Table. (*Continued*)

	HCT (79 pts)	No HCT (38 pts)	P-value logistic regression
Unfavorable cytogenetics (n)	30 (37%)	7 (18%)	0.18
Secondary AML (n)	39 (49%)	15 (39%)	0.32
Early relapse (n) (>5% marrow blasts within 4.9 months of CR1 (range 0.9-10, median 3.75)	0 (0%)	13 (34%)	<0.001

Twenty-four of the 38 (63%) non-HCT patients were HLA-typed and matched donors were found for 13 of these 24 patients (54%; 5 related, 8 unrelated). Seven of the 14 non-typed patients (50%) had financial barriers or refused HLA-typing. Only 2 of these 38 (5%) received HCT beyond CR1.

Conclusion: These data suggest that HCT can be performed in CR1 in the majority of high-risk AML patients in whom it is currently recommended. Patients in whom HCT is not done are characterized by a poorer performance status (but not older age) and by early relapse. In the absence of these 2 factors, >75% of patients with high-risk AML under the age of 75 can receive HCT in CR1. A national study is planned to assess the extent to which these results can be generalized.

229

CLINICAL TRIAL EVALUATING DC/AML FUSION CELL VACCINATION ALONE AND IN CONJUNCTION WITH PD-1 BLOCKADE IN AML PATIENTS WHO ACHIEVE A CHEMOTHERAPY-INDUCED REMISSION

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A promising area of investigation in AML is the development of cancer vaccines that educate host immunity to target leukemia cells, including the stem cell compartment. Our group has developed a cancer vaccine in which dendritic cells (DCs) are fused to autologous tumor cells, resulting in the presentation of multiple tumor antigens and eliciting a broad immune response. A challenge to developing a more effective tumor vaccine is overcoming inhibitory pathways, including the PD1/PDL1 pathway, contributing to tumor-mediated immune suppression. We are conducting a clinical trial in which AML patients who are in remission following chemotherapy receive three monthly doses of DC/AML fusion cells alone (cohort 1) or in conjunction with anti-PD1 antibody, CT-011 (cohort 2). To date, 21 patients (mean age 57 years) have been enrolled. Patients underwent tumor collection from either bone marrow (N = 14), 20 cc of peripheral blood (N = 5), or leukapheresis product (N = 2). The mean tumor yield and viability was $8.43x10^8$ cells and 99% respectively. Patients achieving remission following chemotherapy underwent leukapheresis for DC generation. Adherent peripheral blood mononuclear cells were cultured in the presence of GM-CSF and IL-4 for 5-7 days, and exposed to TNFα for 48 hours to generate mature DCs. One patient died during induction chemotherapy, one patient did not collect a sufficient number of tumor cells for vaccine generation, and 3 patients were removed from study to undergo allogeneic transplantation. Vaccine was generated in 12 patients at a dose of $5x10^6$ fusions cells, mean fusion efficiency of 31%, and viability of 87%. As a measure of their activity as antigen presenting cells, the capacity of fusion cells to stimulate allogeneic T cell proliferation ex vivo was quantified. In contrast to the leukemia cells (mean stimulation index (SI) 4.4), the DC and fusion cells were potent stimulators (mean SI 24.1 and 15.5, respectively). Vaccination was initiated within 12 weeks from count recovery following completion of chemotherapy. 4 patients have completed vaccinations, and 3 are undergoing vaccination. Vaccine related adverse events included vaccine site reactions, ankle pain and edema. Biopsy of a vaccine site reaction demonstrated a dense T cell infiltrate. Peripheral blood is being collected prior to and serially following vaccination. Immune response targeting leukemia cells, leukemic stem cells, and leukemia associated antigens will be assessed.

230

EARLY RESULTS OF A PHASE II STUDY ADDING PERI-TRANSPLANT RITUXIMAB TO NONMYELOABLATIVE CONDITIONING AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) FOR PATIENTS (PTS) WITH HIGH-RISK FLUDARABINE-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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CLL pts who are fludarabine-refractory or possess unfavorable cytogenetics have short survivals with conventional therapies. Nonmyeloablative allogeneic HCT may provide long-term disease control. Disease progression is the major risk within the first year after HCT (median 3.3 months), until development of graft-versus-leukemia (GVL) effects. Treatment with anti-CD20 monoclonal antibody (rituximab) in the early post-transplant period could improve disease control: 1) directly by antibody-dependent cytotoxicity and 2) indirectly by promoting cross-presentation of cell-derived peptides causing earlier and/or more robust GVL effects. To date, 20 pts have been enrolled on a phase II trial comprising fludarabine, 30 mg/m^2 (days -4, -3, and -2) and 2 Gy total body irradiation (day -1) together with rituximab, 375 mg/m^2 (days -3, +10, +24, and +38). Grafts were from HLA-matched related (n = 6) or unrelated (n = 14) donors. Median age was 61 (range 37-74) years. Pts were older, had higher comorbidity scores, more frequently received unrelated grafts, and more frequently had unfavorable cytogenetics compared to a historical control group of 128 pts treated with the same regimen except for peri-transplant rituximab (Table).

Table. Comparison of Pre-transplant Characteristics Among Pts Treated with Nonmyeloablative Conditioning and Allogeneic HCT Either With (n = 20) or Without (n = 128) Rituximab

		No Rituximab (n = 128), n (%)	Rituximab (n = 20), n (%)	p
Age, years	≥60	32 (26%)	14 (70%)	0.0001
	0	51 (32%)	2 (10%)	
HCT-CI scores	1-2	42 (37%)	7 (35%)	0.05
	≥3	35 (31%)	11 (55%)	
Response to last treatment prior to HCT	Relapse/ refractory	73 (57%)	12 (60%)	0.80
	CR or PR	55 (43%)	8 (40%)	
Fludarabine-refractory	Yes	117 (91%)	20 (100%)	0.17
Lymph node size ≥5 cm	Yes	33 (26%)	6 (30%)	0.69
Campath within 12 months prior to HCT	Yes	30 (23%)	5 (25%)	0.88
Donor type	Unrelated	55 (43%)	14 (70%)	0.02
Chromosomal abnormalities	Unfavorable*	50 (64%)	19 (95%)	0.0002
	Favorable†	78 (36%)	1 (5%)	

*Includes deletion 17p, P53 mutation, deletion 11q23, or more than 3 cytogenetic abnormalities.
†Includes deletion 13q, normal chromosomes, and triosomy 12.

After a median follow up of 13.6 (range: 3.4-26.5) months following HCT, none of the 20 pts have experienced progression or

relapse. Five pts have died (median 9 months), 2 from graft-versus-host disease (GVHD), 2 infections, and 1 elected Hospice care after experiencing renal failure. Last disease responses were complete remission (n = 8), partial remission (n = 6), stable disease (n = 5), not-evaluated (n = 1). The incidences of grades II and III-IV acute GVHD were 60% and 15% respectively, and chronic GVHD was 46% at 1-year. Estimated 1-year rate of non-relapse mortality (NRM), relapse, progression-free (PFS), and overall survivals (OS) were 33%, 0%, 67%, and 67% respectively. Patients receiving peri-HCT rituximab had lower HR for relapse (HR:0, p = 0.001), comparable HR for NRM (HR:1, p = 0.9) and OS (HR:0.7, p = 0.45), and a trend for lower HR for PFS (HR:0.5, p = 0.07) compared to the historical control group. At day 84, median CD3 chimerisms were 99% *vs* 95% (p = 0.08), respectively.

After adjusting for the previous 4 significant covariates, PFS was better (HR:0.4, p = 0.04) among the rituximab group. Peri-transplant rituximab is a promising addition to nonmyeloablative HCT and may decrease early disease progression by allowing the generation of potent GVL effects.

231

LEUKEMIC TRANSFORMATION OF PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS: RESULTS OF A TREATMENT ALGORITHM EMPLOYING ALLOGENEIC TRANSPLANTATION USING RELATED AND UNRELATED DONORS

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Leukemic transformation (LT) is a rare but fatal complication of Philadelphia-negative myeloproliferative neoplasms (MPNs) for which optimal treatment strategies are not known. LT is generally considered incurable with induction chemotherapy alone.

At our centre, we have adopted a treatment strategy for LT where patients within the transplant age group who have a reasonable fitness level are offered induction therapy. Subsequently, those who achieve complete remission (CR/CRi) or revert back to a chronic MPN (cMPN) state are considered eligible for allogeneic transplantation (allo-SCT) if a suitable related or unrelated donor is available. Alternatively, those who are not candidates for the aforementioned strategy are offered supportive therapy including clinical trials.

We evaluated clinical outcomes of this treatment approach in 75 patients with LT diagnosed between 1998 and 2011. Prior to LT, MPN diagnoses were: PV, 16%; ET, 16%; primary MF, 28%; post-PV/ET MF, 25%; and MPN-U, 15%. 39 (52%) patients were treated with curative intent (induction chemotherapy +/- allo-SCT) while the remainder were treated with non-curative intent. At the time of LT, the curative intent cohort differed from the non-curative group in terms of median age (57 vs. 72 yrs, P<0.0001), performance status (ECOG≤1 in 92% vs. 58%, p = 0.001), serum albumin (38 vs. 35 g/L, p = 0.008) and the frequency of normal cytogenetics (47% vs. 20%, p = 0.03) respectively.

Among all patients, the 2-year overall survival (OS) from the time of LT was 15%. Outcomes were significantly improved in individuals treated with curative vs. non-curative intent (2-year OS, 25% vs. 4%, P< 0.0001). Among the curative group, 30/39 achieved either CR (n = 19) or reversion to cMPN (n = 11). Suitable donors were identified for 24 (80%) of these responders and 17 (57%) underwent allo-SCT. Median time to transplant was 177 days. Survival of patients undergoing allo-SCT was significantly better compared to those who achieved CR/cMPN post-induction but were not transplanted (2-year OS, 46% (n = 17) vs. 15% (n = 13), P = 0.035). To avoid a time to transplant bias, a landmark analysis was done comparing survival between the transplant cohort and non-transplanted patients who survived at least 177 days (n = 13), and similar results were observed (2-year OS 46% vs. 15%, p = 0.035).

Our results demonstrate the curative potential of intensive induction therapy followed by allo-SCT in select patients with LT preceded by MPN.

232

LOW DAY 100 TRANSPLANT-RELATED MORTALITY (TRM) FOLLOWING CLOFARABINE (CLO) IN COMBINATION WITH CYTARABINE AND TOTAL BODY IRRADIATION (TBI), MYELOABLATIVE CONDITIONING (MAC) AND ALLOGENEIC STEM CELL TRANSPLANTATION (ALLOSCT) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS (CAYA) WITH POOR-RISK ACUTE LEUKEMIA

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Background: CAYA with ALL or AML in third complete remission (CR3), refractory relapse (RR) or induction failure (IF) have an extremely poor prognosis, <20% EFS (Gaynon, BJH, 2005, Wells et al, JCO, 2003). MAC prior to AlloSCT is associated with high TRM and is donor dependent: 5-20% for matched sibling, 10-40% for matched unrelated, and 20-52% for cord blood transplants. CLO, an inhibitor of DNA polymerase and ribonucleotide reductase, has been shown to be safe and induce durable remissions, both in conjunction with busulfan in poor-risk AML (Magenau et al., Blood, 2011) and with Melphalan in poor-risk hematologic malignancies in adults (van Besien et al, ASH,2009). CLO has significant activity in CAYA with relapsed ALL/AML (Jeha et al., JCO 2006,2009) and synergy with cytarabine (Faderl et al, Blood, 2005). We sought to determine safety, day-100 TRM, and overall survival (OS) of CLO, cytarabine and TBI followed by AlloSCT in CAYA with poor-risk ALL/AML.

Methods: This is an ongoing multi-center phase I/II trial of a novel conditioning regimen of CLO (dose escalation: 40mg/m^2 [n = 3], 46 mg/m^2 [n = 3], 52 mg/m^2 [n = 17]) x5d, sequential (4 hrs later) cytarabine 1000 mg/m^2 x6d and TBI (1200cGy) followed by AlloSCT from matched related or unrelated donors in CAYA with ALL/AML in CR3, RR or IF. Pts with unrelated grafts received R-ATG. GVHD prophylaxis consisted of tacrolimus and MMF (Bhatia/Cairo et al., BBMT, 2009). Kaplan-Meier method was used to determine the probabilities of engraftment, GVHD, TRM and OS.

Results: 23 pts, median age: 10.8 yrs (1.5-20.7); M:F: 17:6, ALL/AML: 20:3 (9 CR3, 3 RR, 11 IF), 9 related donors, 14 unrelated donors (8 BM/PBSCs, 6 UCB). Median TNC and CD34 dose was 4.76x10^8/kg and 4.84x10^6/kg for BM/PBSCs and 4.0x10^7/kg and 2.8x10^5/kg for UCB, respectively. Probabilities of neutrophil and platelet engraftment and grade II-IV aGVHD were 100%, 92.8% and 50.8%, respectively. All except one achieved 100% whole blood donor chimerism by day 30. CLO dose was tolerable at 52mg/m^2/d x5d without dose limiting toxicity. Probability of Day 100 TRM was only 5%. Probability of 1-yr PFS and OS were 45% (CI_{95}: 24-83%), and 44.6% (CI_{95}: 24-68%) respectively.

Conclusions: Preliminary results suggest this novel MAC regimen followed by AlloSCT is safe and well tolerated in CAYA with poor-risk ALL/ AML with CLO dose of 52 mg/m^2. Early results are encouraging with respect to low risk of day 100 TRM with this conditioning regimen in this poor-risk population.

233

OUTCOMES OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): IMPACT OF MYELOABLATIVE (MA) VS. REDUCED-INTENSITY CONDITIONING (RIC) REGIMENS, AND IMPACT OF TOTAL BODY IRRADIATION (TBI)-BASED MA VERSUS CHEMOTHERAPY (CT)-BASED MA CONDITIONING

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There has been a marked change in transplant approaches of the CLL patient. MA conditioning has been shown to provide high