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# Fludarabine and cyclophosphamide provides a nonmyeloablative alternative conditioning regimen with low transplant-related mortality and control of high risk disease

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## ABSTRACT

Non-myeloablative allogeneic transplant (NMAT) has a curative potential for patients who are not myeloablative allogeneic transplant (MAT) candidates. We report a phase II trial of a NMAT regimen with cyclophosphamide and fludarabine in 40 patients; 21 of whom had a prior MAT. Day +100 and 1-year transplant-related mortality (TRM) post-NMAT were 13% and 34%, respectively. Day +100 and 1-year Overall/Progression-Free Survival (OS/PFS) were 80%/65% and 43%/25%, respectively. OS was higher in patients with KPS  $\geq$  90 and lower in recipient/donor CMV +/- vs. other combinations. FluCy has low TRM and is curative in about 20% of high-risk patients.

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## 1. Introduction

NMAT has emerged over the last 2 decades as a promising alternative with reduced TRM for patients who would otherwise not be eligible for MAT. Aggressive disease poses a challenge, while patients in complete remission (CR) at the time of transplant can benefit from NMAT [1,2]. We summarize our prospective phase II clinical trial of fludarabine and cyclophosphamide for NMAT, with a focus on evaluating the efficacy of NMAT in patients with high-risk/aggressive disease.

## 2. Methods

This prospective IRB-approved phase II trial enrolled 40 patients from 4/2002 to 12/2008 with hematologic diseases. Eligibility included: age 4–75 years; HLA-suitable donor, KPS  $\geq$  50, adequate organ function, no uncontrolled co-morbidity or infection, and ineligible for MAT.

### 2.1. Conditioning regimen and GvHD prophylaxis

Starting on day –5, fludarabine 25 mg/m<sup>2</sup>/d (actual body weight)  $\times$  5 doses and cyclophosphamide 50 mg/kg/d IV  $\times$  2 doses

(lesser of ideal or adjusted body weight) were given. For graft-versus-host disease (GVHD) prophylaxis, patients received methotrexate 5 mg/m<sup>2</sup> on day +1, +3, and +6, mycophenolate mofetil day –1 to +60, and tacrolimus starting day –1.

### 2.2. Cell dose and neutrophil recovery

Peripheral blood grafts had a minimum total cell dose of  $2 \times 10^6$  CD34+ cells/kg. Marrow grafts had a minimum of  $1 \times 10^8$  nucleated cells/kg. Absolute neutrophil count (ANC)  $> 500/\mu\text{L}$  for three consecutive days defined engraftment. Failure to engraft was no ANC recovery by day +45 post-NMAT. Platelet engraftment was defined as  $> 20,000/\text{mm}^3$  after 7 days with no platelet transfusions.

### 2.3. Response evaluations

Disease response was measured on or before Day +100. The Center for International Blood and Marrow Transplant Registry (CIBMTR) criteria defined remission, relapse and progression. Disease status pre-NMAT was defined using CIBMTR definitions of low, intermediate and high risk [3].

### 2.4. Statistical analyses

Sample size and power calculations were based on the primary endpoint: Day +100 TRM, defined as death due to any cause except underlying disease. The null hypothesis was Day +100

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**Table 1**  
Patient characteristics.

Variable	Total N=40
	n (%)
Gender	
Male	24 (60)
Female	16 (40)
Age (years)	
< 40	7 (18)
40–59	21 (53)
60–75	12 (30)
Diagnosis	
NHL	12 (30)
AML	10 (25)
HL	8 (20)
MDS	5 (13)
MM	2 (5)
ALL	2 (5)
PLL	1 (3)
Karnofsky Performance Score	
90–100	13 (33)
80	12 (30)
< 80	15 (38)
Disease status at BMT	
Complete remission	11 (28)
Primary induction failure/untreated	12 (30)
Relapse	17 (43)
Prior BMT	
No prior BMT	19 (48)
Autologous	19 (48)
Allogeneic	2 (5)
Hematopoietic cell source	
Peripheral Blood	37 (93)
Bone Marrow	3 (8)
GvHD prophylaxis	
FKMMF+/-MTX	38 (95)
FKMTX	2 (5)
Donor type	
Unrelated	25 (63)
Related	15 (38)
Gender matching	
Matched	23 (58)
Mismatched	17 (43)
HLA match	
Matched	28 (70)
Mismatched	12 (30)
Cytomegalovirus serology recipient/donor	
CMV+/+	13 (33)
CMV+/-	13 (33)
CMV--	10 (25)
CMV-/+	4 (10)
ABO matching	
Matched	20 (50)
Major Mismatch	10 (25)
Minor Mismatch	10 (25)
Ejection fraction pre-NMAT	
≥ 60%	23 (58)
< 60%	17 (43)
CIBMTR disease risk category	
High	26 (65)
Intermediate	8 (20)
Low	6 (15)

FK: tacrolimus; MTX: methotrexate; MMF: mycophenolate; CMV: cytomegalovirus.

HLA-match for sibling donors is 6/6 or 8/8, HLA-match for unrelated donors is 8/8 or 10/10.

HLA-mismatch for sibling donors is 7/8, HLA-mismatch for unrelated donors is 8/10, 9/10, or 11/12.

% May not add up to 100% due to rounding.

TRM=25%. A two-stage study design was used with early stopping rules for patient safety. The decision rules yielded a type I error rate=0.0933 and power=0.8709.  $P < 0.05$  was considered statistically significant, with  $P \geq 0.05$ –0.09 considered a trend.

Secondary outcomes included OS, PFS and toxicity. Survival was updated through November 2012. The Kaplan–Meier method was used to construct survival curves, and the log rank test was used to determine statistical significance. OS was measured from day 0 (HCT infusion) to death due to any cause or last follow-up (censor). PFS was calculated from day 0 until date of last follow-up (censor), or documented relapse/progression/death (events). SPSS<sup>®</sup> version 21 software was used for data analysis (IBM Corp., Armonk, NY).

### 3. Results

Patient characteristics are summarized in Table 1. Siblings were HLA-matched ( $N=14$ ) or 1-Ag mismatched ( $N=1$ ). Unrelated donors were HLA-matched ( $N=14$ ) or 1–2 antigen HLA-mismatched ( $N=11$ ). Median time to ANC recovery was 14 days (range 10–21); 3 died before neutrophil engraftment (Day +15, 27, 32) and there were no secondary graft failures. Median time to platelet recovery was 27 days (range 9–120); 7 patients did not nadir below 20,000/mm<sup>3</sup>.

#### 3.1. Treatment related mortality (TRM)

The observed cumulative incidence of TRM at Day +100 was statistically significantly lower than expected at 12.6% (95% CI 2–23%,  $P=0.03$ ). The causes of Day +100 TRM were infection ( $n=4$ ) and regimen-related toxicity ( $n=1$ ).

#### 3.2. Infections

Viral infections post-HCT were documented in 44% of patients ( $n=18$ ). Fungal infections were documented in 17% of patients. Two patients died of bacterial sepsis before engraftment (Day +15, 27).

#### 3.3. GvHD

Cumulative incidence of Grades II–IV acute GvHD by Day +100 was 35% (95% CI 20–51%). Cumulative incidence of extensive chronic GvHD at 1-year was 64% (95% CI 45–83%).

#### 3.4. Overall Survival (OS)

The median follow-up was 5 years (range 2–8 years). Day +100 OS was 80% (95% CI 68–92%); 1 year OS was 43% (95% CI 27–58%); 3 year OS was 19% (CI 7–31%).

The univariate analysis of factors associated with OS is in Table 2. Three pre-NMAT variables, recipient/donor CMV serological status, KPS and disease status were significantly associated with OS (Table 2, Figs. 1a and b), whereas age and donor relation/HLA match were not (Table 2, Fig. 1c).

#### 3.5. Progression free survival (PFS)

By Day +100, 21 (54%) patients achieved a complete remission (half of these later relapsed), 5 (12%) had a partial response (2 died of disease, 3 received other therapy and are all alive >4 years post-NMAT), 2 (5%) had stable disease (both later progressed and died 9 months and 3.8 years post-NMAT), 8 (20%) had progressed (all of whom died 3–38 days later), and 4 (10%) were not evaluable due to early TRM. Day +100 PFS was 64% (CI 49–78%); 1-year PFS was 27% (CI 13–40%); 3-year PFS was 17% (CI 5–28%). The univariate analysis of factors associated with PFS is summarized in Table 2, demonstrating only recipient/donor CMV serological status as significantly associated with PFS.

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