aGvHD

BMT CTN 1501: Sirolimus versus prednisone for initial treatment of acute GvHD

Emily Smith | Jan 30, 2020

High-dose corticosteroids, such as prednisone, are currently standard-of-care treatment for acute graft-*versus*-host disease (GvHD, aGvHD). However, these are only effective in around 50% of patients and cause toxic side effects. The use of clinical and blood biomarker-based tools to estimate severity of GvHD, risk of mortality and response to steroid treatment helps to identify a population of patients with standard risk (SR) GvHD who may be able to receive novel, reduced intensity treatments.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), was funded by the National Heart, Lung and Blood Institute and National Cancer Institute to develop risk-adapted aGvHD therapy trials using clinical and biomarker analyses. The BMT CTN 1501 trial (NCT02806947) was a phase II, multicenter, open-label, randomized trial designed to evaluate the difference in Day 28 complete response (CR)/partial response (PR) rates between sirolimus and prednisone treated patients with SR aGvHD. A key secondary endpoint was Day 28 CR/PR rate with a prednisone dose ≤ 0.25mg/kg/day. Other secondary outcome measures included further efficacy measures, toxicity, potential steroid-sparing effects of sirolimus, long-term outcomes and patient quality-of-life (QoL).

The primary results of the BMT CTN 1501 study were presented by Joseph A. Pidala, H. Lee Moffitt Cancer Center and Research Institute, Tampa, US, during the 2019 TCT Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR. This article summarizes the final results from the trial which were published in January 2020 in Blood.

Clinical and biomarker analysis

- Minnesota (MN) GvHD risk score:
  - Combines aGvHD organ involvement and severity
  - Defines SR and high-risk (HR)
- Ann Arbor (AA) biomarker risk score:
  - Serum biomarker analysis of:
    - Regenerating islet-derived 3-α (REG3)
    - Suppression of tumorigenicity 2 (ST2)
  - Provides a score from 1–3
    - Higher scores indicate a higher risk of mortality
  - In the BMT CTN 1501 trial, an overall SR status was defined as MN-SR and AA1/2

Study design

Patients (n= 127) with MN-SR aGvHD, not previously treated with systemic aGvHD therapy, were enrolled and randomized 1:1 to sirolimus or prednisone (based on MN score only). Biomarker analysis was subsequently conducted and 122 patients with AA1/2 status were included in the primary analysis, whilst five patients with AA3 or missing AA status were excluded.

Consort diagram

Given as number of patients treated with prednisone vs sirolimus

- Randomized: 67 *vs* 60
  - Did not receive study drug: 1 *vs* 7
  - Withdrew consent during study: 1 *vs* 5
- Completed one-year follow-up/died: 66 *vs* 55
  - Died on study: 20 *vs* 13
- Included in primary analysis (MN-SR *and* AA1/2): 64 *vs* 58

Dosing schedule

- Sirolimus: tablet or oral solution
  - Loading dose: 6mg orally if aged > 12 years or 5mg/m^2 if aged ≤ 12 years
  - Maintenance until aGvHD resolution: 10–14ng/mL
  - Post-aGvHD resolution, until at least Day 56: 5–10ng/mL
  - A taper schedule was provided so that patients would have discontinued sirolimus by three months from Day 56
  - Fourteen patients randomized to sirolimus did not complete 56 days as planned, most commonly due to aGvHD progression or flare (n= 6)
  - Twenty-three patients in the sirolimus group received systemic steroids following treatment with sirolimus within the first 56 days of follow-up. The initial response to sirolimus in these patients varied
- Prednisone: 2mg/kg/day for at least three days
  - Suggested taper schedule was provided allowing patients with treatment responsive GvHD in the prednisone group to reach < 0.25mg/kg by Day 28 assessment

Patient characteristics

Given as number of patients treated with prednisone vs sirolimus

Some key patient characteristics are shown in **Table 1**. There was an even distribution between donor type (related bone marrow [BM] or peripheral blood [PB] *vs* unrelated BM or PB). Most patients were diagnosed with acute leukemias (53.1% *vs* 48.3%) or myelodysplastic syndrome/ myeloproliferative disorders (15.6% *vs* 32.8%). The conditioning regimen intensity was fairly split between myeloablative and non-myeloablative/reduced intensity. The human leukocyte antigen (HLA)

match score was mostly 8/8 BM or PB (71.9% *vs* 79.3%), and the graft source was most commonly PB (71.9% *vs* 81.0%). A higher proportion of patients in the prednisone group had a Karnofsky performance 90–100 (65.6%) whilst in the sirolimus group this was mostly <90 (55.2%).

Table 1. Patient characteristics by treatment arm

Baseline characteristic	**Prednisone**	**Sirolimus**
N	64	58
Median age, years (range)	52.4 (0.9–72.7)	58 (7.8–74.7)
AA1 *vs* AA2, %	70.3 *vs* 29.7	65.5 *vs* 34.5
Skin GvHD stage at enrolment, % 0 *vs* 1 *vs* 2 *vs* 3	29.7 *vs* 17.2 *vs* 20.3 *vs* 32.8	34.5 *vs* 13.8 *vs* 24.1 *vs* 27.6
Upper GI stage at enrolment, % 0 *vs* 1	56.3 *vs* 43.8	55.2 *vs* 44.8
Lower GI stage at enrolment, % 0 *vs* 1 *vs* 2	87.5 *vs* 10.9 *vs* 1.6	96.6 *vs* 3.4 *vs* 0
MN risk category, %		
Stage 1–3 skin	50.0	53.4
Stage 1–2 GI	29.7	34.5
Stage 1–3 skin and stage 1 GI	18.8	12.1

Stage 1–3 skin and stage 1–4 liver	1.6	0
aGvHD grade at enrolment, %		
I	25.0	27.6
II	73.4	72.4
III	1.6	0

AA, Ann Arbor; aGvHD, acute graft-*versus*-host disease; GI, gastrointestinal; GvHD, graft-*versus*-host disease; MN, Minnesota

CR/PR rates

- Day 28 and Day 56 CR/PR rates are shown in **Table 2** and were not significantly different between treatment arms
- Day 28 CR/PR rates were significantly higher for sirolimus than prednisone when prednisone was given as a dose ≤ 25mg/kg/day
- However, no differences were found for steroid-refractory aGvHD, disease-free survival (DFS), relapse, non-relapse mortality (NRM) or overall survival (OS, **Table 2**)
- The cumulative incidence of serious (grade 2–3) infections was also not significantly different between treatment arms (p= 0.221)
- Average daily dose of steroid of 56 days was lower in the sirolimus group (p < 0.001)
- Complete discontinuation of immune suppressive therapy was significantly improved (p= 0.049) in the sirolimus group
- When measuring patient-reported outcomes, scores from baseline to Day 180 were statistically and clinically greater for patients with sirolimus when compared to prednisone
- Hyperglycemia was lower in the sirolimus group
    - After adjusting for baseline hyperglycemia, sirolimus was associated with a lower odds at Day 28 (p= 0.029) and Day 56 (p= 0.007) but not at Day 180 (p= 0.16)

Table 2. Treatment responses, 12-month outcome measures and steroid exposure

	Prednisone	**Sirolimus**	**P value**	**Difference**
CR/PR rate				

Day 28 CR/PR rate (n= 117), %	73.0	64.8	0.68	-8.2% 90% CI, -22.3–5.9
Day 56 CR/PR rate (n= 116), %	79.4	64.2	0.07	-15.2% 95% CI, -31.5–1.1
Day 28 CR/PR rate with prednisone ≤0.25mg/kg/day, %	31.7	66.7	**< 0.001**	NR
Steroid exposure				
Average daily dose of steroid over 56 days, median, mg/kg	0.46	0	**< 0.001**	NA
12-month outcomes				
OS, % 95% CI	73.2 60.4–82.4	76.3 62.7–85.5	0.785	NA
DFS, % 95% CI	70.2 57.3–79.8	61.6 47.4–73.0	NR	NA
EFS, % 95% CI	31.2 20.4–42.7	35.9 23.4–48.5	NR	NA
NRM, % 95% CI	14.2 6.9–24.0	16.5 8.1–27.6	NR	NA

Relapse, % 95% CI	15.7 8.0–25.7	21.9 12.0–33.7	NR	NA
cGvHD, % 95% CI	40.6 28.4–52.4	31.4 19.5–44.0	NR	NA
GvHD-free survival, % 95% CI	46.0 33.7–58.3	50.9 37.5–64.4	NR	NA

cGvHD, chronic graft-*versus*-host disease; CR, complete response; DFS, disease-free survival; EFS, event-free survival; GvHD, graft-*versus*-host disease; OS, overall survival; PR, partial response; NA, not applicable; NR, not reported; NRM, non-relapse mortality

Safety

Given as number of patients treated with prednisone vs sirolimus

- Maximum toxicity grade:
  - 0–2: 39.1% *vs* 53.4%
  - 3: 42.2% *vs* 32.8%
  - 4: 14.1% *vs* 12.1%
  - 5: 4.7% *vs* 1.7%
- Serious adverse events: 3 *vs* 8
- Deaths: 17 *vs* 12
  - Recurrence/persistence: 35.3% *vs* 16.7%
  - Graft rejection/failure: 5.9% *vs* 0%
  - aGvHD: 5.9% *vs* 0%
  - Infection: 5.9% *vs* 33.3%
  - Multiple organ failure: 17.6% *vs* 16.7%
  - Interstitial pneumonia: 5.9% *vs* 0%
  - Other: 23.5% *vs* 25.0%
  - Unknown: 0% *vs* 8.3%

Conclusion

Sirolimus was associated with:

- Reduced steroid exposure
- Reduced hyperglycemia
- Reduced grade 2–3 infections
- Improvement in immune suppression discontinuation
- Improvement in patient QoL

In patients identified as having SR aGvHD by clinical and biomarker analysis, sirolimus had similar treatment efficacy to prednisone whilst sparing steroid exposure and toxicity, without compromising long-term patient outcome. Additionally, patient quality of life was improved with sirolimus. These results also demonstrated that a clinically and centrally assessed biomarker-based risk-stratified aGvHD approach is feasible in patients with SR aGvHD. A randomized, phase III, non-inferiority trial is required to confirm these findings in the SR aGvHD subgroup.

References

1. Pidala J. *et al.,* Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. Blood. 2020 Jan 09, 135, 2. DOI: 10.1182/blood.2019003125