The median dose for patients receiving BM (2.7×10^8/Kg) gave the greatest discrimination.

In multivariate analyses, high dose BM compared to PB, was associated with lower TRM (RR = 0.61 ; 95% CI 0.39-0.98; p = 0.04), better Leukemia Free Survival (RR = 0.65; 95% CI 0.46-0.91; p = 0.013), and better Overall Survival (RR = 0.64 ; 95% CI 0.44-0.92; p = 0.016). **Conclusion:** The present study in patients with AML allografted in first remission, indicates a better outcome with marrow as compared to PB, when the dose of marrow infused is rich.

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LONG-TERM FOLLOW UP AFTER NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION FOR RENAL CELL CARCINOMA: THE UNIVERSITY OF CHICAGO EXPERIENCE

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Non-myeloablative hematopoietic allogeneic stem cell transplant (NST) for metastatic renal cell carcinoma (RCC) has been demonstrated to induce remissions in select patients (pts). However, there are no long-term data on response duration, progression after response, or overall survival. We report the long-term follow up of NST for cytokine refractory metastatic RCC at the University of Chicago treated on a single protocol. Between 2/99 and 5/03, 18 pts underwent 19 matched-sibling peripheral harvested NST's after conditioning with fludarabine and cyclophosphamide. Post-transplant immunosuppression was with mycophenolate mofetil until day 60 and tacrolimus tapering at day 90. Median age was 55 years, performance status (PS) was 1 in 6/19 pts (PS = 0 in the remainder), and hemoglobin (Hb) < 12 g/dL in 8/19 (42%). There were 4 partial responses, but all have since progressed with a median response duration of 609 days (range, 107-926). All responders had chronic GVHD and were on immunosuppression when progressive disease (PD) occurred. In 3 of 4 responders, PD occurred at a site of prior response. Among all pts, DLI and/or interferon were given to 3 pts for PD without response. Six pts died early (ED) before day 120. Transplant related mortality was 4/6 among those with ED and 5/18 (28%) overall. Among those without ED or response, 7/9 died from PD. All responders are alive at a median of 1035 days (range 900-1405). The combination of anemia and decreased PS was associated with adverse transplant outcome ($P = .035$) and reduced survival ($P = .004$). Responders had prolonged survival ($P = .002$) compared to non-responders. In conclusion, NST for RCC as performed here leads to long term but not durable partial responses and is associated with prolonged survival in a minority of pts. Risk stratification with simple clinical factors such as anemia and PS > 0 may reduce acute mortality and enrich the population for potential responders, but further improvements in adoptive immunotherapy are necessary before NST can be more generally applied for RCC.

Table. *Influence of Patient Factors on NST for RCC*

Factor	Partial Response (%) N = 4	Other (%) N = 9	Early Death (%) N = 6	Across Groups *P* value N = 19	Survival *P* value N = 18
Pretreatment					
PD at transplant	2 (50)	5 (83)	5 (56)	0.57	.37
Hb < 12 g/dL	1 (25)	3 (33)	4 (67)	.48	.06
PS > 0	0	2 (22)	4 (67)	.06	<.01
Hb < 12 g/dL and/or PS > 0	1 (25)	4 (44)	6 (100)	.04	<.01
GVHD					
aGVHD > 1	0	1 (11)	2/5 (40)	.23	.03
cGVHD, ext	4 (100)	3 (33)	n/a		.76

Nineteen transplants performed with 18 patients. "Other" includes patients who did not respond or suffer early death. Across group comparison uses a two-tailed Fisher's exact test for a 3 × 2 table. Survival analysis is for 18 patients. *P* value derived from univariate log-rank test for each variable.

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ALLOGENEIC TRANSPLANTATION FOR MANTLE CELL LYMPHOMA

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The prognosis of mantle cell lymphoma (MCL) is poor with a median survival of generally less than three years. In an attempt to improve on the outcome of this disease, high dose therapy in the form of both autologous and allogeneic stem cell transplantation (SCT) has been explored. However, recurrences following autologous transplantation are common. Allogeneic SCT offers the potential benefits of an uncontaminated stem cells and a graft versus lymphoma effect.

Thirty-seven patients with MCL underwent allogeneic SCT at five institutions between 1994 and 2003. The median age at transplant was 48 (range 34-59) years; 6 patients were female and 31 male. The median interval from diagnosis to transplant was 11 months (range 4-144 months). Seventy percent of patients had received at least two prior chemotherapeutic regimens and 9% had failed an autologous SCT. Donor source was matched related donor (MRD) in 33 (89%) and matched unrelated donor (MUD) in 4 (11%). Conditioning regimens varied by center; overall 26 patients (70%) received TBI-based conditioning. Donor source was bone marrow in 14 (38%) and peripheral blood in 23 (62%). Fourteen grafts (38%) were T-cell depleted and of these, 7 received T-cell add-back. With a median follow-up for surviving patients of 42 months (range 4-98 months), sixteen patients remain alive post SCT. The cumulative incidence of non-relapse mortality is 32% at day 100 and 41% at one year post transplant, with the vast majority of deaths occurring by one year post transplant. Thirty four of 37 patients were evaluable for acute graft-versus-host disease (GVHD). The cumulative incidence of acute GVHD was 62% at 100 days. Of 20 patients evaluable for extensive chronic GVHD, the cumulative incidence was 30% at one year. Three year estimates of event-free and overall survival are 39% (95% CI 23%-55%) and 45% (95% CI 28%-61%) respectively. Progressive disease has been documented in six patients. This data demonstrates that allogeneic SCT in MCL can result in prolonged disease control in selected, pretreated patients, although nonrelapse mortality remains a significant problem with this approach.

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DISSECTION OF AN MHC MISMATCHED ALLOGENEIC TRANSPLANT MODEL DURING DONOR $CD4^+CD25^+$ T-CELL FACILITATION OF HEMATOPOIETIC PROGENITORS

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Identifying cell populations capable of supporting allogeneic hematopoietic stem/progenitor cell engraftment without inducing GVHD could lead to more potential hematopoietic cell transplant (HCT) recipients and broaden the acceptable donor pool. We have examined the effect of $CD4^+CD25^+$ regulatory (T-reg) cells on engraftment in a sublethal (7.0 Gy TBI) MHC mismatched model by transplanting donor C57BL/6 (B6) T-regs and T-cell depleted bone marrow (BM-TCD) into BALB/c recipients and observed long-term chimerism ($p < .05$) and diminished rejection ($p < .05$). This non-GVHD inducing T-cell population was also associated with significantly greater splenic lineage committed (GM, $p < .001$) and multi-potential (HPP, $p < .05$) donor progenitor colonies 7 days post-BMT. To dissect the allogeneic transplant components involved in this progenitor support, splenic day 7 donor GM progenitors were assessed following transplants eliminating donor T-regs' allo-recognition in the recipient and transplants selectively neutralizing populations in the recipient capable of allogeneic rejection. T-regs from BALB/c × B6 F1 mice significantly increased donor B6 colonies whether transplanted into recipients lacking (BALB/c, $H\text{-}2^d$, $p < .001$) or possessing (BALB.K, $H\text{-}2^k$, $p < .05$) MHC that was allogeneic to the donor T-regs. Importantly, when eliminating the recipients' T-cell resistance by

transplanting B6 BM-TCD into BALB/c *Rag1*$^{-/-}$ or into BALB/c × B6 F1 recipients, co-transplanting B6 T-regs again augmented donor colonies (*Rag1*$^{-/-}$, $p < .001$; F1, $p < .01$). Notably, co-transplantation of B6 T-regs increased the already elevated progenitor colony numbers detected in the absence of NK resistance following transplant of BALB/c × B6 F1 BM-TCD into BALB/c recipients ($p < .001$). Finally, when allogeneic antigen, T-cell resistance, and NK resistance were simultaneously eliminated by transplanting BALB/c BM-TCD and T-regs into BALB/c recipients, significantly greater progenitor colonies were again observed ($p < .01$). In summary, donor $CD4^+CD25^+$ T-cells, which are capable of supporting long-term allogeneic hematopoietic engraftment without inducing GVHD, are able to support splenic day 7 donor progenitors independent of activation by allogeneic antigen in the recipient and suppression of host resistance. Furthermore, the independence from T-cell suppression suggests a novel biological function of this suppressive population. $CD4^+CD25^+$ T-cells may thus be useful clinically in supporting engraftment following HCT.

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EFFECT OF VERY HIGH CD34 CELL DOSE ON THE OUTCOME OF ALLOGENEIC HLA IDENTICAL RELATED TRANSPLANTS

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We analyzed outcome in a group patients who recieved very high CD34 cell dose (≥20 × 10^6 CD34 cells/kg)(Group A). We compared this, with a group of patients who recieved between 3-10 × 10^6 CD34 cells/kg (Group B). There was no significant difference between the groups in recipient age, gender, disease risk or reciept of sex mismatched product. The donor characteristics were also similar between both groups except for CD34 cell doses which was 30.1 ± 10.2 cells/kg in group A and 6.2 ± 2 cells/kg in group B ($p < 0.000001$). The dose of CD3, CD4, CD8, CD19 and CD16/56 subset of cells were also significantly higher in group A than in group B. All but 10 patients in group A recieved a similar conditioning regimen and all but 5 in group A recieved GVHD prophylaxis with single agent cyclosporine. Eight patients in group A recieved alternative ablative conditioning regimens and 2 recieved reduced intensity conditioning regimens. Five patients in group A also recieved methotrexate for GVHD prophylaxis.

The results of the outcome in the two groups are given in the table below. Median time to neutrophil (9.4 ± 2.8 vs 10.4 ± 3.3) and platelet (11.5 ± 4 vs 15.7 ± 13.3) recovery were not significantly different in the two groups. There was a trend towards earlier engraftment in group A compared to group B. While the risk of grade 2-4 GVHD was not significantly different between the two groups, the risk of severe (grade 3/4) acute GVHD and deaths attributable to GVHD were significantly higher in group A compared to group B. Incidence of chronic EGVHD was similar in both groups. There was a trend towards a lower relapse rate in group A, though the progression free survival and overall survival in both the groups were similar.

In conclusion infusion of very high doses of CD34 cells in the setting of a matched related allogeneic stem cell transplanataion is associated with significant increase risk of severe acute GVHD. Infusion of the entire unmanipulated stem cell product when the cell dose is ≥20 × 10^6 CD34 cells/kg is not recommended. The optimal dose remains to be defined.

Table.

CD34	GVHD 2-4	GVHD 3/4	Chronic EGVHD	Death—GVHD	Relapses	Alive (2 years)
Group A						
(n = 31)	**45%**	**22.5%**	**72%**	**16%**	**19%**	**48%**
Group B						
(n = 96)	**50%**	**8.3%**	**75%**	**6.25%**	**32%**	**43%**
P	**0.5**	**0.0028**	**0.54**	**0.0096**	**0.13**	**0.47**

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EVEN COAGULASE NEGATIVE STAPHYLOCOCCUS INFECTIONS FOLLOWING REDUCED INTENSITY TRANSPLANTATION ARE ASSOCIATED WITH INCREASED TRANSPLANT COMPLICATIONS AND POORER OVERALL SURVIVAL

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Reduced intensity transplantation (RIT) is associated with lower transplant related mortality (TRM) but the incidence of infectious complications remains controversial. We analyzed the incidence of bacteremia during the first 100 days post-transplantation in 106 patients with various malignancies who underwent a reduced intensity regimen of extracorporeal photopheresis × 2 cycles, pentostatin 8 mg/m^2 by continuous intravenous infusion over 48 hours, and total body irradiation 600cGy, followed by allogeneic bone marrow stem cell infusion from a 6/6 HLA matched related donor (n = 68), 5/6 HLA matched related donor (n = 8), 6/6 HLA matched unrelated donor (n = 29), or 5/6 HLA matched unrelated donor (n = 1). GVHD prophylaxis consisted of continuous infusion cyclosporin A and short course methotrexate. All patients received fluoroquinolone prophylaxis until neutrophil engraftment. During the first 100 days post-transplantation, grade 2-4 acute GVHD occurred in 19% of patients, and 56 patients (53%) had positive blood cultures. Median days to positive cultures were 21 (range −7 to 97). Blood cultures were positive for coagulase negative staphylococcus (CoNS) (n = 36: 63%), other gram-positive cocci (GPC) (n = 10: 10%), gram-negative rods (GNR) (n=5: 9%), fungus (n = 3: 5%), gram-positive rods (GPR) (n = 2: 4%), or anaerobes (n = 1: 1%). Recurrent infections (same species >30 days later) occurred in 7 patients (7%), and multiple infections with different organisms occurred in 16 patients (15%). Three patients died of sepsis. The incidence of bacteremia was higher in patients with grade 2-4 acute GVHD versus grade 0-1 acute GVHD (70% versus 45%: $p = 0.05$), and in mismatched related or matched unrelated transplants versus matched related transplants (66% versus 46%: $p = 0.05$). Bacteremia was associated with higher day 100 TRM (26% versus 11%: $p = 0.06$) and lower median overall survival (OS) (9 months versus 35 months: $p = 0.01$). CoNS bacteremia had similar day 100 TRM as other GPC bacteremia like staphylococcus aureus and enterococcus (22% versus 38%: $p = 0.37$) and similar day 100 TRM as non-GPC bacteremia (22% versus 30%: $p = 0.61$). There was a trend towards lower median OS in patients with CoNS bacteremia versus other GPC bacteremia (7 months versus 14 months: $p = 0.18$). In patients undergoing RIT, CoNS bacteremia, like other bacteremia, was associated with increased TRM and poorer overall survival. Future studies on RIT will need to address the issue of bacteremia, especially CoNS bacteremia.

Table. *Bacteremia Following Reduced Intensity Transplantation*

	Bacteremia	No Bacteremia	*P* value
Day 100 TRM	**26%**	**11%**	***P* = 0.06**
Median OS	**9 months**	**35 months**	***P* = 0.01**
	CoNS Bacteremia	**Other GPC Bacteremia**	***P* value**
Day 100 TRM	**22%**	**38%**	***P* = 0.37**
Median OS	**7 months**	**14 months**	***P* = 0.18**

Bacteremia is associated with higher transplant-related mortality and lower overall survival. Coagulase-negative staphylococcal bacteremia has a similar TRM and OS as other gram-positive cocci bacteremia.