Combination of bendamustine and cyclophosphomide in graft-versus-host disease prophylaxis in refractory myeloid neoplasms: promising approach to augmentation of graft-versus-leukemia effect

Moiseev I.S., Vlasova Y.Y., Morozova E.V., Epifanovskaya O.S., Afanasyeva K.S., Beynarovich A.V., Zhogolev D.K., Kanunnikov M.M., Rogacheva Y.A., Rudakova T.N., Volkov N.P., Bondarenko S.N., Kulagin A.D.

RM Gorbacheva Research Institute, Pavlov University, Saint-Petersburg, Russian Federation

e-mail: moisiv@mail.ru

Introduction: Efficacy of salvage allogeinic hematopoietic stem cell transplantation (HSCT) in myeloid neoplasms not responding to chemotherapy and targeted therapies remains limited. Our group have recently demonstrated augmented graft-versus-leukemia (GVL) effect with substituting cyclophosphamide with bendamustine in graft-versus-host disease (GVHD) prophylaxis regimen (Moiseev et al., TCT, 2021). Nonetheless this original regimen was associated with significant toxicity due to poorly controlled cytokine release syndrome (CRS). To overcome this limitation we conducted a pilot single-center study of GVHD. prophylaxis with a combination of cyclophosphamide with bendamustine in refractory myeloid malignancies.

Patients and methods: The prospective (NCT04943757) Phase I single-arm study evaluated GVHD prophylaxis regimen consisting of bendamustine 50 mg/m2/day on days +3,+4, cyclophosphamide 25 mg/kg/day on days +3,+4 (PTCBCy), tacrolimus 0.03 mg/kg from day+5 to day+100 and mycophenolate mofetil 30 mg/kg/day on days 5-35. Patients received reduced intensity FB2 or FB3 conditioning according to performance status. Main inclusion criteria were: diagnosis of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) or blast crisis of chronic myeloid leukemia (CML) or other myloid neoplasms (MPN) with high tumor burden, no hematological response to previous therapies, absence of severe organ dysfunction. Thirty patients were included into the interim analysis. Median age was 42 years (range 18-69). AML was an indication for HSCT in 22, MDS in 6 and 2 patients had CML and MPN.were classified as salvage patients. 29% received myeloablative conditioning, 71% - reduced intensity (table 1).

Results: Median follow-up at the time of the analysis was 5 months (range 2-18). Engraftment was documented in 87% of patients. Median time to engraftment was 18 days (range 12-35). Complete response (CR) was achieved in 83% of patients and 73% were minimal residual disease (MRD)-negative. With the limited follow up overall survival was 67% (95%CI 43-82%), while event-free survival (including graft failure as event) was 36% (95%CI 14-58%) (figure A). Disease progression or relapse was the major cause of failure and was documented in 55% of patients (95%CI 26-76%). On the other hand, the combination regimen was associated with low toxicity and GVHD incidence. The cumulative incidence of Grade II-IV acute GVHD was 3% and observed in one patient. Additionally 5 patients had grade 1 acute GVHD. In lanmark analysis at 100 days the incidence of chronic GVHD was 24% (95%CI 5-50%). Chronic GVHD was manifested as liver overlap syndrome in the majority of these patients. CRS was documented in 20% of patients and only in 2 it was grade 4-5. Most common target of CRS was liver (in 17%) , pancreas (in 10%) and kidneys (7%) (Figure B). CRS was effectively controlled by tocilizumab, ruxolitinib and high dose steroids in all, but one patient. All CRS cases were associated with increased serum ferritin (median 26400 ng/ml, range 12570-206500). Non-relapse mortality was 7% (95%CI 1-19%). Preliminary flow cytometry analysis demonstrated the same pattern of early immunological recovery, preservation of central memory T-cells and induction of tolerance by PD-1L positive monocytes as in the single-agent bendamustine study (Figure C).

Table 1. Characteristics of patients and transplantations

Characteristic	% (n)
Diagnosis	
aCML	3% (1)
MDS	20% (6)
De novo AML	54% (16)
Secondary AML	20% (6)
CML	3% (1)
Type of donor	
Matched related	27% (8)
Matched unrelated related	50% (15)
Haploidentical	23% (7)
First allograft	90% (27)
Second allograft	10% (3)
Reduced intensity conditioning	77% (23)
Myeloablative conditioning	23% (7)
Previous induction courses, median (range)	2 (1-12)
Genetic abnormalities	
High-risk karyotype abnormalities	40% (12)
Complex karyotype	20% (6)
ASXL1	6% (2)
FLT3-ITD	23% (7)
KMT2A	3% (1)
TP53	3% (1)
Blast at transplantation, median (range)	12 (6-86%)

Figure A. Overall and event-free survival in the general group (left) and impact of donor type on event-free survival (right)

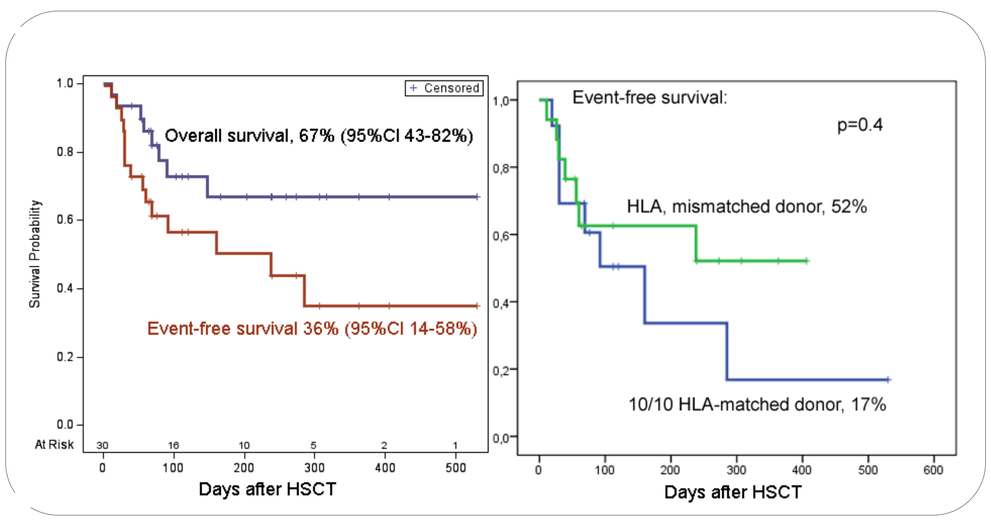


Figure B. Organ involvement in patients with CRS

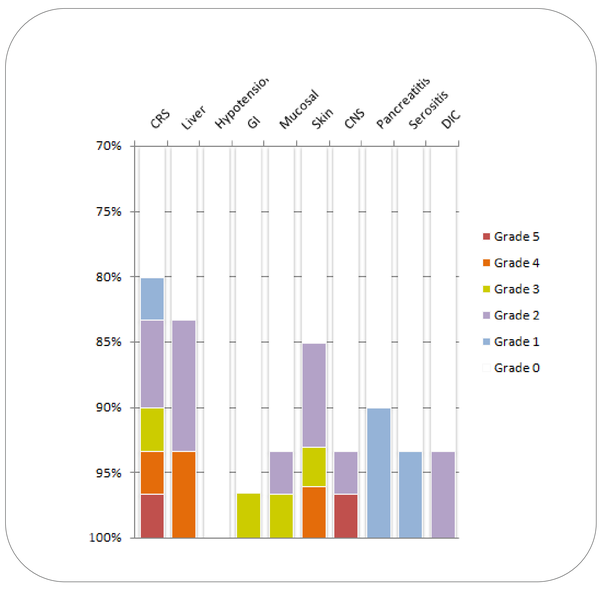
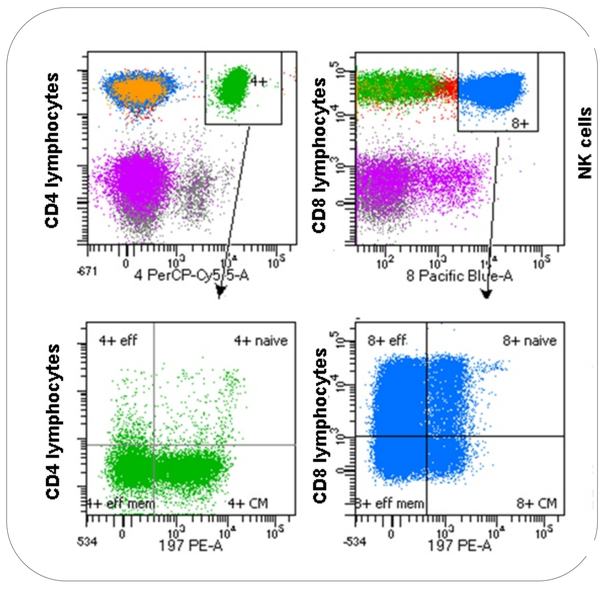


Figure C. Example of immunological recovery



Conclusion: This pilot trial demonstrated that PTBCy combination prophylaxis provides the level of safety compared to conventional GVHD prophylaxis regimens with maintenance of GVL patterns. The study continues enrollment of patients.

Disclosure
The authors declare no conflicts of interest.