A randomized phase II trial of tacrolimus, mycophenolate mofetil and sirolimus after non-myeloablative unrelated donor transplantation

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SUPPLEMENTAL DATA (ONLINE ONLY)

FOR

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LIST OF SUPPLEMENTAL ITEMS:

Supplemental Patients and Methods Information

Eligibility criteria

Included in this study were patients with advanced hematological malignancies treatable by allogeneic HCT who were >50 years old or if ≤50 years old were considered to be at high risk for regimen-related toxicity associated with a high-dose transplant. All donors were unrelated and had high-resolution typing for HLA-A, -B, -C, -DRB1 and -DQB1. Only donors who were matched at the allele level (10/10) or had no more than a single allele disparity for either HLA-A, -B, or -C were allowed.[1]

The hematological malignancies included were aggressive non-Hodgkin lymphomas (NHL); low-grade NHL with <6 months duration of complete remission (CR) between courses of therapy; mantle cell lymphoma; chronic lymphocytic leukemia (CLL) that did not meet the National Cancer Institute's Working Group criteria for CR or PR or relapse within 12 months after FLU or other nucleoside analogue-containing therapy, had failed FLU-cyclophosphamide-rituximab therapy, had 17p deletion or progressed to prolymphocytic leukemia (PLL) or T-cell CLL or PLL; Hodgkin lymphoma (HL) that had at least failed frontline therapy. Multiple myeloma (MM) that had failed prior chemotherapy and consolidation of chemotherapy by autografting prior to nonmyeloablative HCT was permitted. Chronic myeloid leukemia (CML) beyond first chronic phase, myelodysplastic syndrome (MDS) or myeloproliferative disease (MPD) after myelosuppressive therapy or HCT, or Waldenstrom's macroglobulinemia after failing two courses of therapy were also permitted. Finally, patients with AML, acute lymphoblastic leukemia (ALL), CML, MDS or MPD were allowed if they had <5% marrow blasts at time of transplant. Exclusion criteria are described in the online supplemental patients and methods section.

Patients were excluded from the trial if they were pregnant or breast-feeding; had rapidly progressing intermediate- or high-grade NHL unless in minimal disease state; chronic myelomonocytic leukemia, acute leukemia with blasts in the peripheral blood detected by standard pathology; central nervous system involvement refractory to intrathecal chemotherapy; infection with human immunodeficiency virus, bacterial, viral or fungal infections unresponsive to therapy; decompensated liver disease; lung carbon monoxide diffusion capacity (DLCO) < 40%, forced expiratory volume (FEV1) <40, or dependency on supplementary oxygen; symptomatic coronary artery disease or cardiac ejection fraction < 35%; poorly controlled hypertension; or a Karnofsky performance score < 60%.

Patient evaluations

Blood levels of tacrolimus and sirolimus were monitored on day 0 and twice weekly by immunoassay for the first month and then weekly until start of taper or discontinuation. For patients treated with sirolimus, serum triglyceride levels were measured every other week until day +56, then once per month until discontinuation of treatment. In these patients haptoglobin was also assessed every other week until day +56 and then as indicated, and schistocytes were assessed weekly until day +56.

Chimerism analysis was performed as previously described.[2] Peripheral blood $CD3^+$ T-cell chimerism studies were performed on days +28, +84 and +365; if the patient had <50% donor chimerism on day 28, additional analyses were performed on days +56 and +180. If the patient was not >95% $CD3^+$ T-cell donor chimerism at 1 year, analyses were repeated annually. Natural killer (NK) cell (CD56) and granulocyte (CD33) chimerisms were obtained on days +28 and +84, respectively. Full donor chimerism was defined as > 95% donor $CD3^+$ T-cells, and graft rejection was defined as the inability to detect at least 5% donor $CD3^+$ T-cells in peripheral blood. Detectable donor chimerism was considered evidence of engraftment.

Bone marrow aspirates were obtained for disease assessment on days 28 and 56 post-transplant, while aspirates and biopsies were assessed on days 84, 180, 1 year, 1.5 years and annually for 5 years as clinically indicated.

If there was evidence of persistent disease in presence of mixed chimerism or progression/relapse in the absence of GVHD on day 80 posttransplant, all immunosuppressive agents were rapidly tapered to allow GVT effects to occur. If no response was observed (20% increase in donor chimerism or development of GVHD) or the attending physician believed that patient required very aggressive therapy for rapidly progressive disease, patients were considered treatment failures and taken off protocol. In the event of GVHD standard recommendations for tacrolimus/prednisone were followed.

For the purpose of survival analysis, patients were followed past the time point of relapse or DLI. Toxicities were determined using the Common Toxicity Criteria, Version 2.0.[3]

All patients received standard prophylaxis against infections as previously published.[4] Diagnosis, clinical grading, and treatment of acute and chronic GVHD were performed by local investigators according to established criteria.[5,6] Tumor responses were assessed using standard criteria and PCR, cytogenetics, FISH and flow cytometric-based methods as appropriate.

Statistical analyses

Overall and progression-free survival was estimated by the Kaplan-Meier method. Cumulative incidences of relapse/progression, NRM, acute and chronic GVHD, use of systemic therapy, and infection were estimated by standard methods for competing risks. Cox regression analysis

incorporating competing risks when appropriate was used for comparative analysis of all time-to-event endpoints, and all comparative p-values for these endpoints were derived from hazard ratio (HR) analysis. Patients taken off protocol were censored for GVHD and use of systemic steroids in the analyses, while relapse/progression, NRM, overall and progression free survival were included for the entire follow-up period. Comparative analyses of chimerism and engraftment (ANC and platelet nadirs and number of days below threshold), and numbers of platelet and red blood cell infusions were by Kruskal-Wallis test. Comparative analyses of proportions of patients experiencing toxicity, and requiring G-CSF support, platelet transfusions, and red blood cell transfusions were by chi-squared test. All p-values are 2-sided and are not adjusted for multiple comparisons.

References for Supplemental Data

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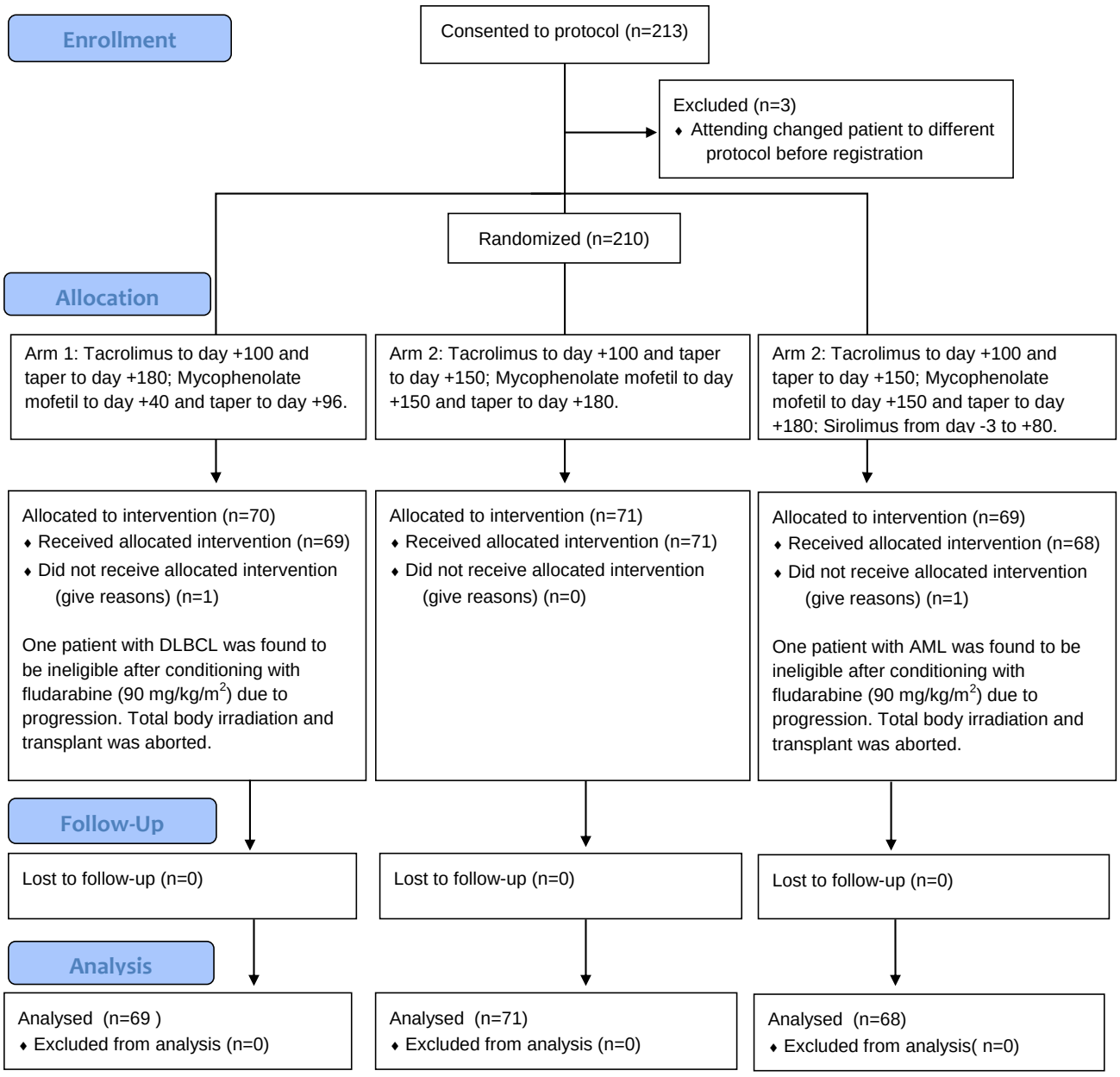
Supplemental Figure S1. Consort 2010 flow diagram



Supplemental Table S1. Participating transplant centers.

Participating Centers
Fred Hutchinson Cancer Research Center*
Rocky Mountain Cancer Center
Rigshospitalet
Emory University
Medical College Wisconsin
University of Tübingen Medical Center
University of Utah Medical Center
University of Leipzig
VA Puget Sound Health Care System/FHCRC
LDS Hospital
University of Cologne

***Coordinating center**

Supplemental Table S2. Acute GVHD organ staging and biopsy confirmation

	Arm 1 (n=69)	Arm 2 (n=71)	Arm 3 (n=68)
Overall Grade			
0	19 (28%)	28 (39%)	34 (50%)
1	6 (9%)	9 (13%)	2 (3%)
2	35 (51%)	24 (34%)	23 (34%)
3	8 (12%)	10 (14%)	9 (13%)
4	1 (1%)	0	0
Skin Stage			
0	36 (52%)	37 (52%)	60 (88%)
1	10 (14%)	11 (15%)	3 (4%)
2	8 (12%)	9 (13%)	3 (4%)
3	15 (22%)	14 (20%)	1 (1%)
4	0	0	1 (1%)
Gut Stage			
0	34 (49%)	46 (65%)	36 (53%)
1	26 (38%)	15 (21%)	23 (34%)
2	4 (6%)	6 (8%)	7 (10%)
3	4 (6%)	2 (3%)	1 (1%)
4	1 (1%)	2 (3%)	1 (1%)
Liver Stage			
0	69 (100%)	71 (100%)	68 (100%)
Grade 2-4 Biopsy Confirmed	72%	71%	88%

Supplemental Table S2. Toxicities in the treatment arms according to the Common Toxicity Criteria.

	Arm 1 (n=69)				Arm 2 (n=71)				Arm 3 (n=68)				
	Maximum grade				Maximum grade				Maximum grade				P*
Toxicity (no.)	1	2	3	4	1	2	3	4	1	2	3	4	
Renal	7	3	1	0	3	4	2	0	9	6	5	1	0.08
Hepatic	2	0	2	0	0	2	2	0	1	1	1	0	0.83
Gastrointestinal	0	3	8	1	2	3	4	0	2	4	6	0	0.31
Constitutional symptoms	0	3	1	0	0	0	2	0	0	1	1	0	0.80
Cardiac	0	0	7	0	1	1	0	4	0	0	3	2	0.60
Pulmonary	0	0	5	1	0	2	5	4	0	1	4	3	0.74
Coagulation	0	0	0	0	0	0	0	0	1	0	0	1	0.36
Hemorrhagic	0	0	1	0	0	0	1	0	0	0	1	0	0.99
Metabolic/laboratory	0	1	1	0	1	0	1	0	2	1	1	0	0.99
Infection/neutropenia	0	0	0	0	0	0	3	2	0	1	1	2	0.09
Neurology	0	2	4	0	0	1	1	0	0	1	6	0	0.14
Dermatology	1	1	0	0	0	2	0	0	0	0	1	0	0.36
Pain	1	0	1	0	0	0	1	0	0	0	0	0	0.61
Musculoskeletal	0	1	0	0	0	0	2	0	0	0	0	0	0.14
Any (except blood/marrow)	5	4	22	2	4	7	12	7	8	5	18	5	0.54

* P-value for comparison of proportion of patients with grade 3-4 toxicity among arms.