Efficacy and influencing factors of allogeneic hematopoietic stem cell transplantation in treatment of 71 children with leukemia

Bing-Lei Zhang, Jian Zhou, Tian-Xi Lyu, Rui-Rui Gui, Ying-Ling Zu, Feng-Kuan Yu, Hui-Fang Zhao, Zhen Li, Juan Wang, Yan-Li Zhang, Wen-Lin Zhang, Yue-Wen Fu, Xu-Dong Wei, Bai-Jun Fang, Yu-Fu Li, Ke-Shu Zhou, Yong-Ping Song

Department of Hematology, Tumor Hospital Affiliated to Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan 450003, China.

To the Editor: Leukemia is a malignant proliferative disease that has become the most common malignancy in children, accounting for 40.5% of malignant cancers children.[1] Although chemotherapy can effectively treat children, some patients with high-risk and relapsed acute lymphoblastic leukemia (ALL) and acute myelocytic leukemia (AML) failed to achieve long-term relief. For these patients, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the best choice. However, many factors may impact the efficacy of allo-HSCT. We retrospectively analyzed the clinical data of 71 children with leukemia treated using allo-HSCT to observe the clinical efficacy and analyze the possible influencing factors.

Our institutional review board (IRB) approved the protocol, and guardians of all patients signed consent forms approved by the IRB. Overall, 71 patients were included, aged 1 to 14 (median 9) years; 46 boys and 25 girls. A total of 34 patients had ALL, 32 had AML, four had chronic myelocytic leukemia, and one had juvenile myelomonocytic leukemia. Details regarding the patient cohort are provided in Table 1.

In the study, 55 patients received a busulfan-cyclophosphamide-based (Bu/Cy-based) regimen, 0.8 mg/kg q6 h × 4 days, Cy 40 to 60 mg/kg × 2 days. Overall, 16 patients received a total body irradiation-cyclophosphamide-based (TBI/Cy-based) regimen, 4 to 5 Gy × 2 days, Cy 40 to 60 mg/kg × 2 days. For GVHD prophylaxis, MSD received cyclosporine A (CsA) and short-course methotrexate (MTX), and AD received CsA, MTX, mycophenolate mofetil (MMF), and rabbit anti-human thymocyte immunoglobulin (ATG). CsA plasma concentrations were monitored twice a week and maintained at 200 to 400 ng/mL. All patients were prevented from potentially contacting infections as much as possible pre-transplantation. Alprostadil was administered to prevent hepatic vein of occlusion disease (HVOD). Hydration and alkalization of urine were performed to prevent hemorrhagic cystitis. During transplantation, all blood products were irradiated before infusion. Patients began to receive granulocyte colony-stimulating factor 5 μg/kg, from +5 days to the day when the white blood cell and neutrophil counts returned to normal.

Neutrophil engraftment day was defined as the first day of three consecutive days with absolute neutrophil count greater than 0.5 × 10^9/L. Platelet engraftment day was defined as the first of seven consecutive days with platelet count >20 × 10^9/L, without transfusion support for at least seven days. After hematopoietic reconstitution, bone marrow sample was obtained for evidence of implantation. Quantitative PCR was used to detect short tandem repeat gene signature, or sex chromosome analysis. Overall survival (OS) was defined as the length of time from HSCT to death from any cause, or the last follow-up. Disease-free survival (DFS) was defined as the length of time from the HSCT to the last follow-up or first event (relapse or death from any cause).

All analyses were performed using SPSS version 21.0 (SPSS Inc., USA). P < 0.05 was considered statistically significant. Survival curves for DFS and OS were estimated using the Kaplan-Meier method, and the groups were compared using the log-rank test. Cox proportional hazards regression was used to identify the risk factors associated with OS and DFS rates.

We found that 70 patients reconstituted successfully, and one patient experienced failure because of early graft rejection and severe infection. The hematopoietic reconstitution rate was 98.6%. The median implantation time of neutrophils and platelets in the evaluable patients was 13th (9–26) day and 14th (9–46) day, respectively. Follow-up

Access this article online

Quick Response Code: Scan or click to access

Website: www.cmj.org

DOI: 10.1097/CM9.000000000000150

Correspondence to: Dr. Yong-Ping Song, Department of Hematology, Tumor Hospital Affiliated to Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan 450003, China.

E-Mail: songyongping001@126.com

Copyright © 2019 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2019;132(7)

Received: 06-11-2018 Edited by: Li-Shao Guo
Table 1: Outcomes of patients who underwent allo-HSCT: univariate analysis (n=71).

| Variables                                      | Patients, n (%) | OS       |        | DFS       |        |
|------------------------------------------------|----------------|----------|--------|-----------|--------|
|                                                |                | (mean ± SD)% |      | (mean ± SD)% |      |
| Gender                                         |                |            | 0.143 |            | 0.169 |
| Male                                           | 46 (64.8)      | 40.26 ± 7.40 |    | 33.80 ± 6.99 |    |
| Female                                         | 25 (35.2)      | 69.18 ± 10.69 |    | 54.35 ± 9.90 |    |
| Primary disease                                |                |            | 0.336 |            | 0.536 |
| AML                                            | 32 (45.1)      | 60.80 ± 9.87 |    | 48.74 ± 8.99 |    |
| ALL                                            | 34 (47.9)      | 39.27 ± 7.40 |    | 31.35 ± 7.01 |    |
| AML-CR1                                        |                |            | 0.014 |            | 0.048 |
| High risk                                      | 14 (63.6)      | 23.78 ± 7.69 |    | 23.41 ± 7.78 |    |
| Non-high risk                                  | 8 (36.4)       | 94.50 ± 10.76 | 0.035 | 81.25 ± 10.79 |    |
| Disease status at HSCT                         |                |            | 0.336 |            | 0.536 |
| First CR                                       | 35 (49.3)      | 68.96 ± 8.88 |    | 59.46 ± 8.33 |    |
| Second CR                                      | 23 (32.4)      | 33.78 ± 7.36 |    | 27.15 ± 6.53 |    |
| Third CR and NR                                | 10 (14.1)      | 25.96 ± 12.58 | 0.071 | 24.93 ± 11.89 |    |
| Extramedullary infiltration                    |                |            | 0.003 |            | 0.028 |
| Yes                                            | 12 (16.9)      | 23.66 ± 11.68 |    | 18.76 ± 11.15 |    |
| No                                             | 59 (83.1)      | 57.46 ± 7.29 |    | 45.44 ± 6.55 |    |
| Conditioning regimen                            |                |            | 0.003 |            | 0.028 |
| Bu/Cy-based                                    | 55 (77.5)      | 64.31 ± 7.62 |    | 49.45 ± 6.96 |    |
| TBI/Cy-based                                   | 16 (22.5)      | 19.48 ± 6.85 |    | 18.20 ± 7.05 |    |
| Donor source                                   |                |            | 0.601 |            | 0.330 |
| MSD                                            | 28 (39.4)      | 47.67 ± 9.35 |    | 34.50 ± 7.90 |    |
| AD                                             | 43 (60.6)      | 57.45 ± 8.13 | 0.090 | 50.16 ± 8.06 |    |
| Stem cell donors                                |                |            | 0.599 |            | 0.522 |
| HLA identical                                   | 44 (62.0)      | 54.25 ± 7.71 |    | 44.25 ± 7.04 |    |
| HLA mismatched                                  | 27 (38.0)      | 31.63 ± 4.56 |    | 24.51 ± 4.98 |    |
| Sex of donor–recipient                          |                |            | 0.369 |            | 0.159 |
| Sex identical                                   | 46 (64.8)      | 51.82 ± 8.37 |    | 36.28 ± 7.27 |    |
| Sex-incompatibility                             | 25 (35.2)      | 53.68 ± 9.59 |    | 52.25 ± 9.50 |    |
| Donor–recipient ABO compatibility               |                |            | 0.018 |            | 0.126 |
| ABO-compatible                                  | 32 (45.1)      | 36.30 ± 7.80 |    | 33.53 ± 7.73 |    |
| ABO-incompatible                                | 39 (54.9)      | 67.54 ± 9.17 |    | 49.36 ± 8.63 |    |
| Stem cell source                                |                |            | 0.090 |            | 0.277 |
| PBSC                                           | 59 (83.1)      | 49.68 ± 6.83 |    | 39.97 ± 6.11 |    |
| BM and PBSC                                    | 12 (16.9)      | 18.43 ± 1.50 |    | 15.41 ± 2.26 |    |
| Acute GVHD                                      |                |            | 0.774 |            | 0.321 |
| Yes                                            | 50 (70.4)      | 51.76 ± 8.24 |    | 37.37 ± 7.03 |    |
| No                                             | 21 (29.6)      | 53.89 ± 10.09 | 0.373 | 54.48 ± 10.14 |    |
| Grade II-IV aGVHD                               |                |            | 0.303 |            | 0.303 |
| Yes                                            | 36 (50.7)      | 44.85 ± 8.29 |    | 35.75 ± 7.71 |    |
| No                                             | 35 (49.3)      | 59.75 ± 9.74 | 0.784 | 49.09 ± 8.72 |    |
| Chronic GVHD                                    |                |            | 0.622 |            | 0.622 |
| Yes                                            | 21 (29.6)      | 34.61 ± 6.04 |    | 31.08 ± 6.00 |    |
| No                                             | 50 (70.4)      | 36.23 ± 8.08 | 0.231 | 43.71 ± 7.40 |    |
| Lung infection                                  |                |            | 0.411 |            | 0.411 |
| Yes                                            | 34 (47.9)      | 45.73 ± 9.28 |    | 42.91 ± 8.67 |    |
| No                                             | 37 (52.1)      | 57.57 ± 8.98 |    | 38.76 ± 6.49 |    |
| Hemorrhagic cystitis                            |                |            | 0.056 |            | 0.399 |
| Yes                                            | 26 (36.6)      | 27.19 ± 6.34 |    | 28.21 ± 6.30 |    |
| No                                             | 45 (63.4)      | 60.70 ± 8.24 | 0.771 | 44.90 ± 7.31 |    |
| EBV infection                                   |                |            | 0.864 |            | 0.864 |
| Yes                                            | 20 (28.2)      | 42.36 ± 6.95 |    | 29.71 ± 7.76 |    |
| No                                             | 51 (71.8)      | 51.84 ± 7.51 | 0.044 | 42.99 ± 6.82 |    |
| CMV infection                                   |                |            | 0.128 |            | 0.128 |
| Yes                                            | 37 (52.1)      | 37.74 ± 7.10 |    | 30.30 ± 6.87 |    |
| No                                             | 34 (47.9)      | 63.93 ± 9.26 |    | 49.55 ± 8.37 |    |

Data are expressed as n (%) or mean ± standard deviation. AD: Alternative donor; BM: Bone marrow; Bu: Busulfan; CMV: Cytomegalovirus; CR: Complete remission; Cy: Cyclophosphamide; DFS: Disease-free survival; EBV: Epstein-Barr virus; GVHD: Graft-vs-host disease; HLA: Human leukocyte antigen; HSCT: Hematopoietic stem cell transplantation; MSD: Matched sibling donor; NR: Non-remission; OS: Overall survival; PBSC: Peripheral blood stem cell; TBI: Total body irradiation.
was performed through outpatient or inpatient routes or via telephone. The end of the study period was July 1, 2018, and the median follow-up time was 16 (1.5–106) months. Fifty (70.4%) patients had acute graft-vs-host disease (aGVHD) and 21 (29.6%) had chronic GVHD (cGVHD). Grade II-IV aGVHD were observed in 36 (37%) patients. No significant difference between the various GVHD groups was observed. HVOD did not appear in all patients. At the end of the observation, 19 patients relapsed, and 31 died. Twenty-two patients (31%) died from transplant-related complications: 14, severe infection; three, cerebral hemorrhage; two, hemorrhage of the digestive tract; two, severe GVHD; and one, cardiac insufficiency.

In univariate analysis, sex, primary disease, donor source, stem cell donors, sex of donor–recipient, stem cell source, lung infection, hemorrhagic cystitis, and EBV infection were not statistically significant for either OS or DFS. Disease status at HSCT (P=0.036), high-risk AML-CR1 (P=0.014), conditioning regimen (P=0.003), donor–recipient ABO compatibility (P=0.018), and CMV infection (P=0.044) had significant effects on OS. Extramedullary infiltration (P=0.047), high-risk AML-CR1 (P=0.048), and conditioning regimen (P=0.028) had significant effects on DFS [Table 1]. The 3-year DFS and OS were 39.3% and 49.7%, respectively. Survival curves are presented in Figure 1A. Multivariate analysis revealed that disease status at HSCT (RR=1.727, 95% CI 1.067–2.795, P=0.026), high-risk AML-CR1 (RR=8.851, 95% CI 1.019–76.884, P=0.048), and conditioning regimen (RR=2.613, 95% CI 1.255–5.439, P=0.01) were affected factors for OS. Conditioning regimen (RR=2.123, 95% CI 1.061–4.247, P=0.033) was an affected factor for DFS. Survival curves are presented in Figure 1B–E.

In recent years, allo-HSCT has been widely used in the treatment of leukemia, and its efficacy has been improved remarkably; the 5-year OS was noted to be as high as 70%, and 5-year DFS was also approximately 66%.[2] However, the results are still not completely satisfactory. Transplant-related complications and post-transplant relapse remain to be pressing problems. Improving survival rate and quality of life are still the primary goals.

Currently, the choice of transplantation for patients with ALL-CR1 and AML-CR1 is unclear. It was considered that ALL-CR1 and AML-CR1 were not the absolute indications of transplantation. In particular, with the continuous improvement of chemotherapy regimens and the application of some new targeted drugs, most patients in CR1 were inclined to undergo consolidation chemotherapy as
we found that serious infection was the main cause of relapse-related mortality. These results may be related to plant-related mortality was the leading cause of death; damage, and immune dysfunction. In our study, trans-


tation, due to neutropenia, treatment-related mucosal



the most important reason for death in early transplanta-



tion patients post-HSCT and found that severe infection was



in patients who received salvage chemotherapy ($P < 0.01$). Moreover, the European Leukemia Net AML Working Party showed that the high-risk cytogenetic cohorts can achieve a major benefit with allo-HSCT in CR1; in addition, the indication for allo-HSCT in intermediate risk AML patients has been favored by recent studies and recommendations. Our study showed that patients who were in CR1 at HSCT had significantly higher DFS than those in CR2, CR3, and NR. However, the difference was not significant ($P > 0.05$), which may be related to factors such as short follow-up. Furthermore, disease status at HSCT and high risk of AML-CR1 were factors that affected OS ($P < 0.05$). Therefore, early allo-HSCT may benefit some patients with greater survival.

Conditioning is a key step in the success of HSCT. At present, the conditioning regimens of allo-HSCT for leukemia mainly include Bu/Cy-based and TBI/Cy-based regimens. Tomizawa et al$[3]$ compared the efficacy of two conditioning regimens in high-risk AML of children and adolescents and showed that the Bu/Cy-based regimen had significantly higher 3-year OS than the TBI-based regimen (81.3% vs. 60.9%). In our study, the univariate analysis showed that 3-year OS and DFS with the Bu/Cy-based regimen were both significantly higher than those with the TBI/Cy-based regimen. At the same time, TBI/Cy-based regimen was a factor that affected OS. Lucchini et al$[8]$ also demonstrated that patients receiving a Bu/Cy-based regimen had a lower incidence of relapse and higher OS and DFS. Therefore, the Bu/Cy-based regimens may be a better option for children with leukemia. Gutierrez-Aguirre et al$[9]$ analyzed the effects of ABO-incompatibility on GVHD and OS and found that ABO-incompatibility significantly improved OS and increased the incidence of GVHD, but the differences were not significant. In our series, the univariate analysis showed that ABO-incompatibility was a factor that affected OS, but the multivari-



ate analysis showed no statistical significance. Further observation and follow-up studies are required to elucidate this aspect.

Sahin et al$[10]$ retrospectively analyzed infections in patients post-HSCT and found that severe infection was the most important reason for death in early transpla-



tion, due to neutropenia, treatment-related mucosal damage, and immune dysfunction. In our study, trans-



plant-related mortality was the leading cause of death; 31.0% was transplant-related mortality and 12.7% was relapse-related mortality. These results may be related to the limited sample size and follow-up time. In addition, we found that serious infection was the main cause of transplant-related mortality, especially pulmonary infec-



tion, and the proportion was as high as 60%, which seriously threatened patient survival. Tomizawa et al$[3]$ found that grade II-IV aGVHD was associated with low OS of high risk AML in children and adolescents ($P=0.049$). However, the effects of cGVHD and grade II-IV aGVHD on OS were not significant in our study, which may be related to factors such as the classification of disease types, risk stratification, and short follow-up. Therefore, it is necessary to further refine relevant influencing factors and expand the sample size for systematic analysis.

In summary, allo-HSCT was a safe and effective method for leukemia treatment in children after induction chemotherapy, which could significantly improve the survival and prognosis of patients. Additionally, we found that disease status at HSCT, high-risk AML-CR1, extramedullary infiltration, conditioning regimen, donor–recipient ABO compatibility, and CMV infection influenced the survival of children with leukemia after allo-



HSCT.

Funding

This study was supported by a grant from Henan Medical Science and Technique Foundation (No. SBGJ2018085).

Conflicts of interest

None.

References

1. Friederike E, Tengfei L, George L, Giddings BM, Torres Alvarado G, Stelianarova-Foucher E, et al. Incidence of childhood cancer in Costa Rica, 2000–2014: an international perspective. Cancer Epidemiol 2018;56:21–30. doi: 10.1016/j.canepe.2018.07.004.

2. Shim YJ, Lee JM, Kim HS, Jung N, Lim YT, Yang EJ, et al. Comparison of survival outcome between donor types or stem cell sources for childhood acute myeloid leukemia after allogenic hematopoietic stem cell transplantation: a multicenter retrospective study of Study Alliance of Yeungnam Pediatric Hematology-oncology. Pediatr Transplant 2018;22:e13249. doi: 10.1111/petr.13249.

3. Xu L, Chen H, Chen J, Han M, Huang H, Lai Y, et al. The consensus on indications, conditioning regimen, and donor selection of allogeneic hematopoietic cell transplantation for hematological diseases in China—recommendations from the Chinese Society of Hematology. J Hematol Oncol 2018;11:33. doi: 10.1186/s13045-018-0564-x.

4. Cornelissen JJ, Versluis J, Passweg JR, van Putten WL, Manz MG, Maertens J, et al. Comparative therapeutic value of post remission approaches in patients with acute myeloid leukemia aged 40–60 years. Leukemia 2015;29:1041–1050. doi: 10.1038/leu.2014.332.

5. Ciftciler R, Demiroglu H, Buyukasik Y, Aladag E, Aksu S, Haznedaroglu IC, et al. Efficacy and feasibility of allogeneic hematopoietic stem-cell transplantation in the treatment of refractory acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 2018. pii: S2152-2650(18)31425-3. doi: 10.1016/j.clml.2018.11.016.

6. Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhauser M, Juliusson G, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. Nat Rev Clin Oncol 2012;9:579–590. doi: 10.1038/nrclinonc.2012.150.

7. Tomizawa D, Yoshida M, Kondo T, Miyamura T, Taka T, Adachi S, et al. Allogeneic hematopoietic stem cell transplantation for children and adolescents with high-risk cytogenetic AML: distinctly poor
outcomes of FUS-ERG-positive cases. Bone Marrow Transplant 2018;1. Epub ahead of print. doi: 10.1038/s41409-018-0273-7.

8. Lucchini G, Labopin M, Boisnot E, Dalissier A, Dalle JH, Cornish J, et al. Impact of conditioning regimen on outcomes for children with acute myeloid leukemia undergoing transplantation in first complete remission. An analysis on behalf of the Pediatric Disease Working Party of the European Group for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2017;23:467–474. doi: 10.1016/j.bbmt.2016.11.022.

9. Gutiérrez-Aguirre CH, Gómez-De-León A, Alatorre-Ricardo J, Cantú-Rodríguez OG, González-Llano O, Jaime-Pérez JC, et al. Allogeneic peripheral blood stem cell transplantation using reduced-intensity conditioning in an outpatient setting in ABO-incompatible patients: are survival and graft-versus-host disease different? Transfusion 2014;54:1269–1277. doi: 10.1111/trf.12466.

10. Sahin U, Toprak SK, Arilla PA, Arilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. J Infect Chemother 2016;22:505–514. doi: 10.1016/j.jiac.2016.05.006.

How to cite this article: Zhang BL, Zhou J, Lyu TX, Gui RR, Zu YL, Yu FK, Zhao HF, Li Z, Wang J, Zhang YL, Zhang WL, Fu YW, Wei XD, Fang BJ, Li YF, Zhou KS, Song YP. Efficacy and influencing factors of allogeneic hematopoietic stem cell transplantation in treatment of 71 children with leukemia. Chin Med J 2019;132:860–864. doi: 10.1097/CMJ.0000000000000150