GvHD Prophylaxis

Prophylaxis of graft-versus-host disease (GvHD) with sirolimus plus cyclosporine, and mycophenolate mofetil

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GvHD is a severe complication of allogeneic hemopoietic stem cell transplantation (allo-HSCT) and is associated with high non-relapse mortality. The risk of developing GvHD is enhanced with minimum-intensity conditioning using non-myeloablative regimen consisting of fludarabine and low-dose total body irradiation before HSCT.[1] Calcineurin inhibitor and mycophenolate mofetil are used as standard immunosuppression after grafting; however, the rates of acute GvHD (aGvHD) remain high. Therefore, a new approach is needed to improve the prevention of aGvHD, especially after HSCT from mismatched unrelated donors.

On 24 June 2019, Brenda Sandmaier from the Fred Hutchinson Cancer Research Center, Seattle, WA, US and colleagues, published in Lancet Haematology results from a multicenter randomized phase III clinical trial evaluating the use of sirolimus, cyclosporine, and mycophenolate mofetil (CMMS) for prevention of GvHD (NCT01231412).[2] The study aimed to confirm previous findings of the lower incidence of aGvHD in patients receiving CMMS compared to standard treatment alone. It also evaluated the immunomodulatory effect of the combination after a longer treatment of 180 days instead of 80 days.[3]

Study design and patient characteristics

- Patients with advanced hematological malignancy suitable for allogeneic-HSCT, with Karnofsky score ≥ 60 and aged ≥ 50 years were randomly assigned to one of the study arms
  - standard GVHD prophylaxis with cyclosporine and mycophenolate mofetil (CMM) or
  - combination of cyclosporine and mycophenolate mofetil, with sirolimus (CMMS)
- All patients received fludarabine (30 mg/m² per day) 4, 3, and 2 days before total body irradiation (2 or 3 Gy) on the day of HSCT
- Donors were unrelated and high-resolution matched for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 at the allele level or mismatched at no more than a single allele for HLA-A, HL-B or HLA-C
- Peripheral blood stem cells for the graft transplant were mobilized by granulocyte colony-stimulating factor (10 µg/kg)
- Patients were treated with
  - Cyclosporine - 5 mg/kg twice daily starting 3 days before HSCT, and in the absence of GvHD tapered from day 96 to day 150
    - CMM group - 400 ng/mL for the first 28 days and thereafter 150–350 ng/mL
    - CMMS group - 350 ng/mL for the first 28 days and thereafter at 120–300 ng/mL
  - Mycophenolate mofetil - 15 mg/kg three times daily from day 0–30,
    - CMM group – followed by twice daily until day 150, and in the absence of GvHD tapered off by day 180

- CMMS group – followed by twice daily until day 40

- Sirolimus - 2 mg once daily starting from three days before HSCT, then maintained at 3–12 ng/mL to day 150, and in the absence of GvHD tapered off by day 180

Table 1. Selected patient characteristics.

Characteristics	CMM	CMMS
Age (years)	61 (53–67)	63 (58–68)
Sex		
Female	27 (35%)	28 (31%)
Male	50 (65%)	63 (69%)
Donor age (years)	26 (22–34)	25 (22–35)
Sex of patient /donor		
Male/female	23 (30%)	12 (13%)
Other combination	54 (70%)	79 (87%)
Previous CMV infection of patient/donor (%)		
Negative/negative	16 (21%)	37 (41%)
Positive/positive	26 (34%)	17 (19%)
Previous high-dose (%)		
Autologous	19 (25%)	37 (14%)
Allogeneic	4 (5%)	0

Time from first transplantation (days)	297 (93–1188)	94 (75–552)
Disease histology		
Acute myeloid leukemia	25 (32%)	41 (45%)
Myelodysplastic syndrome	14 (18%)	15 (16%)
Chronic myeloid leukemia	1 (1%)	1 (1%)
Acute lymphoblastic leukemia	6 (8%)	9 (10%)
Non-Hodgkin lymphoma	12 (16%)	15 (16%)
Chronic lymphocytic leukemia	9 (12%)	5 (5%)
Hodgkin lymphoma	2 (3%)	0
Multiple myeloma	8 (10%)	4 (4%)
Relapse risk (Kahl) (%)		
Low	20 (26%)	30 (33%)
Standard	47 (61%)	46 (51%)
High	10 (13%)	15 (16%)
Donor recipient ABO match		
Match	41 (53%)	44 (48%)
Major mismatch	15 (19%)	28 (31%)
Minor mismatch	19 (25%)	18 (20%)

CMV, cytomegalovirus;

The cumulative incidence of grade 2–4 aGVHD at day 100 post-transplant was a primary endpoint of the study. Secondary endpoints included overall survival (OS), progression-free survival (PFS), non-relapse mortality defined as the time from transplantation to death without progression/relapse of the malignant disease, and a cumulative incidence of grade 3–4 acute and chronic GvHD (cGvHD).

Results

The Data and Safety Monitoring Board halted the trial early after 168 patients received the allocated intervention, because of a significant survival advantage among patients in the triple-drug group. For safety and efficacy analysis data from 77 patients in the CMM group and 90 in the CMMS group was included. Median follow up was 48 months (31-60), during which all but 2 patients from the CMM arm had sustained engraftment.

The cumulative incidence of grade 2–4 aGvHD at day 100 was significantly lower with CMMS compared with the standard therapy group (26% and 52% respectively; HR 0.45, 95% CI 0.28–0.73, *p*=0.0013). Moreover, the incidence of aGVHD of skin was significantly lower amongst patients receiving CMMS (18% *vs* 55%, *p*< 0.0001). However, there were no significant differences in the incidence of grade 3–4 acute and cGvHD were observed between treatment groups. Although a similar proportion of patients experienced cGvHD in both groups, more patients in the CMM group progressed from aGvHD into cGvHD compared to the CMMS group (64% and 28% of patients respectively).

Table 2. Non-relapse mortality (NMR) and survival data at 1 and 4 years.

	CMMS		CMM	
	At one year	At four year	At one year	At four year
NMR	4%	16%	16%	32%
PFS	77%	64%	59%	41%
OS	86%	70%	64%	46%

The efficacy data presented in Table 2 demonstrate lower non-relapse mortality in the CMMS group compared to CMM which was mainly related to GvHD (HR 0.48, 95% CI 0.26–0.90, *p*=0.021). Overall, non-relapse mortality was four-fold lower in the CMMS group (8% *vs* 32%). Patients receiving CMMS had also increased PFS compared to those on standard CMM therapy. Overall survival was also enhanced in patients receiving sirolimus in addition to the standard therapy (HR 0.62, *p*=0.035). There were no differences in the frequency of relapse or progression between study groups at 1 year or 4 after HSCT.

There were no significant differences in the frequency of non-haemopoietic toxic effects by day 100 post-transplantation (25% in the CMMS group *vs* 34% in CMM group; HR 0.84; *p*=0.52). The Grade 3 and 4 adverse events are presented in Table 3. Moreover, the cumulative incidence of bacterial infections (45% in the CMMS group and 37% in the CMM group, HR 1.05; *p*=0.81), fungal infections (12% *vs* 18%, HR 0.77; *p*=0.48), and viral infections (29% *vs* 41%, HR 0.64; *p*=0.05) at 1 year was

similar between the study groups. The CMV reactivation or CMV infection up to 1 year after transplantation was less common in the CMMS group (38%, 95% CI 25–51 in CMMS *vs* 69%, 95% CI 57–81 in the CMM group; HR 0.35 (0.21–0.60), *p*=0.0001).

Table 3. Adverse events (AEs).

	CMM (n=77)		CMMS (n=90)	
	Grade 3	Grade 4	Grade 3	Grade 4
Renal and urinary disorder	6 (8%)	0	9 (10%)	0
Hepatic	9 (12%)	1 (1%)	3 (3%)	1 (1%)
Gastrointestinal	3 (4%)	0	1 (1%)	1 (1%)
Cardiac	6 (8%)	0	1 (1%)	1 (1%)
Pulmonary	5 (6%)	3 (4%)	5 (5%)	5 (6%)
Coagulation	2 (3%)	0	1 (1%)	0
Blood and lymphatic system	3 (4%)	0	0	0
Neurology	2 (3%)	0	1 (1%)	0
Dermatology	1 (1%)	0	0	0

Conclusions

The addition of sirolimus to CMM for aGvHD prophylaxis significantly reduced the cumulative incidence of aGvHD and consequently significantly improved OS and PFS when compared to standard treatment with CMM alone. Therefore, based on these results, the CMMS combination should be used as GvHD prophylaxis regimen for patients treated with non-myeloablative conditioning and mismatched unrelated donor HSCT.

Although, there were imbalances in baseline characteristics between study groups in female donor to male patient recipient sex mismatch, patient/donor CMV seropositivity, previous HSCT, and Kahl risk group, adjustment for these factors did not alter HR results or conclusions made from the unadjusted results.

References

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