

# “Focus on...” session: allogeneic transplantation

## 037 RISK FACTOR ANALYSIS OF ALLOGENEIC HEMAPOIETIC CELL TRANSPLANTATION (HCT) FOR FOLLICULAR LYMPHOMA (FL). A RETROSPECTIVE STUDY ON BEHALF OF THE EBMT (THE EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION) LYMPHOMA WORKING PARTY AND THE CIBMTR (CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH) LYMPHOMA WORKING COMMITTEE.

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Optimal timing of allogeneic HCT for FL is unknown. Transplant recipients without available HLA match sibling donors (sib) usually proceed to HCT with alternate donors later in their disease course. We previously compared outcomes of 702 patients who received sib (n=504) or unrelated donors (URD) (N=198) HCT from 1997 to 2005, from 171 centers worldwide. URD HCT recipients had poorer risk FL with more previous lines of therapy, including autologous HCT. Adjusted probabilities for three-year progression free (PFS) and overall survival (OS) were 49% vs. 60% (p=0.02) and 54% vs. 69% (p<0.01) for URD and sib HCT, respectively. Karnofsky performance score <80 (KPS80), ≥5 lines of therapy (chemo5), prior autologous HCT (pAuto), not in complete response at time of transplant (notCR) and myeloablative conditioning regimen (myelo) were associated with higher mortality irrespective of donor type. Subset analysis of 446 patients (URD n=163, sib n=283) with complete data on all five significant risk factors for survival was further explored. Hazard ratios of all factors were ≥1.3 (range 1.3 to 2.9) and a score was calculated according to the magnitude of the impact on survival. Individual scores were 3 for KPS80; 2 for chemo5 and pAuto; and 0.5 for notCR and myelo risk factors. Patients with overall scores of ≥3 experienced significantly higher overall mortality, and thus defined as unfavorable risk score. Three-year probability of OS in patients with unfavorable risk score were 45% vs. 68% (p<0.01) for URD and sib, respectively. Among patients with overall scores of <3, corresponding probabilities were 61% vs. 78% (p<0.01). Although further validation of this risk score is required, these results demonstrate that better patient selection, timing of transplantation and conditioning intensity are important determinants of outcomes. Additionally, improvements of URD HCT outcomes in patients without unfavorable risk score may assist in expanding the uses of alternative donor transplants for treatment of FL.

## 038 ALLOGENEIC TRANSPLANTATION (ALLOHCT) FOR PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) PROGRESSING AFTER AUTOLOGOUS TRANSPLANTATION (AUTOHCT). ON BEHALF OF THE WRITING COMMITTEE, CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH (CIBMTR), MEDICAL COLLEGE OF WISCONSIN, MILWAUKEE, WI

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**Introduction/Background:** There is no consensus on the optimal transplant strategy for MCL. AlloHCT is variably used as a front line transplant strategy, reserved for patients with high risk disease or those relapsing after AutoHCT.

**Materials and Methods:** We analyzed the outcomes of 105 patients with MCL relapsing after a prior AutoHCT and then receiving AlloHCT between 1996 and 2007, reported to the CIBMTR.

**Results:** Patients received myeloablative (14) or reduced intensity (91) conditioning (RIC) regimens with a clear shift in practice to near exclusive (97% from 2005-2007) use of RIC regimens in later years. The analysis was therefore restricted to the RIC cohort. Median age at AlloHCT was 55 yrs with 26% above age 60. The cohort was heavily pretreated with 68% receiving more than 3 prior regimens of chemotherapy, 30% with KPS <90 and 30% with chemotherapy resistance. Median time from AutoHCT to AlloHCT was 32 months. Donors were unrelated in 92%, peripheral blood the preferred graft source (84%) and a variety of RIC regimens used with 34% involving total body irradiation.

Mortality at 30 days was 11%. Non-relapse mortality (NRM) at 1 year was 31% and 37% and 46% at 3 and 5 years, respectively. The incidence of relapse was 25% at 1 year and 34% at 3 years with no further relapses beyond 3 years. Progression free survival (PFS) at 1, 3 and 5 years was 44, 29 and 20% respectively whereas corresponding overall survival was 57, 47 and 37% respectively. The incidence of grade 2-4 acute graft versus host disease (GVHD) was 42% while chronic GVHD rates were 44% at 1 year and 50% at 3 and 5 years. Covariates associated with superior outcomes will be identified using Cox models.

**Conclusions:** In the setting of relapse after AutoHCT, RIC AlloHCT may result in long-term disease free survival in a significant subset of patients. The low incidence of late relapses suggests long term disease control from an allogeneic graft-vs-tumor effect. NRM and chronic GVHD rates remain limiting factors even with RIC regimens.

## 039 REDUCED INTENSITY ALLOGENEIC STEM CELL TRANSPLANTATION FOR MANTLE CELL LYMPHOMA: THE EBMT EXPERIENCE

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The role of reduced intensity allogeneic stem cell transplantation (RIST) in the management of mantle cell lymphoma remains controversial. We have conducted a retrospective analysis of 325 patients with MCL who have undergone a (RIST) between 2000 and 2008. 252 (78%) were male and the median age at transplant was 57 years (range 30-70). 193 (59%) of patients had received 3 or more lines of prior therapy and 153 (47%) had undergone a previous autologous SCT. The median time from diagnosis to transplant was 35 months (range 3-177). The disease status at transplant was; CR 123, PR 133, refractory disease/untested relapse 69. Conditioning for RIST was achieved with fludarabine+alkylating agent in 221, fludarabine+TBI in 77, and a variety of other RIST regimens in 27. Transplants were performed from 189 matched family donors, 113 matched unrelated donors and 23 mismatched donors. T cell depletion with either CAMPATH or ATG was performed in 162 transplants. Successful and durable engraftment occurred in 315 patients. Acute graft versus host disease (GVHD) developed in 170 patients and chronic GVHD developed in 111 of 261 patients surviving beyond 100 days. There were 104 transplanted related deaths with infection and GVHD accounting for the majority of these deaths. The resulting 100 day and 3 yr non-relapse mortality rates (NRM) were 12 and 34% respectively. NRM was associated with refractory disease at transplant (RR=1.9 p=0.005) use of an unrelated donor (RR=1.6 p=0.04) and T replete transplants (RR=1.7 p=0.009). One hundred patients relapsed at a median time of 8 months (range 1-52 months) post transplant. The cumulative incidence of relapse at 1 and 4 yrs was 24% and 36% respectively. Disease relapse was associated with refractory disease at transplant (RR=2.6 p<0.01) and T cell depletion of the graft with CAMPATH (RR= 2.5 p<0.01). The KM estimate of the PFS at 1 and 3 years was 49% and 32% respectively. PFS was significantly worse for patients with refractory disease (RR=1.9, p<0.01), 3 or more lines of prior therapy (RR= 1.5, p=0.01), use of an unrelated donor (RR=1.4 p=0.04) or those transplanted without ATG in the conditioning regimen (RR=1.4, p=0.02). The overall survival at 1 and 3 yrs was 62% and 44% respectively and was associated with refractory disease (RR 2.3,

$p < 0.001$ ). In summary RIST may achieve durable remissions in a significant number of patients even in those failing a prior autologous SCT. However outcomes are adversely affected by chemorefractory disease and use of an unrelated donor. Whilst T cell depletion protects against GVHD and NRM it is associated with a higher risk of relapse.

#### 040 ALLOGENEIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH RELAPSED OR CHEMOREFRATORY T-CELL LYMPHOMA: ROLE OF HIGH INTENSITY CONDITIONING

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**Introduction:** Patients with relapsed T-cell lymphoma carry a dismal prognosis. Emerging evidence suggests a role of allogeneic stem cell transplantation (SCT) in this situation.

**Patients and Methods:** Between 2003 and 2011, peripheral blood SCT from matched related (MRD, n=33) and matched unrelated (MUD, n=33) donors had been provided to 66 consecutive patients with refractory or relapsed aggressive T-cell malignancies, comprising cases of peripheral T-cell lymphomas not otherwise specified (PTCL NOS, n= 23), PTCL AILT (n=12), anaplastic large cell lymphoma (ALCL, n= 11), T-lymphoblastic lymphoma (T-LBL, n=6), T-prolymphocytic leukemia (T-PLL, n=7), CD4+/CD56+ blastic plasmacytoid DC neoplasm (DPCL, n=2), panniculitis like T-cell lymphoma (PLTCL, n=3), systemic progression of primary cutaneous T-cell lymphoma (CTCL, n=1) and NK/T-cell lymphoma (n=1). Preparatory therapy, in part within the DSHNHL R3 trial, consisted of high intensity conditioning, mainly the FBC-12 regimen (fludarabine 125 mg/m<sup>2</sup>, oral busulfan 12 or 8 mg/kg bw, cyclophosphamide 120 mg/kg body weight).

**Results:** Transplantation related mortality at day 100 occurred in 19/66 (29%) patients. After a median observation of 12 (range 1 to 86) months, 48% and 46% patients were alive and disease-free, respectively. Ten patients experiencing disease relapse received immunomodulatory treatment (WI, DLI), resulting in complete remission in five patients, partial remission in one patient and progressive disease in four patients. Immunomodulatory treatment was associated with graft-versus-host disease (GVHD) in all patients, leading to GVHD-associated deaths in CR in two patients. Three patients with relapse after allogeneic SCT achieved long-term remissions (> 12 months) by immunomodulatory therapy, two patients with T-PLL and one patient with ALCL.

**Conclusion:** Allogeneic PBSCT following high-intensity conditioning can induce durable disease remission in a significant proportion of patients with relapsed or refractory aggressive T-cell malignancies.

#### 041 HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR EXTRANODAL NK/T-CELL LYMPHOMA, NASAL-TYPE: THE JAPAN SOCIETY FOR HEMATOPOIETIC CELL TRANSPLANTATION (JSHCT) LYMPHOMA WORKING PARTY

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**Introduction:** Extranodal NK/T-cell lymphoma (ENKL) is a rare subtype of lymphoma with generally poor prognosis. The efficacy of hematopoietic stem cell transplantation (HSCT) for ENKL was examined using the Japan Society for Hematopoietic Cell Transplantation (JSHCT) registry database.

**Methods:** The Lymphoma Working Group of JSHCT surveyed the database and retrospectively analyzed. Of 11,267 transplants for all types of lymphoma, a total of 134 HSCT were conducted for 120 ENKL patients with sufficient data for analysis.

**Results:** There were 75 male and 45 female with a median age of 47 years (range: 18-70). The median follow-up length of survivor was 27 months. In total, 74 patients received allogeneic HSCT (60 with 1st SCT and 14 with 2nd SCT) and 60 received autologous PBSCT (Auto). The donor of allogeneic 1st SCT for was relatives in 27, unrelated bone marrow (UR-BM) in 10, and cord blood (CB) in 23. For 1st SCT, 63 patients were in complete response (CR) (41 Auto, 10 relative, 5 UR-BM, and 7 CB), 12 were in partial response (PR) (5 Auto, 4 relative, 1 UR-BM, and 2 CB), and 45 were on disease (14 Auto, 13 relative, 4 UR-BM, and 14 CB). Among patients who received SCT in CR, the 2-year overall survival (OS) was significantly better for those received autologous SCT ( $P=0.03$ ). In contrast, no difference was found among patients who received SCT in non-CR state ( $P=0.92$ ). The OS of patients who received 2nd SCT was 27% at a median follow-up of 18 months.

**Conclusion:** Although good patients were selected, autologous SCT is a preferred strategy for patients with ENKL who achieved CR. Any type of HSCT is a potential option for patients in non-CR. The 2nd SCT is beneficial for a part of patients.

Table. The 2-year OS for patients who received HSCT

	CR		Non-CR	
	N	2y-OS	N	2y-OS
Auto	41	87%	19	32%
Related	10	56%	17	33%
UR-BM	5	60%	5	40%
CB	7	48%	16	28%

#### 042 BENDAMUSTINE IN COMBINATION WITH FLUDARABINE AND RITUXIMAB: A PHASE I-II NOVEL NONMYELOABLATIVE CONDITIONING FOR ALLOGENEIC STEM CELL TRANSPLANTATION (AST) IN PATIENTS WITH LYMPHOID MALIGNANCIES

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**Background:** We have previously reported upon the use of fludarabine, rituximab and cyclophosphamide as a nonmyeloablative conditioning for lymphomas (Khouri et al, Blood; 111:5530). Bendamustine (Treanda), is a novel hybrid compound that combines the properties of an alkylating agent with those of a purine analog. In addition, bendamustine was found to be effective in pts who failed to respond to alkylating agents. In order to improve outcomes in AST, we substituted cyclophosphamide with bendamustine in the conditioning.

**Methods:** Bendamustine was given intravenously in an escalated dose of 70, 90, 110, 130 mg/m<sup>2</sup> daily on days -5 to -3 prior to transplantation, together with 30 mg/m<sup>2</sup> of fludarabine given on the same days. Rituximab was given at a dose of 375 mg/m<sup>2</sup> on day -13 and 1000 mg/m<sup>2</sup> on days -6, +1, and +8, as previously described. Tacrolimus and methotrexate was used for GVHD prophylaxis. In addition, thymoglobulin of 1 mg/kg was given on days -2, -1 in pts receiving an unrelated donor.

**Results:** The study included 16 pts [Mantle cell=5 (blastic =3), Follicular =4, CLL/Richter's=4, Large cell=3]. Median age was 58 (range, 30-70) years. Median prior treatments was 3 (range, 1-4). At transplant, 8 pts (50%) were in CR, 6 (37%) in PR, and 2 pts (13%) had stable disease. Peripheral blood was the source of graft in 15/16 pts. Twelve pts (75%) received their transplants from HLA-compatible siblings and 4 (25%) from unrelated donors. The number of pts who received the 70, 90, 110, 130 mg/m<sup>2</sup> daily doses of bendamustine were 2, 3, 3, and 8 pts, respectively. Nine pts (56%) did not nadir to an ANC < 500, and 13 (81%) did not experience a platelet count < 20,000/mm<sup>3</sup>. Median donor T cells at days 30 and 90 were 70% and 90%, respectively. Two pts developed acute GVHD (one had grade 1, one had grade II); two of 13 evaluable pts developed chronic GVHD. With a median follow-up time of 6 months (range, 3-20 months), the overall survival and progression-free survival rates were 87% and 78%, respectively. Fungal infection was the cause of the only death observed. The maximal grade of other observed toxicities was 3. No DLT was observed.

**Conclusions:** Our results represent the first report to suggest that combining bendamustine at a dose up 130 mg/m<sup>2</sup> daily x 3 days, together with fludarabine and rituximab is safe and constitutes a well tolerated conditioning for AST. We are treating pts with this regimen in the outpatient setting. The study is currently ongoing to verify its safety and assess its efficacy in a larger cohort of pts.