Intensified conditioning with high-dose total marrow irradiation and myeloablative chemotherapy reduces risk of relapse without increasing toxicity in allogeneic hematopoietic stem cell transplant for high-risk myeloid malignancies: a phase II study

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Supplemental Methods

Other eligibility criteria

Other criteria for the enrollment of patients were according to standard eligibility criteria for myeloablative HSCT: patients must have had a Karnofsky performance score >80, left ventricular ejection fraction > 50%, bilirubin <2x upper limit of normal, liver enzymes < 2.5x the upper limit of normal, creatinine clearance of >30mL/min, diffusing capacity of the lungs for carbon monoxide (DLCO) >50% of predicted, forced expiratory volume (FEV1) >50% of predicted, and forced vital capacity (FVC) >50% of predicted (after correction for hemoglobin).

Donors

All donors received granulocyte colony-stimulating factor at 10 to 12μg/kg subcutaneous daily for 5 days before peripheral blood stem cell collection. Patients and donors were matched at HLA-A, B, C, DR and DQ by low resolution (related) or high resolution (unrelated) molecular typing. Peripheral blood stem cells were obtained from HLA-matched related, matched unrelated or 1-antigen mismatched unrelated donors.

Busulfan administration

Busulfan was administered on days -5 to -2 at varying doses to target the total AUC of 4800μM/min. Busulfan was administered intravenously at 3.2mg/kg on day -5 and -4, and pharmacokinetic (PK) study was obtained for the first dose with subsequent

adjustment of the final 2 doses on days -3 and -2. If unable to obtain PK, busulfan was administered at 3.2mg/kg daily on days -5 to -2.

Graft-Versus-Host-Disease

All patients received GVHD prophylaxis with standard methotrexate and tacrolimus. Methotrexate was administered on day 1 at 10mg/m2 and on days 3, 6 and 11 at 5mg/m2. Tacrolimus was started on day -2 and tapered starting on day 180, as long as the patient did not show any signs of GVHD, in which case tacrolimus was continued at the treating physician's discretion. Patients receiving allografts from unrelated donors or related donors with 1 antigen mismatch also received rabbit anti-thymocyte globulin (rATG; Thymoglobulin, Genentech, Cambridge, MA) at 0.5mg/kg intravenously on day -3 and 2mg/kg on days -2 and -1 (total 4.5mg/kg). Standard grading systems were used for acute and chronic GVHD evaluation[1,2].

Supportive Care

Patients received levofloxacin, acyclovir, and fluconazole once neutropenic or starting on day 5. Levofloxacin was continued for the duration of neutropenia. Fluconazole was continued until day 30 and acyclovir was continued until day 180. Pneumocystis prophylaxis was done from day 30 to day 180 with sulfamethoxazole-trimethoprim, dapsone or pentamidine. Cytomegalovirus monitoring was performed routinely per our institutional protocol, and treatment was started preemptively. Granulocyte-colony stimulating factors were not permitted.

Toxicity and Engraftment Measurement

Acute toxicities were graded by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[3]. Neutrophil engraftment was defined as the first day of absolute neutrophil count (ANC) >500/mm^3 for three consecutive days. Platelet engraftment was defined as the first day of platelet count sustained >20,000/mm^3 for 3 consecutive days without transfusions in the preceding 7 days.

Study Endpoints and Statistical Analysis

Medians were used to report numerical variables and percentages were used for categorical variables. Survival curves were estimated using Kaplan-Meier methods for DFS, OS, GRFS and RR. All analyses were performed using GraphPad Prism version 9 (GraphPad, San Diego, CA, USA).

Table S1. Non-infectious organ toxicities of 30 patients with high-risk myeloid malignancies undergoing HSCT with FluBu4/TMI conditioning.

	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal tract				
Mucositis	2 (7%)	10 (33%)	15 (50%)	2 (7%)
Nausea/vomiting	16 (53%)	9 (30%)	3 (10%)	-
Diarrhea	17 (57%)	11 (37%)	2 (7%)	-
Transaminitis	-	-	3 (10%)	-
Bilirubinemia	-	-	2 (7%)	-
Diverticulitis	-	1 (3%)	-	-
Enterocolitis	-	2 (7%)	-	-
Esophagitis	-	1 (3%)	-	-
Rectal Ulcers	-	1 (3%)	-	-
Pulmonary				
Pneumonitis	1 (3%)	-	-	-
Respiratory failure	-	-	-	1 (3%)
Cardiac				
Atrial Flutter	-	1 (3%)	-	-
Atrial Fibrillation	-	1 (3%)	1 (3%)	-
Genitourinary				
Acute kidney injury	1 (3%)	1 (3%)	-	1 (3%)
Hypernatremia	-	-	1 (3%)	-
Hyponatremia	-	1 (3%)	-	-
Testicular pain	-	1 (3%)	-	-
Menorrhagia	1 (3%)	-	-	-
Dermatologic				
Rash	-	3 (10%)	-	-
Hand-foot syndrome	1 (3%)	1 (3%)	-	-
Sacral decubitus ulcer	-	1 (3%)	-	-
Central nervous system				

Altered mental status	-	1 (3%)	-	-
Venous system				
Deep venous thrombosis	-	2 (7%)	-	-
Ocular				
Episcleritis	1 (3%)	-	-	-
Eye pain	1 (3%)	-	-	-

Table S2. Infectious complications of 30 patients with high-risk myeloid malignancies undergoing HSCT with FluBu4/TMI conditioning.

Documented infectious complications	
Clostridium difficile (%)	6 (20%)
Septic shock (%)	5 (17%)
Bacteremia (%)	5 (17%)
Fungal pneumonia (%)	2 (7%)
Bacterial pneumonia (%)	2 (7%)
Cellulitis (%)	2 (7%)
Oral herpes simplex (%)	2 (7%)
Urinary tract infection (%)	1 (3%)
Toxoplasmosis (%)	1 (3%)
Enterocolitis (%)	1 (3%)
Tinea cruris (%)	1 (3%)
Oral thrush (%)	1 (3%)
Upper respiratory infection (%)	1 (3%)
Diverticulitis (%)	1 (3%)

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