Haploidentical Stem Cell Transplantation for Acute Myeloid Leukemia: Current Therapies, Challenges and Future Prospective

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Haploidentical stem cell transplantation (haplo-SCT), an alternative donor source, offers a curative therapy for patients with acute myeloid leukemia (AML) who are transplant candidates. Advances in transplantation techniques, such as donor selection, conditioning regimen modification, and graft-versus-host disease prophylaxis, have successfully improved the outcomes of AML patients receiving haplo-SCT and extended the haploidentical transplant indications for AML. Presently, treating de novo AML, secondary AML, therapy-related AML and refractory and relapsed AML with haplo-SCT can achieve comparable outcomes to those of human leukocyte antigen (HLA)-matched sibling donor transplantation (MSDT), unrelated donor transplantation or umbilical cord blood transplantation. For some subgroups of AML subjects, such as patients with positive pretransplantation minimal/measurable residual disease, recent studies suggest that haplo-SCT might be superior to MSDT in decreasing relapse and improving survival. Unfortunately, for patients with AML after haplo-SCT, relapse and infections remain the causes of death that restrict further improvement in clinical outcomes. In this review, we discuss the recent advances and challenges in haplo-SCT for AML treatment, mainly focusing on unmanipulated haplo-SCT protocols. We provide an outlook on future prospects and suggest that relapse prophylaxis, intervention, and treatment, as well as infection prevention and therapy, are areas of active research in AML patients who receive haploidentical allografts.

Keywords: acute myeloid leukemia, haploidentical stem cell transplantation, relapse, infection, graft-versus-leukemia-effect

INTRODUCTION

Allogeneic stem cell transplantation (allo-SCT) remains a curative therapy for patients with acute myeloid leukemia (AML) (1–19). However, the lack of human leukocyte antigen (HLA)-matched sibling donors (MSDs) restricts the wide use of allo-SCT in the clinic (20–22). To overcome the deficiency of donors, many efforts have been made to search for alternative donors (4, 6, 9, 23–27), including haploidentical donors (HIDs), HLA-matched unrelated donors (MUDs), and umbilical cord blood. Among these alternative donors, haploidentical allografts are the most attractive because
successful application of haploidentical transplantation will ensure that almost every allograft candidate has a donor (4, 6, 9, 24–26). In the 1970s and 1980s, the clinical outcomes after bone marrow transplantation from HLA-mismatched family donors using a conditioning regimen similar to HLA-matched sibling donor transplantation (MSDT) in treating patients with AML were not acceptable because the long-term survival rate was less than 20% (28). In the 1990s, the introduction of a T-cell depletion (TCD) strategy followed by a myeloablative conditioning regimen improved the outcomes of haploidentical SCT (haplo-SCT) in the treatment of AML (29, 30). After 2000, the successful application of haplo-SCT based on immune tolerance induced by granulocyte colony-stimulating factor (G-CSF) and antithymocyte globulin (ATG, The Beijing Protocol) and haplo-SCT based on immune tolerance induced by posttransplant cyclophosphamide (PTCy, The Baltimore Protocol) in transplant candidates with hematological diseases (21, 31–36), such as patients with AML, allowed haploidentical allografts to be used worldwide, and it is a reality that almost everyone has a donor (Figure 1). The detailed history perspective and the biological differences of the abovementioned three haplo-SCT protocols has been extensively reviewed by others and by us elsewhere (22, 37–39).

In the past two decades, advances in the establishment of algorithms for best haploidentical donor selection (40–42), optimization of conditioning regimens (43–45), shifts from TCD grafts to unmanipulated bone marrow and/or peripheral blood harvests (3, 5, 21, 46, 47), enhancement of hematopoietic recovery through endothelial cell-directed N-acetyl-L-cysteine intervention and/or donor-specific antibody desensitization (34, 48, 49), biomarker-directed graft-versus-host disease (GVHD) prophylaxis (50–52), minimal/measurable residual disease (MRD)-directed relapse intervention (7, 53), and approaches for enhancing immunologic recovery (54–56) have successfully improved the outcomes of patients with hematological malignancies, especially those with AML receiving haplo-SCT. Unfortunately, for subjects with AML who underwent haploidentical allografts, relapse and infections remain the causes of death that restrict further improvement in clinical outcomes (57, 58). In this review, we discussed the current therapies and challenges in haplo-SCT for AML treatment, mainly focusing on unmanipulated haploidentical transplant protocols. We provide an outlook on future prospects and suggest that relapse prophylaxis, intervention, and treatment, as well as infection prevention and therapy, are areas of active research in AML patients who receive haploidentical allografts.

**CURRENT THERAPIES FOR AML WITH HAPLOIDENTICAL ALLOGRAFTS**

**Extension of Haploidentical Transplant Indications for AML**

The indications of AML for haploidentical protocols were significantly extended from adverse subjects to high-risk subgroup cases of favorable ones in the past two decades (5, 11, 13, 22, 59–61). First, for inter/high-risk de novo AML patients in complete remission 1 (CR1), our group demonstrated that for both adults and pediatric patients (5, 59, 60), haplo-SCT as postremission therapy achieved a lower CIR and superior survival in both MRD-negative and MRD-positive groups compared with those of patients treated with chemotherapy alone. Second, for favorable de novo AML cases in CR1, haplo-SCT could be used to improve outcomes in the following subgroup patients: i) t(8;21) AML cases that did not achieve major molecular remission (MMR)/MRD negativity, which were defined as >3-log reduction in RUNX1/RUNX1T1 transcripts (>0.4%) compared with the pretreatment baseline of 388% in Peking University Institute of Hematology, after the second consolidation therapy or those exhibiting the loss of MMR (defined as RUNX1/RUNX1T1 transcript levels >0.4% in MMR patients) within 6 months of achieving MMR (7, 61). ii) AML patients with NPM1 mutations (NPM1 m) failed to achieve a >4-log reduction in peripheral blood MRD after induction therapy (11). iii) For NPM1 wild-type standard-risk AML cases, those who were MRD-positive after second course induction (13). iv) CBFB-MYH11-positive AML patients with CBFB-MYH11/ABL levels >0.1% after two cycles of consolidation therapy (62). Third, other indications include secondary AML, therapy-related AML, and relapsed or refractory AML (R/R AML) (63, 66–75) (Tables 1–3).

The extension of indications promotes the use of haploidentical allografts in patients with AML worldwide (76, 77). According to the data of the Chinese Blood and Marrow Transplantation Register Group (CBMTRG) (76), haploidentical donors have been the first donor source for AML since 2013. The number of AML patients who received haplo-SCT reached nearly 2000 in 2015. In a recent survey by the European Society for Blood and Marrow Transplantation (EBMT) (77), the number of haplo-SCTs in Europe 2019 (n=1813) was listed as the third transplant modality for AML. In 2019, the number of haplo-SCTs was more than two thousand and comparable to that of MSDT according to the report of the Center for International and Marrow Transplant Research (CIBMTR), although fewer than 700 AML patients received haplo-SCT (78).

**OUTCOME COMPARISON BETWEEN HAPLO-SCT AND OTHER TRANSPLANT MODALITIES**

In 2006, our group demonstrated for the first time that treating leukemia patients with haplo-SCT achieved comparable 2-year nonrelapse mortality (NRM), cumulative incidence of relapse (CIR), and 2-year probabilities of leukemia-free survival (LFS) and overall survival (OS) to those of MSDT (31), suggesting that haplo-SCT is a feasible approach with acceptable outcomes. Since then, a series of retrospective or prospective studies reported by others (4, 10, 26, 64–70, 74, 75, 79–87) and us (6, 88–90) compared the outcomes of AML patients who either received haplo-SCT or other allografts, including MSDT, HLA-matched unrelated donor transplantation (MUDT) and
FIGURE 1 | Summary of historical perspective and conditioning regimens of different haploidentical stem cell transplantation modalities for AML. (A) The historical perspective of haplo-SCT for AML. (B) University of Perugia: myeloablative conditioning and ex vivo TCD with “megadose” CD34+ cell allografts. (C) Peking University: myeloablative conditioning based on immune tolerance induced by G-CSF and ATG. (D) Johns Hopkins University: nonmyeloablative conditioning with high-dose PT/Cy. Panels (B–D) were adapted from Aversa et al. (Blood, 1994), Luznik et al. and Cieri et al. (Biol Blood Marrow Transplant, 2008; Biol Blood Marrow Transplant, 2015), and Huang et al. (Bone Marrow Transplant, 2006), respectively. AML, acute myeloid leukemia; Haplo-SCT, haploidentical stem cell transplantation; Tregs, regulatory T cells; TCN, conventional T cells; MSDT, human leukocyte antigen (HLA)-matched sibling donor transplantation; G-CSF, granulocyte colony-stimulating factor; ATG, antithymocyte globulin; PT/Cy, posttransplantation cyclophosphamide; TBI, Total body irradiation; SS-BM, steady-state bone marrow; G-PB, G-CSF-stimulated peripheral stem cells; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; G-BM, G-CSF-stimulated bone marrow harvests; MTX, Methotrexate; Bu, Busulfan; CSA, Cyclosporin A. *Subcutaneous injection starting on Day 4 and continuing until recovery of neutrophils to >1000/mm³ for 3 days. #Tacrolimus was initiated at a dose of 1 mg i.v. daily, adjusted to achieve a therapeutic level of 5–15 ng/mL and then converted to oral form until discontinuation. If there was no active GVHD, tacrolimus was tapered off by Day 180. **Sirolimus (orally, monitored 2 times each week to maintain a target therapeutic plasma level of 8 to 14 ng/mL during the first 2 months after transplantation, thereafter of 5 to 8 ng/mL until discontinuation). ##Patients 50 years old or older were conditioned with the same regimen as in (D), except for lower dosages of Bu (6–8 mg/kg) and Cy (1.0 g/m²/d).
| Authors          | Pros | Pt. N. | Age* | Remission status | SCT type | 2–4 aGVHD | cGVHD | Relapse | NRM | LFS | OS | GRFS |
|------------------|------|--------|------|------------------|----------|-----------|-------|---------|-----|-----|----|------|
| Ciurea SO, et al. (4) | Yes  | 231    | 28   | Inter- or high-risk AML in CR1 | Haplo-SCT | 36% | 42% | 28% | 32% | 33% | 28% | 28% | 31% |
| Wang Y, et al. (6)  | No   | 558    | 45   | HLA-CR2 (36%)/AD (19%) | Haplo-SCT | 13% | 15% | 13% | 15% | 13% | 15% | 12% | 14% |
| Ruggeri A, et al. (64) | No   | 3511   | 50   | Later CR (28%)/AD (38%)# | Haplo-SCT | 19% | 19% | 19% | 19% | 19% | 19% | 19% | 19% |
| Versluis J, et al. (65)@ | No   | 333    | 25   | Inter- or high-risk AML in CR1 | Haplo-SCT | 31% | 32% | 32% | 32% | 32% | 32% | 32% | 32% |
| Ruggeri A, et al. (64) | No   | 163    | 56   | CR1 (56%) | UCBT | 33% | 34% | 34% | 34% | 34% | 34% | 34% | 34% |
| Brissot E, et al. (68) | No   | 199    | 51.9 | Refractory (41%)/relapse (59%) | Haplo-SCT | 33% | 34% | 34% | 34% | 34% | 34% | 34% | 34% |
| Battipaglia G, et al. (63) | No   | 389    | 52   | Refractory (42%)/relapse (58%) | Haplo-SCT | 28% | 27% | 27% | 27% | 27% | 27% | 27% | 27% |
| Konuma T, et al. (22) | No   | 1102   | 51   | CR1(76%)/≧CR2(24%) | Haplo-SCT | 39% | 37% | 37% | 37% | 37% | 37% | 37% | 37% |

*the median age of patients.

**indicates that patients with poor-risk AML were enrolled in this study.

†indicates that haplo-SCT and MSDT (10/10) had lower CIRs than MSDT (P<0.01 for all).

‡indicates that UCBT experienced lower RFS than MSDT (P<0.01 for all).

#indicates that the percentages of patients in the haplo-SCT group with CR2 or AD were higher than those of the MSDT group (P<0.0001) or the UCB group (P<0.0001).

‡‡indicates P<0.01 compared with that of MSDT.

‡‡‡indicates P=0.02 compared with that of haplo-SCT.

AML, acute myeloid leukemia; haplo-SCT, haploidentical stem cell transplantation; Pros, prospective; Pt, patient; N, number; SCT, stem cell transplantation; GVHD, graft-versus-host disease; aGVHD, acute GVHD; cGVHD, chronic GVHD; NRM, nonrelapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, GVHD and relapse-free survival; NA, not available; Rel, relapse; CR2, complete remission; MUDT, human leukocyte antigen (HLA)-matched unrelated donor transplantation; yr, year; MSDT, HLA-matched sibling donor transplantation; AD, advanced disease; UCBT, umbilical cord blood transplantation; HR, hazard ratio; MMUDT, mismatched MUDT; d, day.
### TABLE 2
Published PKIU studies comparing haplo-SCT with chemotherapy alone in adult and pediatric AML cases.

| Author, Yr, Ref. | Pts (No.) | Diagnosis | Disease status | Treatment modality | Conditioning regimen | relapse | NRM | LFS | OS | Prospective study |
|------------------|-----------|-----------|----------------|-------------------|----------------------|---------|-----|-----|----|-------------------|
| Huang XJ, et al. (5) | 58 | Inter/high-risk | CR1 | Haplo-SCT | MAC | 12% at 4yr * | 0% at 4yr | 74% at 4yr * | 78% at 4yr * | Yes |
| Zhu HH, et al. (7) | 40 | High-risk | CR1 | Chemotherapy | NA | 58% at 4yr | 12% at 4yr | 44% at 4yr | 55% at 4yr | |
| Lv M, et al. et al. (53) | 85 | Inter-risk | CR1 | Haplo-SCT | MAC | 12% at 3yr * | 0% at 3yr | 74% at 3yr * | 78% at 3yr * | Yes |
| Hu GH, et al. (55) | 28 | High-risk | CR1 | Haplo-SCT | MAC | 18% at 5yr ** | HR=0.238 | 87% at 5yr ** | 83% at 5yr | No |
| Xue YJ, et al. (54) | 33 | Inter-risk | CR1 | Chemotherapy | NA | 50% at 5yr | P=0.032 | 62% at 5yr | 71% at 5yr | |

PKIU, Peking University Institute of Hematology; MSDT, human leukocyte antigen-matched sibling donor transplantation; haplo-SCT, haploidentical stem cell transplantation; Yr, year; Ref., reference; No., number; aGVHD, acute graft-versus-host disease; NRM, nonrelapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, GVHD and relapse-free survival; pre-MRD, pretreatment minimal residual disease; Ad, advanced disease; MA, myeloablative; G-PB, granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood harvests; G-BM, G-CSF simulated bone marrow harvests; NA, not available.

*P<0.01 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

**P<0.01 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

†P<0.05 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

‡P=0.059.

*Indicate event-free survival.

### TABLE 3
Studies on haploidentical allografts with superior graft-versus-leukemia effects to those of MSDT.

| Author, Yr, Ref. | Pts (No.) | Diagnosis | Disease status | Transplant modality | Conditioning regimen | Stem cell source | 2–4 aGVHD | Chronic GVHD | relapse | NRM | LFS | OS | GRFS |
|------------------|-----------|-----------|----------------|-------------------|----------------------|-----------------|-----------|--------------|---------|-----|-----|----|------|
| Chang YJ, et al. (1) | 34 | AML (pre-MRD) | Inter+Ad (84%) | Haplo-SCT | MA (100%) | G-PB+G-BM (100%) | NA | NA | 19% at 4yr * | 7% at 4yr | 74% at 4yr * | 83% at 4yr * | NA |
| Zhao XS, et al. (1) | 107 | AML (pre-MRD) | Inter+Ad (82%) | MSDT | MA (100%) | G-PB+G-BM (100%) | NA | NA | 55% at 4yr | 12% at 4yr | 33% at 4yr | 38% at 4yr | NA |
| Zhao XS, et al. (1) | 14 | FLT3+ AML (pre-MRD) | ≥CR2 (29%) | Haplo-SCT | MA (100%) | G-PB+G-BM (100%) | 36% | 36% at 2yr | 31% at 2yr * | 8% at 2yr | 63% at 2yr * | 71% at 2yr * | NA |
| Zheng FM, et al. (1) | 69 | AML high-risk | ≥CR2 (20.3%) | MSDT | MA (100%) | G-PB+G-BM (72.5%) | 34.8% | 35% at 3yr | 16% at 3yr * | 11% at 3yr | 73% at 3yr | 75% at 3yr | NA |
| Guo HD, et al. (1) | 23 | AML high-risk | ≥CR2 (26.1%) | MSDT | MA (100%) | G-PB+G-BM (60.9%) | 13.0% | 14% at 3yr | 39% at 3yr | 0% at 3yr | 61% at 3yr | 73% at 3yr | NA |
| Yu S, et al. (1) | 106 | AML high-risk | CR1 (100%) | Haplo-SCT | MA (100%) | G-PB+G-BM (100%) | 40% | 39% at 3yr | 14% at 3yr | 15% at 3yr | 71% at 3yr | 72% at 3yr | 60% at 3yr |

MSDT, human leukocyte antigen-matched sibling donor transplantation; haplo-SCT, haploidentical stem cell transplantation; Yr, year; Ref., reference; No., number; aGVHD, acute graft-versus-host disease; NRM, nonrelapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, GVHD and relapse-free survival; pre-MRD, pretreatment minimal residual disease; Ad, advanced disease; MA, myeloablative; G-PB, granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood harvests; G-BM, G-CSF simulated bone marrow harvests; NA, not available.

*P<0.01 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

**P<0.01 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

†P<0.05 for relapse, LFS and OS compared between haplo-SCT and chemotherapy.

‡P=0.035 for GRFS compared between haplo-SCT and MSDT.
umbilical cord blood transplantation (UCBT). Here, we mainly focused on published studies that compared the outcomes between HIDs and other donors in the last five years (Table 1).

**Clinical Outcomes Between Haplo-SCT and MSDT**

In 2015, researchers from China reported the results of a multicenter, prospective study that compared the outcomes of AML patients in CR1 who either underwent haplo-SCT (n=231) or MSDT (n=219) (6). Wang et al. (6) observed similar 3-year CIR (HR=1.06, P=0.85), NRM (HR=0.58, P=0.14), LFS (HR=0.83, P=0.42), and OS (HR=0.83, P=0.42) between the two transplant modalities. These results, together with other studies (69, 82, 91), suggest that haplo-SCT based on immune tolerance induced by GSF and ATG is a valid alternative as a postremission treatment of intermediate- or high-risk AML patients in CR1 lacking an identical donor. In 2019, after analyzing data obtained from the CIBMTR database, Rashidi et al. (79) demonstrated that patients with AML in CR1 who received PT-Cy-based haplo-SCT (n=336) had comparable outcomes in 3-year CIR (HR=0.88, P=0.27), NRM (HR=1.26, P=0.16), LFS (HR=1.06, P=0.50), and OS (HR=1.15, P=0.15) and significantly lower chronic GVHD (HR=0.38, P<0.01) than those who received MSDT (n=869). These results suggest that haplo-SCT is an alternative source for AML cases in CR1 (Table 1).

Except for the two studies reported by Rashidi et al. and Wang et al. (6, 79), other scholars also confirmed the similarity between haplo-SCT and MSDT in treating AML in CR2, secondary AML, poor-risk AML and refractory/relapsed AML (Table 1) (64, 70, 80). More recently, in a prospective multicenter cohort study, Yu et al. (92) showed that treating high-risk AML in CR1 with haploidentical allografts could significantly decrease the cumulative incidence of positive posttransplant MRD (18% vs. 42%, P<0.001) and increase the probability of 3-year GVHD and relapse-free survival (63% vs. 43%, P=0.035) with those who received allografts from MSDs. These results suggest that haplo-SCT has a stronger graft-versus-leukemia (GVL) effect than MSDT in high-risk AML patients in CR1 (92). Thus, increasing evidence supports the notion that haplo-SCT should be recommended as one of the optimal postremission therapy choices for transplant candidates with AML.

In a recent meta-analysis, Yang et al. (93) demonstrated that haplo-SCT, either the Baltimore protocol or the Beijing protocol, could achieve comparable 1-year CIR (OR, 0.83; P=0.180) and NRM (OR, 0.98; P=0.910) to those of MSDT in another meta-analysis, which included 24 studies and 11,359 cases. Overall, the literature published thus far (64, 70, 80) suggests that for patients with AML, MSDs remain the first choice when HIDs are also available due to the early delayed immune recovery and higher infection rate following haplo-SCT compared to those with MSDT (58, 94).

**Clinical Outcomes Between Haplo-SCT and UCBT**

In 2009, Huang et al. (81) reported that treating hematological malignancies with haplo-SCT (n=219) could achieve comparable outcomes, including 2-year chronic GVHD (54% vs. 40%, P=0.17), CIR (12% vs. 18%, P=0.12), NRM (20% vs. 18%, P=0.98), LFS (67% vs. 61%, P=0.98) and OS (74% vs. 74%, P=0.74), to those of MUDT (n=78), although higher grades II to IV acute GVHD (HR=1.72, P=0.046) were observed in the haplo-SCT cohort. These preliminary data indicate that haplo-SCT could be an alternative source for patients with hematological malignancies who lack MSDs or MUDs (81). In another retrospective pair-matched comparative study of the EBMT database with data from the Beijing Protocol, Sun et al. (10) showed comparable outcomes between haplo-SCT and MUDT for treating AML patients in CR1, suggesting that HIDs could be an alternative stem cell source when a fully matched URD is not available.

For poor-risk AML in CR1, Versluis et al. (70) observed that haplo-SCT could achieve comparable outcomes to those of 10/10 matched MUDT but superior outcomes to those of 9/10 matched MUDT. Patients with refractory/relapsed AML who underwent haploidentical allografts experienced comparable outcomes to those of patients who received either MUDT or mismatched unrelated donor transplantation (MMUDT) (85). Ongoing prospective, randomized studies are performed to validate the disadvantages and advantages between haploidentical allografts and MUDT (NCT04067180 and NCT04232241), although current data (4, 24, 70, 83, 85, 86, 95) suggest that an HID is a valid option for high-risk AML patients in CR1 or with active disease as well as R/R AML.

Based on the results of the meta-analysis, Arcuri et al. (96) observed that treating hematological malignancies with PTCy-based haplo-SCT could achieve a similar OS rate (HR, 0.98) to MUDT. However, the incidence of all forms of GVHD (2–4 aGVHD, HR, 0.52; cGVHD, HR, 0.25) and NRM (HR, 0.85) was lower after haplo-SCT than after MUDT. Gagelmann et al. (97) showed that, compared with MMUDT, haplo-SCT with PTCy was associated with reduced all-cause mortality (OR, 0.75) and better outcomes (OR, 0.51). Overall, HIDs could be an alternative stem cell source for treating subjects with AML, especially poor-risk subjects, who lack MSDs in experienced centers due to easy access to first and second stem cell harvests, although the current algorithm suggests that MUDs (10/10) should be preferred to HIDs (42, 98).

**Clinical Outcomes Between Haplo-SCT and UCBT**

In 2011, a 2 parallel multicenter phase 2 trial performed by Brunstein et al. (99) provided preliminary results indicating that the outcomes between double UCBT and haplomarrow transplantation with reduced intensity conditioning (RIC) regimens in treating leukemia and lymphoma are comparable to those reported after MUDT. However, from the point of view of graft acquisition and early direct charges, haplo-SCT may result in early cost savings over double UCBT and may be preferred by transplant centers and patients with more limited resources, as described by Kanate et al. (100).
Among different studies remain controversial. Therefore, meta-analyses (71), suggests that haplo-SCT might be better than UCBT in treating AML. Dholaria et al. demonstrated that 9/10 MUDT with PTCy may be preferred over UCBT if a 10/10 matched unrelated donor is not available (72). Prespecified analysis of secondary end points demonstrated lower 2-year NRM after haplo-SCT than that of UCBT (11% vs. 18%, \( P=0.04 \)), which led to higher OS after haplo-SCT compared with that of UCBT (57% vs. 46%, \( P=0.04 \)), but the PFS was comparable (35% vs. 41%, \( P=0.41 \)). Fuchs et al. (65) suggested that although both donor sources extend access to RIC transplantation, analyses of secondary end points, including OS, favor HIDs.

More recently, in 2 parallel phase II trials, 368 patients aged 18 to 70 years with chemotherapy-sensitive lymphoma or acute leukemia in CR were randomly assigned to the UCBT group (n=186) or haplo-SCT group (n=182) (65). Prespecified analysis of secondary end points demonstrated lower 2-year NRM after haplo-SCT than that of UCBT (11% vs. 18%, \( P=0.04 \)), which led to higher OS after haplo-SCT compared with that of UCBT (57% vs. 46%, \( P=0.04 \)), but the PFS was comparable (35% vs. 41%, \( P=0.41 \)). Fuchs et al. (65) suggested that although both donor sources extend access to RIC transplantation, analyses of secondary end points, including OS, favor HIDs.

In a recent meta-analysis, Wu et al. (71) found that haplo-SCT was associated with a lower NRM (0.72, 95% CI 0.64 to 0.80), leading to superior OS (OR, 0.74, 95% CI, 0.68 to 0.80) and PFS (0.77, 95% CI 0.72 to 0.83) compared with UCBT. Overall, the available published literature (65, 70, 84, 100), especially meta-analyses (71), suggests that haplo-SCT might be better than UCBT in treating AML.

Overall, the landscape of allografts for hematological malignancies apparently changed with the position alteration of haplo-SCT in AML treatment (5, 11, 13, 22, 59–61). Most scholars agree that for patients with hematological malignancies, including AML, who lack MSDs and urgent transplantation, HIDs could be selected first. Impressively, based on the dataset of the Acute Leukemia Working Party of the EBMT registry, Dholaria et al. demonstrated that 9/10 MUDT with PTCy may be preferred over UCBT if a 10/10 matched unrelated donor is not available (72) (Figure 2A). Currently, a few retrospective studies compared the clinical outcomes between the Beijing Protocol and the Baltimore protocol in treating patients with hematological malignancies (73, 101, 102), however, the results among different studies remain controversial. Therefore, prospective, multicenter, randomized studies are needed.

**Could HIDs Be Selected First for Subgroup AML Patients to Decrease the Relapse Rate?**

According to the current opinion, MSDs remain the first choice for transplant candidates with AML, although comparable outcomes were observed between haplo-SCT and MSDT (42, 105). However, we found that for all AML patients with positive pretransplantation MRD, haplo-SCT patients experienced a lower NRM and better LFS and OS than MSDT patients (25, 106–109). These results suggest a stronger GVL effect of HIDs than MSDs. We further confirmed the stronger GVL effects after haplo-SCT than MSDT in AML subgroups with positive pretransplantation MRD, including (t(8;21) AML (25), Flt3 mutation-positive AML (110), and high-risk AML patients in CR1 (92) (Table 3). Interestingly, the stronger GVL effect of HIDs compared with MSDs was also confirmed in ALL patients with positive pre-MRD (111) and lymphoma subjects (105). More recently, a study from the Acute Leukemia Working Party of the EBMT showed that ALL patients treated with haplo-SCT experienced a significantly lower 2-year CIR than those of patients receiving MSDT (HR=0.63, \( P=0.002 \)) (112), which provides new evidence supporting the stronger GVL effect of HIDs.

More recently, haploidentical and major histocompatibility (MHC)-matched transplant models were established by Guo et al. (25) after infusion of leukemia cells that carried the human AML-ETO or MLL-AF9 fusion gene to investigate the immune cell dynamic response during leukemia development in vivo. They showed that haplomatching the MHCs of leukemia cells with recipient mouse T cells prolonged leukemic mouse survival and reduced leukemia burden (25). The stronger GVL activity in the haplo-SCT group was mainly induced by decreased apoptosis and increased cytotoxic cytokine secretion, including tumor necrosis factor-\( \alpha \), interferon-\( \gamma \), pore-forming proteins and CD107a secreted by T cells or natural killer (NK) cells (25).

Overall, in contrast to the traditional notion that MSDs remain the first choice, recent advances in haploidentical transplantation settings raise a new idea (92, 105, 107, 108, 110–114): for some subgroups of AML patients, HIDs might be chosen first (19), although further research is needed before this could be included in the donor selection algorithm (115, 116).

**Could the Best HIDs Be Selected to Decrease CIR of AML?**

Donor characteristics are important variables for transplant outcome determination. In haplo-SCT settings, we and other researchers suggest a donor selection algorithm for which the key issue is that the younger the better (42, 117, 118). Regarding the best donor selection in AML patients treated with haplo-SCT, NK cell alloreactivity (KIR ligand mismatch between recipients and donors) was associated with better survival in AML patients who received haplo-SCT with ex vivo TCD. However, in unmanipulated haplo-SCT settings, KIR ligand mismatch was not associated with better survival of acute leukemia patients (42, 119, 120). Our group found that, compared to subjects with KIR ligand mismatch, cases with KIR ligand match were associated with rapid quantitative and functional NK cell recovery, which could contribute to lower CIR and better survival of AML cases.
treated with the Beijing Protocol (121). In a recent multicenter retrospective study, 1270 patients with acute lymphoma, including AML (n=1019) and ALL (n=251), received haplo-SCT using a myeloid ablative conditioning regimen or RIC. Cannani et al. (40) showed that for cases with age >40, donor age (>40) was correlated with higher NRM and inferior LFS and OS. Unfortunately, the current algorithm for the best HID selection is mainly based on the results obtained from the total patient population (41, 122). Therefore, multicenter, prospective studies are needed to answer the question of who is the best HID for AML patients, especially in unmanipulated haplo-SCT settings.

Could We Incorporate Novel Methods With Haplo-SCT for R/R AML Treatment?
Venetoclax (VEN), a BCL-2 inhibitor, has been approved for unfit, older patients with AML (123, 124). In a recent study, sixty-eight patients, including newly diagnosed AML (ND AML) and R/R AML, were enrolled [phase IB (PIB), 16 (R/R); phase IIA (PIIA), 29 (ND); phase IIB (PIIB), 23 (R/R)]. Fludarabine (Flu), cytarabine (Ara-C), G-CSF, and idarubicin (IDA) + VEN (FLAG-IDA+VEN) were administered to all subjects. FLAG-IDA induction consisted of 28-day cycles of intravenous (iv) Flu (30 mg/m²) and Ara-c (1.5–2 g/m² iv) on days (d) 2–6, IDA (iv; ND-AML: 8 mg/m² d4–6; R/R-AML: 6 mg/m² d 4–5), and G-CSF (5 μg/kg d1–7). For patients in the PIB arm, VEN was administered as follows: 200 mg d1–21 (n=8), d1–14 (n=5); 400 mg d1–14 (n=3). For cases in the PIIA and PIIB arms, VEN was administered at 400 mg D1–14. After induction therapy, 67% of patients with R/R-AML (including 57% [n=8] subjects receiving prior allo-SCT) and 83% with sAML, t-AML, or ts-AML attained a CRc (CR+CRi). Eighteen (46%) R/R-AML cases, including 75% (n=6) of responding R/R patients who experienced a prior allo-SCT, were transitioned to allo-SCT. DiNardo et al. (125) further showed that for cases with R/R-AML, improved OS was observed in patients with consolidative allo-SCT in CRc versus without (median OS: NR [14 to not estimated (NE)] v 7 [4 to NE].
months; \(P=0.009\). This study provides a promising approach, combining FLAG-IDA+VEN with allografts, for the treatment of R/R AML.

To treat a patient with FUS-ERG+ AML who relapsed after allo-SCT within 3 months and resisted multianti-short chemotherapy, donor lymphocyte infusion (DLI), Yao et al. (126) used donor-derived CD123-targeted CAR T cells (CART123) as part of a conditioning regimen for haplo-SCT. They observed a reduced blast level in BM within 2 weeks, which coincided with CAR copy expansion. After achieving full donor chimerism, this patient achieved CR with incomplete blood count recovery. These results suggest that CART123 in combination with haplo-SCT could be used as a therapy for relapsed AML subjects.

Overall, available data suggest that (125, 127–137), several other novel methods, such as ivosidenib, gilteritinib, flotetuzumab, quizartinib, CD33/CD3 bispecific T-cell engager antibody, and CAR- NK cells, could be successfully used for R/R AML patient therapy either alone or combined with allo-SCT, including haploidentical allografts (Table 4).

### Could We Incorporate Other Approaches for AML Relapse Treatment and Prevention After haplo-SCT?

The outcomes of AML patients who relapse after allografts remain poor, with a 5-year OS of less than 20%, and either DLI or second allo-SCT is prescribed (138). More recently, Cui et al. (139) enrolled 6 AML patients who relapsed after transplantation. The median percentage of CD38 expression on blasts in the bone marrow of these patients was 95% before CD38-targeted CAR-T cell (CAR-T-38, from autologous and 2 from donors) treatment. Four of six (66.7%) patients achieved CR or CR with incomplete count recovery (CRI) 4 weeks after the initial CAR-T-38 cell therapy. The CIR at 6 months was 50%. The median times of OS and LFS of these cases were 7.9 and 6.4 months, respectively. One patient who relapsed 117 days after the first CAR-T-38 treatment achieved remission after the second CAR-T-38 cell infusion. The side effects of these patients were manageable. There were no off-target effects on monocytes and lymphocytes. Although there was a limited number of cases and a relatively short follow-up time were presented by Cui et al. (139), their preliminary data highlight the clinical utility and safety of CAR-T-38 cell therapy in treating relapsed AML following allo-SCT. Several trials (NCT02782546, 04024761, 03300492) investigating the feasibility of immunotherapy with NK cells are ongoing (Table 4).

Considering the poor outcomes of HR-AML, a number of strategies for relapse prophylaxis or prevention have been used in the clinic (140). In a phase II, open-label, multicenter, randomized controlled trial (141), 204 HR-AML subjects with negative MRD who had received allo-SCT (mainly haplo-SCT, n=148) 60–100 days before were randomly (1:1) assigned to either no intervention (non–G-Dec group) or rhG-CSF combined with minimal dose Dec (G-Dec group: 100 mg/m² of rhG-CSF on Days 0–5 and 5 mg/m² of Dec on Days 1–5). Gao et al. (141) observed that patients in the G-Dec group experienced a lower 2-year CIR (15.0% vs. 38.3%, \(P=0.01\)) accompanied by rapid recovery of CD8+ T cells, NK cells, and regulatory T cells compared with patients in the non–G-Dec group, both of which led to higher LFS (HR=0.38, \(P=0.01\)) and OS (HR=0.45, \(P=0.01\)). No differences in the 2-year chronic GVHD without relapse between the two groups (23.0% vs. 21.7%, \(P=0.81\)) were shown. The authors (141) suggest that rhG-CSF combined with minimal-dose Dec maintenance therapy following transplantation can reduce the CIR, leading to the acquisition of GVL effects and immune tolerance.

Impressively, data from two independent randomized trials (15, 142) show that sorafenib maintenance posttransplantation, including haplo-SCT, prevents disease relapse in patients with FLT3-ITD AML both with negative or positive MRD after allograft transplantation, resulting in an OS benefit. A previous study by Mathew et al. (143), in allograft settings, showed that sorafenib increased IL-15 production by FLT3-ITD+ leukemia cells. IL-15 further caused an increase in CD8+CD107a+IFN-γ T cells with high levels of Bcl-2 and reduced PD-1 levels, and this cell subset could eradicate leukemia in secondary recipients. These studies (15, 142) provided strong evidence indicating that targeted posttransplant maintenance therapy should be a new treatment paradigm for AML, although questions remain. Moreover, additional studies are needed to investigate the optimal initial time and duration of sorafenib maintenance after allo-SCT as well as to elucidate the underlying mechanisms of sorafenib activity in the allograft setting.

In summary, the successful application of new strategies following allografting (15, 137, 142, 144), such as rhG-CSF combined with minimal-dose Dec, Aza plus VEN (NCT04809181), and targeted agent maintenance, could help AML patients avoid hematological relapse as much as possible, thus decreasing the CIR and improving the survival rate (Figure 2B).

### Could Infections Be Effectively Prevented Using Adoptive Cell Therapy?

In haplo-SCT with the G-CSF modality, the cumulative incidence of cytomegalovirus (CMV) DNAemia varies from 63.7 to 66.1% and remains one of the main causes of morbidity and mortality. BKV and EBV infection are also frequent in haplo-SCT and a risk factor for worse survival except for CMV infection (58, 145). For cases with refractory CMV infection who failed to respond to ganciclovir, foscarnet, and cidofovir, adoptive T-cell therapies, such as CMV-specific T-cells (CMV CTLs), represent a promising approach (146, 147). Using a humanized HCMV-infected mouse model, our group further elucidated that systemic HCMV infection could be combated after first-line therapy with CMV CTLs via in vivo promotion of the recovery of graft-derived endogenous CMV CTLs (55). These studies provide substantial evidence suggesting that refractory CMV infection could be successfully treated by adoptive transfer of CMV CTLs. Future studies should focus on risk factor-directed intervention or the development of new drugs for CMV infections in haplo-SCT settings.

Olson et al. (148) performed a clinical trial in which HLA-matched third-party BKV-specific CTLs were infused into 59 patients who developed BKV-HC following allo-SCT. They
In summary, recent studies (147) showed some promising clinical trials focusing on patients with R/R AML or those who received haplo-SCT.

TABLE 4 | Ongoing clinical trials focusing on patients with R/R AML or those who received haplo-SCT.

| ClinicalTrials.gov Identifier | Randomized study | Estimated Study Completion Date | Aim of the study |
|-------------------------------|------------------|---------------------------------|------------------|
| NCT04067180                  | Yes              | August 2028                     | To evaluate whether haplo-SCT is as good as URD SCT for the treatment of AML. |
| NCT02732546                  | No               | January 30, 2024                | To evaluate the whether CIML NK could improve LFS of AML patients receiving haplo-SCT. |
| NCT04232241                  | Yes              | November 2024                   | To compare anti-leukemic activity between MUDT (10/10) and haplo-SCT for patients with AL. |
| NCT03384225                  | Yes              | July 31, 2022                   | To evaluate if CBA could decrease relapse after haplo-SCT in HR/R AML compared with FBA. |
| NCT03300492                  | No               | January 31, 2023                | Safety, Feasibility of Pre-emptive therapy With in Vitro Expanded NK Cells in AML/MDS Patients receiving Haplo-HSCT (Phase I/II). |
| NCT04679401                  | No               | October 31, 2023                | Immunosuppression-free Treg-cell Graft-engineered haplo-SCT in R/R AML/MDS (Phase I). |
| NCT04060277                  | Yes              | July 22, 2022                   | To Evaluate the Safety and Efficacy of SMART101 Injection to Accelerate IR After TCD allo-SCT in Patients With AL (Phase I). |
| NCT04809181                  | No               | March 19, 2026                  | To investigate the safety and efficacy of anti-CD123 CAR-T cells in patients with R/R CD123+ AML. |
| NCT04959003                  | No               | September 2026                  | To investigate the feasibility and safety of CD123-targeted CAR-T cell therapy for patients with R/R AML. |
| NCT04599543                  | No               | November 15, 2023               | To evaluate the safety and efficacy of IL3 CAR-T Cell Therapy for R/R Acute Myeloid Leukemia. |
| NCT04689004                  | No               | January 15, 2024                | The Safety and Efficacy of NKG2D CAR-T Cell Therapy for Patients With R/R AML. |
| NCT03473437                  | No               | December 31, 2022               | The CAR-T cells (single CAR-T or double CAR-T cells with CD33,CD38,CD56,CD123,CD117,CD133, CD34 or MuC) for R/R AML. |
| NCT04014881                  | No               | July 1, 2022                    | To evaluate the safety and efficacy of anti-CD123 CAR-T cells in patients with R/R CD123+ AML. |
| NCT03971799                  | No               | December 2024                   | To determine The safety and feasibility of anti-CD33 CAR-T cells in children and AYAs with R/R AML. |
| NCT04010877                  | No               | December 31, 2023               | The feasibility, safety and efficacy of multiple CAR T-cell therapy targeting CD123 or CD33 in patients with R/R AML. |
| NCT04272125                  | No               | July 1, 2023                    | To evaluate the efficacy and safety of CD123-targeted CAR-T cell therapy for patients with R/R AML. |
| NCT04835519                  | No               | April 8, 2024                   | To evaluate safety and tolerability of functionally enhanced CD33 CAR-T cells in patients with R/R AML. |
| NCT04219163                  | No               | July 31, 2038                   | CAR T-cells for The Treatment of AML Expressing CLL-1 Antigen. |
| NCT04678336                  | No               | January 2036                    | To explore the safety, feasibility, and efficacy of CART123 cells in pediatric subjects with R/R AML. (Phase I). |
| NCT04762485                  | No               | February 28, 2024               | This is a phase 1/2 study to evaluate the efficacy and safety of CAR-T cells targeting CD7 for patients with R/R CD7 positive AL. |
| NCT04766840                  | No               | December 1, 2023                | To Evaluate the Safety and Efficacy of Donor-derived CAR-T Cells for patients with R/R AML. |
| NCT03631576                  | No               | August 10, 2021                 | This study aims to assess the safety and toxicity of CD123/CLL1 CAR-T Cells to patients with R/R AML. |
| NCT04318678                  | No               | July 1, 2025                    | To explore the safety of autologous, CD123-CAR T cells in patients (≥21 years) with R/R CD123+ AML. |
| NCT04803929                  | No               | March 1, 2026                   | To investigate the safety and efficacy of novel iLT3-targeted CAR-T cell therapy for patients with R/R AML (M4/M5). |
| NCT04789408                  | No               | January 2024                    | A Phase 1 Open-label, Multicenter Study Evaluating an Autologous Anti-CLL-1 CAR T-cell therapy in Subjects With R/R AML. |
| NCT03190278                  | No               | October 2022                   | Phase I first-in-human study evaluating the safety and efficacy of UCART targeting CD123 in patients with R/R AML. |

AML, acute myeloid leukemia; Haplo-SCT, haploidentical stem cell transplantation; URD SCT, unrelated donor SCT; CIML NK, cytokine-induced memory-like natural killer cells; LFS, leukemia-free survival; AL, acute leukemia; MUDT, human leukocyte antigen-matched unrelated donor transplantation; CBA, cladribine-based conditioning; FBA, fludarabine-based conditioning regimen; HR, high-risk; R, refractory; R/R, relapsed/refractory; Treg, regulatory T cells; CAR-T, chimeric antigen receptor (CAR)-expressing T cells; Aza, azacitidine; VEN, venetoclax; MRD, minimal residual disease; TCD, T cell depleted; SMART101, human T lymphocyte progenitor; IR, immune recovery; IL-3, interleukin-3.

observed a rapid response to BKV-CTL infusion. The Day 14 and Day 45 overall response rates were 67.7% and 81.6%, respectively. No patient lost a previously achieved response. There were no cases of de novo grade III or IV GVHD, graft failure, or infusion-related toxicities. BKV-CTLs were observed in patient blood samples up to 3 months postinfusion, and their in vivo expansion predicted a clinical response. This study suggests that off-the-shelf BKV-CTLs are a safe and effective therapy for the management of patients with BKV-HC after allo-SCT (148). Therefore, rapid reconstitution of immunity to a broad range of viral and fungal infections can be achieved using a multipathogen-specific T-cell product (147, 149).

In summary, recent studies (147) showed some promising preliminary data and ongoing clinical trials on AML relapse prophylaxis, intervention, and treatment (Figure 2B and Table 4), as well as infection prevention and therapy. Both of these factors will pave the way for outcome improvements for patients with AML who undergo haploidentical allografts.

FUTURE PROSPECTS

In the next five to ten years, the issue of relapse and infections remains to be solved, although haplo-SCT has been rapidly expanded in AML treatment (5, 11, 13, 22, 59–61). Regarding relapse, elucidating the mechanisms underlying leukemia recurrence remains the most important way to find novel targets for intervention or treatment of relapse. Recently, the application of single-cell sequencing techniques has been used for the following purposes (150–160): i) identifying differentiated AML cells with immunosuppressive properties; ii) dissecting the clonal heterogeneity of AML; iii) providing novel insights into...
the clonal evolution and resistance mechanisms of leukemia cells; iv) identifying novel targets for AML therapy; and v) highlighting the profound impact of AML on NK cell heterogeneity. These advances provide new clues and suggest that we could further discover new mechanisms underlying leukemia relapse after transplantation based on the abovementioned new techniques as well as in vitro and in vivo functional experiments.

In addition, based on current available data (25, 106, 108, 113, 140, 161), at different timepoints (pre- and posttransplantation), realization of individual therapy of AML by combining haplo-SCT with other novel methods (113), such as CAR-T therapy, target agents, and others, should be investigated. Could changing positive MRD to negative MRD pretransplantation further improve clinical outcomes? Which is the best method for positive pretransplantation MRD eradication? For patients with intermediate- or adverse-stratification, should maintenance after transplant be given routinely? To answer these questions, prospective, multicenter, randomized clinical trials are urgently needed.

Infections, especially viral infections, are of concern. Both in the Beijing Protocol and the Baltimore Protocol, the delayed reconstitution of CMV-specific CTLs and NK cells was associated with CMV reactivation (58, 145). Therefore, enhancing CMV-specific CTL and NK cell recovery represents a future direction for virus infection prevention, including CMV, EBV, and BKV. Unfortunately, overcoming the functional impairments of adaptive NK cells to produce IFN-γ (162), a phenomenon due to the virus-induced expression of lymphocyte activation gene 3 and programmed cell death protein 1 checkpoint inhibitors, remains to be investigated. In addition, a phase II multicenter, randomized trial is ongoing to investigate the protective function of the CMV-MVA triplex vaccine in adult recipients who received haplo-SCT (NCT 04161885).

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**CONCLUSION**

Recent advances in haploidentical allografts have significantly changed their position in AML treatment (5, 11, 13, 22, 59–61). Their combination with novel therapies, such as CAR-T cells and Ven, could make more R/R patients with AML eligible for curative haplo-SCT who previously experienced poor outcomes when receiving allografts in relapse or NR status (125). Ongoing studies focusing on relapse, infections, and hematopoietic and immunological reconstitution enhancement would further improve haploidentical transplant outcomes of AML. In the long term, biomarkers (163, 164), such as MRD, directed donor selection (108), conditioning selection (14), and immunological enhancement for relapse intervention (165), will help us realize precision medicine in the setting of haplo-SCT for treating patients with AML.

**AUTHOR CONTRIBUTIONS**

Y-JC and X-JH designed the study. All authors contributed to data interpretation, manuscript preparation, and approval of the final version.

**FUNDING**

This work was partly supported by grants from the Beijing Municipal Science and Technology Commission (Z181100009618032) and the National Key Research and Development Program of China (2017YFA0104500).
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