Successful hematopoietic stem cell transplantation with haploidentical donors and non-irradiation conditioning in patients with Fanconi anemia

Jing-Zhi Wang, Xiao-Jun Huang, Yuan-Yuan Zhang, Fei-Fei Tang, Ting-Ting Han, Xiao-Dong Mo, Yu-Qian Sun, Yu-Hong Chen, Yu Wang, Xiao-Hui Zhang, Lan-Ping Xu

Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Research Unit of Key Technique for Diagnosis and Treatments of Hematologic Malignancies, Chinese Academy of Medical Sciences, 2019RU029, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing 100044, China.

To the Editor: Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for bone marrow (BM) abnormalities in Fanconi anemia (FA). However, patients with FA cannot tolerate the toxicity of the therapeutic regimen for acquired aplastic anemia, which mainly contains 200 mg/kg cyclophosphamide (CTX), and low-dose CTX regimens are considered more suitable. Some centers have also added different doses of irradiation to the conditioning regimen.[1] Due to their side effects on growth and development and the possibility of developing a secondary malignant disease, some trials have replaced the irradiation with fludarabine. Moreover, data on transplants from haploidentical donors are scarce.

From June 2013 to February 2020, we conducted 15 consecutive haploidentical allogeneic HSCTs in patients with FA (eight boys and seven girls; median age: 8 years) prepared with a non-irradiation conditioning regimen [Table 1]. All patients tested positive for chromosomal breakage and the diagnosis was confirmed by gene mutation analysis, except for one patient. BM failure, as per the criteria for aplastic anemia, was observed in 12 patients, while three patients had myelodysplasia with increased blasts or obvious dysplasia in the marrow. All donors were parents (two mothers and 13 fathers) and were negative in the chromosome breakage analysis. The *HLA* genotype disparity was 3/6 (A, B, and DRB1) in two patients, 4/6 in one patient, 4/8 (A, B, C, and DRB1) in six patients, 5/10 (A, B, C, DRB1, and DQ) in four patients, and 6/10 in two patients. All patients received a preparative regimen consisting of 60 to 80 mg/kg CTX, 150 mg/m^2 fludarabine, and 10 mg/kg thymoglobulin [rabbit anti-lymphocyte globulin (ATG)]. Graft-versus-host disease (GVHD) prophylactic regimen consisted of cyclosporine A, mycophenolate mofetil, and short-term methotrexate. All patients received antibiotic prophylaxis with broad-spectrum antifungal agents and oral trimethoprim-sulfamethoxazole and acyclovir. All donors were primed with granulocyte colony-stimulating factor (G-CSF) from day −3 to day 02. BM stem cells were collected on day 01 and peripheral stem cells were harvested on day 02. All patients received G-CSF from day 6 until the neutrophil count exceeded 1×10^9 cells/L.

Neutrophils of all patients engrafted within 15 days (median: 11 days). The median time of platelet recovery was 18 days (ranging from eight days to 62 days). All patients achieved 100% donor chimerism at 4 weeks post-transplantation. Acute GVHD (aGVHD), diagnosed according to the Seattle criteria, was observed in 14 patients, among whom, 6 had grade III–IV aGVHD. Thirteen patients were successfully treated with prednisolone alone or in combination with basiliximab. Patient one, who experienced grade IV aGVHD affecting the skin, liver, and gut received additional therapy. Chronic GVHD was observed in three of the 11 evaluable patients and affected the skin in all the patients and the bowel in one patient, who showed a good response to steroids.

The conditioning regimen was well tolerated by all patients. Toxicity was evaluated according to the World Health Organization toxicity criteria for chemotherapy. Transaminase levels increased slightly in 11 patients and reverted to normal levels soon thereafter. Six patients developed mucositis but recovered rapidly. Nine patients developed cytomegalovirus antigenemia, which was resolved with ganciclovir. Epstein-Barr virus was detected in

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001471

Correspondence to: Prof. Lan-Ping Xu, Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing 100044, China
E-Mail: lpxu_0415@sina.com

Chinese Medical Journal 2021;134(20)
Received: 23-02-2021 **Edited by:** Peng Lyu

Table 1: Transplant characteristics of patients with Fanconi anemia.

No. of patients	Sex	Age (years)	BM status	Donor	HLA	Dose of CTX (mg/kg)	Acute GVHD, grade	Chronic GVHD	Outcome (months after SCT)
1	Male	8	AA	Father	5/10	80	4	Skin	Alive (82.5)
2	Female	9	MDS	Mother	3/6	80	3	NE	Dead (1.5)
3	Female	5	AA	Mother	4/8	80	1	None	Alive (26.5)
4	Female	8	AA	Father	4/8	80	1	Skin, gut	Alive (18)
5	Male	9	AA	Father	6/10	80	3	None	Alive (17.5)
6	Female	9	AA	Father	5/10	60	2	None	Alive (14)
7	Male	8	AA	Father	4/8	60	1	None	Alive (12)
8	Male	8	AA	Father	4/8	60	3	None	Alive (11.5)
9	Male	6	MDS	Father	4/8	60	2	None	Alive (10.5)
10	Female	6	AA	Father	5/10	60	3	Skin	Alive (9.5)
11	Female	11	AA	Father	4/8	60	2	None	Alive (9)
12	Male	4	AA	Father	5/10	60	2	None	Alive (8.5)
13	Male	10	AA	Father	3/6	60	4	NE	Alive (3)
14	Female	10	AA	Father	4/6	60	1	NE	Alive (2)
15	Male	6	MDS	Father	6/10	60	0	NE	Alive (1)

AA: Aplastic anemia; BM: Bone marrow; CTX: Cyclophosphamide; GVHD: Graft-versus-host disease; HLA: Human leukocyte antigen; MDS: Myelodysplastic syndrome; NE: Not evaluable; SCT: Stem cell transplantation

three patients and one patient required rituximab therapy. No sinusoidal obstruction syndrome was observed.

Fourteen patients were alive with a median follow-up of 10.5 months (ranging from 1 month to 82.5 months), of whom, 12 recovered with a normal blood count and 2 had mild thrombocytopenia. Patient 2 died from intracranial and lung infections on day 51. The estimated 1-year disease-free survival rate was 92.9%. No secondary tumors occurred, but more attention was needed in the further follow-up.

Patients with FA have been treated with HSCT for approximately four decades, with encouraging results being reported in recent years of overall survival (OS) >80% in cases of matched sibling donors and approximately equivalent in an alternative donor (AD). However, few studies reported results involving haploidentical donors. In 2016, a Brazilian study described 30 cases of haploidentical donor transplantations with total body irradiation (TBI) conditioning, which presented a 1-year OS of 72%.[1] Here, we report the outcome of 15 patients with FA from a single clinical center, who underwent HSCT using haploidentical donors with a non-irradiation regimen. To the best of our knowledge, this is a relatively large sample cohort of haploidentical transplantation with a satisfying engraftment rate and an acceptable incidence of GVHD without irradiation reported to date. All 15 patients engrafted, of whom 14 survived with a median follow-up of 10.5 months.

In transplantations for FA, most conditioning regimens contain TBI or thoracoabdominal irradiation in combination with low-dose CTX. The negative effect of irradiation on developing secondary malignancies has led researchers to explore other possible regimens without irradiation. Using a preparation consisting of 120 to 150 mg/m^2 fludarabine plus 40 mg/kg CTX and ATG, investigators from England performed four matched-related or unrelated donor transplantations, and all patients survived for 11 to 51 months after transplantation.[2] Ayas *et al*[3] compared two regimens in matched-related transplantations; one comprised 20 mg/kg CTX, fludarabine, and ATG, and the other comprised 20 mg/kg CTX, irradiation, and ATG. Overall, the outcome in the fludarabine cohort was much better (95.2% *vs.* 75.9%). However, in haploidentical donor transplants, only 1/5 of the patients engrafted under a similar regimen of 20 to 30 mg/kg CTX, 150 mg/m^2 fludarabine, and ATG.[4] Mehta *et al*[5], who added four doses of busulfan (BU) to the CTX, fludarabine, and ATG combo in AD transplant (including six mismatched related donors), had to decrease the dose of BU because one patient developed sinusoidal obstruction syndrome. In the present study, the dose of CTX was slightly increased to ensure good engraftment and avoid irradiation and BU, with a satisfactory survival rate.

Graft failure is a major obstacle to AD transplantation. De Medeiros *et al*[6] transplanted 47 patients, among whom, only 51% achieved complete hematopoietic recovery. Moreover, the European Society for Blood and Marrow Transplantation (EBMT) reported that the cumulative neutrophil recovery at 30 days post-transplant was 83% in unrelated donor cases. Motwani *et al*[4] reported only one engraftment among five HSCTs with haploidentical donors. Recently, 2 out of 30 patients suffered engraftment failure in haploidentical BM transplantation with post-transplantation CTX.[1] In the current study, all 15 patients achieved complete engraftment rapidly, which was an encouraging outcome.

Another difficulty for transplants with ADs is the high incidence of GVHD. The International Blood and Marrow Transplant Research Center reported 51% grade II–IV aGVHD in transplantations with matched unrelated donors. EBMT data revealed a similar result, with 34% of patients experiencing grade III–IV aGVHD. In our series, aGVHD was observed in 14 patients, among whom, 6 had grade III–IV aGVHD. Among the first five patients who received 80 mg/kg CTX, three developed grade III–IV

aGVHD. Some studies suggest that toxicity from conditioning may play an important role in the pathogenesis of aGVHD. Therefore, the dose of CTX was reduced to 60 mg/kg in the following patients. As expected, grade III–IV aGVHD was reduced by approximately 50%. However, such a high aGVHD incidence remains worrisome. A previous report described an aGVHD rate below 20% in patients who received post-transplantation CTX.[1] This could be included in our protocol in the future.

Thus, our data show that haploidentical donor transplantation under a non-irradiation conditioning regimen could be a suitable alternative to improve the outcome in patients with FA. Considering the small number of patients and the short follow-up period of this study, further studies are needed to validate our results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/or his/her guardian has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients or his/her guardian understand that his/her/their name(s) and initials will not be published and due efforts will be made to conceal his/her/their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

References

1. Bonfim C, Ribeiro L, Nichele S, Loth G, Bitencourt M, Koliski A, *et al*. Haploidentical bone marrow transplantation with post-transplant cyclophosphamide for children and adolescents with Fanconi anemia. Biol Blood Marrow Transplant 2017;23:310–317. doi: 10.1016/j.bbmt.2016.11.006.
2. de la Fuente J, Reiss S, McCloy M, Vulliamy T, Roberts IAG, Rahemtulla A, *et al*. Non-TBI stem cell transplantation protocol for Fanconi anaemia using HLA-compatible sibling and unrelated donors. Bone Marrow Transplant 2003;32:653–656. doi: 10.1038/sj.bmt.1704219.
3. Ayas M, Siddiqui K, Al-Jefri A, El-Solh H, Al-Ahmari A, Khairy A, *et al*. Factors affecting the outcome of related allogeneic hematopoietic cell transplantation in patients with Fanconi anemia. Biol Blood Marrow Transplant 2014;20:1599–1603. doi: 10.1016/j.bbmt.2014.06.016.
4. Motwani J, Lawson SE, Darbyshire PJ. Successful HSCT using nonradiotherapy-based conditioning regimens and alternative donors in patients with Fanconi anaemia – Experience in a single UK centre. Bone Marrow Transplant 2005;36:405–410. doi: 10.1038/sj.bmt.1705071.
5. Mehta PA, Davies SM, Leemhuis T, Myers K, Kerman NA, Prockop SE, *et al*. Radiation-free, alternative-donor HCT for Fanconi anemia patients: Results from a prospective multi-institutional study. Blood 2017;129:2308–2315. doi: 10.1182/blood-2016-09-743112.
6. De Medeiros CR, Bitencourt MA, Zanis-Neto J, Maluf ECP, Carvalho DS, Bonfim CS, *et al*. Allogeneic hematopoietic stem cell transplantation from an alternative stem cell source in Fanconi anemia patients: analysis of 47 patients from a single institution. Braz J Med Biol Res 2006;39:1297–1304. doi: 10.1590/s0100-879x2006001000005.

How to cite this article: Wang JZ, Huang XJ, Zhang YY, Tang FF, Han TT, Mo XD, Sun YQ, Chen YH, Wang Y, Zhang XH, Xu LP. Successful hematopoietic stem cell transplantation with haploidentical donors and non-irradiation conditioning in patients with Fanconi anemia. Chin Med J 2021;134:2518–2520. doi: 10.1097/CM9.0000000000001471