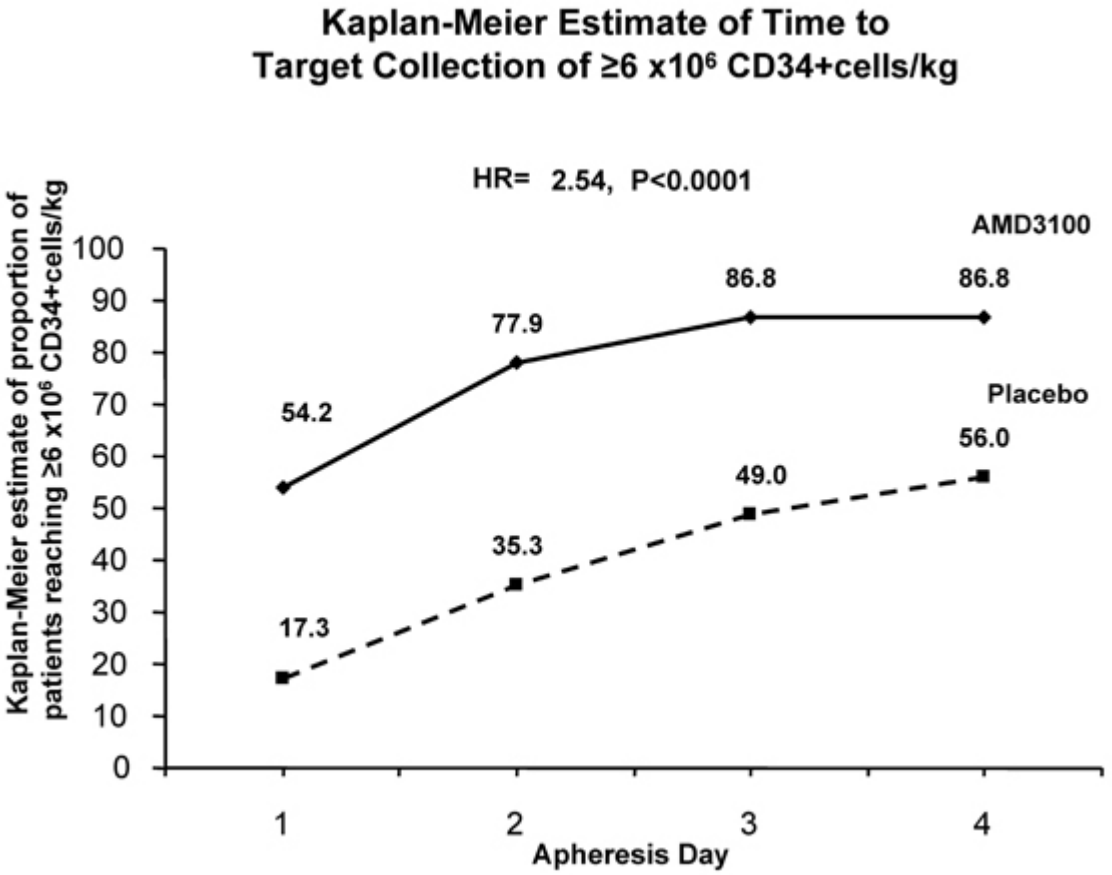
Monday, December 10, 2007 11:00 AM

Session Info: Simultaneous Session: Clinical Results: Alternative Donor Transplantation-Umbilical Cord Blood and Comparative Studies, Selection Criteria, and New Approaches (11:00 a.m.-12:30 p.m.)

[445] A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (Plerixafor)+G-CSF vs. G-CSF+Placebo for Mobilization in Multiple Myeloma (MM) Patients for Autologous Hematopoietic Stem Cell (aHSC) Transplantation. Session Type: Oral Session

John DiPersio, Edward A. Stadtmauer, Auayporn P. Nademanee, Patrick Stiff, Ivana Micallef, J. Angell, G. Bridger, Gary Calandra, for the 3102 Investigators Washington University, St. Louis, MO, USA; University of Pennsylvania, Philadelphia, PA, USA; City of Hope, Duarte, CA, USA; Loyola University, Chicago, IL, USA; Mayo Clinic, Rochester, MN, USA; Genzyme Corporation, Cambridge, MA, USA

AMD3100, Plerixafor (A)+G-CSF (G) have effectively allowed aHSC mobilization in Phase I and II studies. This Phase III, multicenter, randomized, double-blind, placebo controlled study compares the safety and efficacy of A+G Vs. placebo (P)+G to mobilize and transplant patients with MM. Methods: Adult MM patients requiring an aHSC transplant, in first or second CR or PR were eligible to participate. Patients were declared for single or tandem transplant with the second transplant occurring within 6 months from the first. Patients received G (10μg/kg/day) subcutaneously (SQ) for 4 days; on the evening of Day 4 they received either A (240μg/kg SQ) or P. Patients underwent apheresis on Day 5 after an AM dose of G and 10-11 hours after administration of study treatment. Patients continued to receive the evening dose of study treatment followed by AM dose of G and apheresis for up to a total of 4 apheresis or until ≥6 x 10^6 CD34+ cells/kg were collected. Patients who failed to collect ≥2 x 10^6 CD34+ cells/kg were eligible for rescue therapy with A+G, without unblinding of randomized treatment. Only study cells were used for transplant. The primary endpoint was the percentage of patients who achieved ≥6 x 10^6 CD34+ cells/kg in 2 or less apheresis days. All patients will be followed for ≥12 months post-transplant. Results: 302 patients were enrolled and randomized into the study. All have completed 100 days follow-up and are included in this intent-to-treat analysis. Baseline characteristics were similar between groups. The primary endpoint was met in 106/128 (72%) patients in the A+G group and 53/154 (34%) patients in the P+G group, p<0.0001.



The figure shows that 54% of A+G patients reached target after 1 day of apheresis but 56% P+G patients required up to 4 days of apheresis to reach target. 7 patients in the P+G group required rescue therapy and all collected ≥2 x 10^6 CD34+ cells/kg after A+G rescue. 142 patients (96%) in A+G group and 136 patients (88%) in the P+G group underwent transplant. Tandem transplants were performed in 32 and 28 patients in A+G and P+G groups, respectively. Median time to engraftment was Day 11 for PMN and Day 18 for platelets in both groups. Grafts were durable in all patients in both group at ≥100 days post-transplant. Patients in the A+G group experienced more GI effects and injection site erythema than patients in the P+G group. These adverse events were generally mild. There were no drug related serious adverse events in either group. Conclusions: In this study, the addition of AMD3100 to G-CSF is generally safe and well tolerated and is superior to G-CSF alone for aHSC mobilization in MM patients. A+G patients were statistically significantly more likely to achieve target earlier than P+G patients and had successful transplant.

Abstract #445 appears in Blood, Volume 110, issue 11, November 16, 2007
Keywords: AMD3100|Multiple Myeloma|Phase III

Monday, December 10, 2007 1:30 PM

Session Info: Simultaneous Session: Autologous Transplantation for Myeloma: Induction, Mobilization, and Biologic Correlates (1:30 p.m.-

[LB2] Antibody-Based Depletion of Hematopoietic Stem Cells Empties Niches for Efficient Transplantation. Session Type: Late Breaking Session

Agnieszka Czechowicz, Daniel L. Kraft, Deepta Bhattacharya, Irving L. Weissman Institutes of Medicine, Stanford University School of Medicine, Stanford, CA, USA

Hematopoietic stem cells (HSCs) are used therapeutically in bone marrow/hematopoietic stem cell transplantation (BMT/HSCT) to correct hematolymphoid abnormalities. Upon intravenous transplantation, HSCs can home to specialized bone marrow niches, self-renew and differentiate and thus generate a new, complete hematolymphoid system. Unfortunately BMT has had limited applications, due to the risks associated with the toxic conditioning regimens, such as irradiation and chemotherapy, that are deemed necessary for HSC engraftment. Elimination of these toxic conditioning regimens could expand the potential applications of BMT to include many non-malignant hematologic disorders, a wide variety of autoimmune disorders such as diabetes and multiple sclerosis, as well as in the facilitation of organ transplantation. The exact function of these traditional myeloablative conditioning regimens is not clear. To elucidate the barriers of HSC engraftment, we transplanted 50-1000 purified HSCs (Ckit+Lin-Sca1+CD34+CD150-) into immunodeficient, Rag2-/- or Rag2-/-gc-/- recipient mice and show that HSC engraftment levels rarely exceed 0.5% following transplantation without toxic conditioning, indicating that the immune system is not the only barrier to engraftment. Additionally, we did not observe a significant increase in HSC engraftment when HSC doses of >250 cells were transplanted. Even when up to 18000 HSC were transplanted, we did not see a linear increase in HSC engraftment, indicating that the increased doses of HSCs transplant inefficiently. We believe this is due to the naturally low frequency of available HSC niches, which we postulate may result from the physiologic migration of HSCs into circulation. Conversely, separation of the graft into small fractions and the subsequent time-delayed transplantation of these doses did result in increased engraftment due to the natural physiologic creation of new available HSC niches. When 1800 HSC were transplanted daily for seven days, the engraftment was 6.1-fold higher than transplantation of 12800 HSC in a single bolus. Here, we provide evidence that, aside from immune barriers, donor HSC engraftment is restricted by occupancy of appropriate niches by host HSCs. Through elimination of host HSCs we are able to increase available HSC niches for engraftment. We have developed a novel system where HSCs can be eliminated by targeting C-kit, a cell surface antigen that is highly expressed on the surface of HSCs. Cultivation of HSCs with ACK2, a depleting antibody specific for c-kit, prevented stem-cell factor (SCF) dependent HSC proliferation in vitro and resulted in cell death. Administration of ACK2 to mice led to the rapid and transient removal of >98% of endogenous HSCs in vivo thus resulting in equal numbers of available niches for engraftment. Following ACK2 clearance from serum, transplantation of these animals with donor HSCs led to chimerism levels of up to 90%, representing a 180-fold increase as compared to unconditioned animals. This non-myeloablative conditioning regimen had few side effects, other than temporary loss of coat color. The HSCs in even untransplanted animals rapidly recovered and animals remained healthy and fertile. This work redefines the way we approach BMT/HSCT, and places great emphasis on the necessity to create available HSC niches prior to transplantation. Extrapolation of these methods to humans may enable efficient yet mild conditioning regimens for transplantation, thus expanding the potential applications of BMT/HSCT.
Keywords: Conditioning|Bone Marrow Transplant|Hematopoietic Microenvironment

Tuesday, December 11, 2007 7:45 AM

Session Info: Late-Breaking Abstracts Session: (7:30 a.m.-9:00 a.m.)