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aGvHD

TCT Meeting 2019 | Results of the phase II ABA2 trial: abatacept for acute GvHD prophylaxis in unrelated donor transplantation

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On 23 February 2019, at the 2019 TCT | Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR in Houston, Texas, USA, Ben K. Watkins from the Aflac Cancer and Blood Disorders Center, Emory University, Atlanta, GA, USA, presented the results of a phase II multicenter, randomized, double-blind, placebo-controlled ABA2 trial (NCT01743131) evaluating abatacept for acute graft-versus-host disease (aGvHD) prevention.[1]

Dr. Watkins began his talk by discussing that a major challenge with unrelated transplants is the lack of an available matched donor within patient populations, although expansion to include mismatched donors increases the availability of a match for patients.[2] However, there is a risk associated with mismatched unrelated donor transplants, including an increase in treatment-related mortality at one year (45 [95% CI, 42–49] *vs* 36 [95% CI, 34–38]), and an increase in the presence of grade III-IV aGvHD at 100 days post-transplant (37 [95% CI, 34–40] *vs* 28 [95% CI, 26–30]).[3] The inhibition of T cell co-stimulation and prevention of T cell activation by abatacept (CTLA4-Ig), a recombinant soluble fusion product of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and immunoglobulin G1 (IgG1), has been previously demonstrated. A phase I feasibility study using short-course abatacept in unrelated donor transplant suggested the safety of abatacept in this population and the potential efficacy in the prevention of severe aGvHD.[4]

Patients were divided into two cohorts:

- HLA-mismatched cohort ('7/8')
  - N = 40
  - Compared to CIBMTR matched pre-specified cohorts with or without ATG for additional immunoprophylaxis
  - Patients received a calcineurin inhibitor, methotrexate (on days +1, +3, +6, and +11), and abatacept (10 mg/kg, on days −1, +5, +14, and +28)
- HLA-matched cohort ('8/8')
  - N = 140
  - Randomized double-blind arm
  - Patients received a calcineurin inhibitor plus methotrexate (on days +1, +3, +6, and +11), and either placebo or abatacept (10 mg/kg, on days −1, +5, +14, and +28)

The primary endpoint of the study is the cumulative incidence of severe aGvHD at day 100 post-transplant in the two study arms. Secondary endpoints include the cumulative incidence of serious infection, engraftment, relapse, overall survival (OS), severe (grade III-IV) aGvHD free survival (GFS) up to day 180, and the cumulative incidence of severe (grade III-IV) aGvHD up to day 180.

Key findings

In the '7/8' cohort:

Results shown as abatacept vs no ATG vs ATG groups, where applicable

- A reduction of grade III-IV aGvHD at 6 months with abatacept: 3% *vs* 32% ($P = 0.0003$) *vs* 22% ($P = 0.0054$)
- Significant improvement in GFS with abatacept: 97% *vs* 55% ($P < 0.0001$) *vs* 59% ($P < 0.0001$)
- Disease-free survival (DFS) at 2 years: 78% *vs* 32% ($P = 0.00017$) *vs* 54% ($P = 0.019$)
- Low relapse rates at 2 years: 8% *vs* 21% ($P = 0.0999$) *vs* 18% ($P = 0.2345$)

In the '8/8' cohort:

Results shown as abatacept vs placebo groups, where applicable

- No significant difference in relapse rate between groups: 14% *vs* 21%, $P = 0.3289$
- No significant difference in transplant-related mortality between groups: 7% *vs* 15%, $P = 0.1266$
- Reduction in grade III-IV aGvHD at 6 months in the abatacept group compared to placebo: 7% *vs* 15%, $P = 0.065$
- Severe GFS at day 180 significantly improved in abatacept group: 89% *vs* 77%, $P < 0.05$

Comparison of '7/8' with '8/8' cohorts:

Results shown as '7/8' abatacept vs '8/8' placebo groups, where applicable

- DFS rates at 1 year: 82% *vs* 65%, $P = 0.045$
- OS rates at 1 year: 87% *vs* 77%, $P = 0.098$
- Rate of grade II-IV aGvHD at 6 months were improved in the abatacept group: 42% *vs* 64%, $P = 0.012$
- Rate of grade III-IV aGvHD at 6 months were improved in the abatacept group: 3% *vs* 15%, $P = 0.033$

Taken together, these findings indicate that short-course (four doses) of abatacept is safe and effective in the prevention of aGvHD without compromising relapse. Furthermore, Dr. Watkins concluded that the addition of abatacept improved aGvHD and DFS rates in mismatched donor transplants when compared to matched donor transplants receiving no additional immunoprophylaxis. This potentially allows the expansion of the donor pool and makes mismatched donor transplant an option for a greater number of people.

References

1. Watkins B.K. *et al.* T cell costimulation blockade with CTLA4-ig (abatacept) for acute GvHD prevention in HLA matched and mismatched unrelated donor transplantation: results of the first phase 2 trial. 2019 Feb 23. 2019 TCT Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR, Houston, Texas, USA.
2. Gragert L. *et al.* HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014 Jul 24; 371(4): 339–348. DOI: 10.1056/NEJMsa1311707.
3. Lee S.J. *et al.* High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007 Dec 15; 110(13): 4576–4583. DOI: https://doi.org/10.1182/blood-2007-06-097386.
4. Koura D.T. *et al.* In vivo T cell costimulation blockade with abatacept for acute graft-versus-host disease prevention: a first-in disease trial. Biol Blood Marrow Transplant. 2013 Nov; 19(11): 1638–1649. DOI: 10.1016/j.bbmt.2013.09.003.