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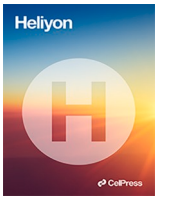

Review article

Expert consensus on microtransplant for acute myeloid leukemia in elderly patients -report from the international microtransplant interest group

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ABSTRACT

Recent studies have shown that microtransplant (MST) could improve outcome of patients with elderly acute myeloid leukemia (EAML). To further standardize the MST therapy and improve outcomes in EAML patients, based on analysis of the literature on MST, especially MST with EAML from January 1st, 2011 to November 30th, 2022, the International Microtransplant Interest Group provides recommendations and considerations for MST in the treatment of EAML. Four major issues related to MST for treating EAML were addressed: therapeutic principle of MST (1), candidates for MST (2), induction chemotherapy regimens (3), and post-remission therapy based on MST (4). Others included donor screening, infusion of donor cells, laboratory examinations, and complications of treatment.

1. Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. Patients over 60 years old account for more than 50% of all AML patients with the median age at diagnosis of nearly 70 years. In the past few decades, due to the application of intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT), the cure rate of adult AML patients less than 60 years old has increased significantly, reaching 35–40% or more, but the outcome remains poor for those aged over 60 years with a median survival rate less than around one year. The poor outcome of elderly AML (EAML) patients is mainly related to the characteristics of high risk cytogenetic and molecular biology of leukemia itself including complex chromosomal karyotype, high risk

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genetic changes and secondary to myelodysplastic syndrome (MDS), which have worse treatment response and a shorter survival time. Additionally, elderly patients often have poor physical status, organ dysfunction and slow hematopoietic and immunologic recovery precluding the use of intensive treatments [1–6]. In recent years, the number of EAML patients receiving reduced intensity conditioning allo-HSCT has increased with encouraging results for carefully selected patients, but the risks of transplant-related mortality (TRM), graft-*versus*-host disease (GVHD) and other side effects have limited its use [7–13]. Developments in immunotherapy and therapies targeting molecules such as FLT3, IDH1/2, or BCL-2 (venetoclax) combined with the hypomethylating agents, decitabine or azacitidine, have improved the remission and early survival rates of EAML patients, however, except for those who receive allo-HSCT, long-term outcome is still poor with one-year overall survival (OS) of 10–36% [14–19].

Microtransplant (MST) is a novel immunotherapeutic model based on allo-HSCT and cell therapy which was first reported by the Chinese team [20]. In 2011, Ai and Guo et al. published the first randomized clinical trial of a small cohort of elderly AML patients demonstrating that infusion of HLA-mismatched G–CSF–mobilized peripheral blood stem cells (GPBSC) combined with chemotherapy (MST) could increase complete remission (CR) rates, improve the survival and avoid GVHD in comparison to chemotherapy alone [21]. Other published data, including single and multi-center studies, from China, the United States and Europe, showed the main benefits of MST for EAML patients were high CR rates and leukemia-free survival (LFS) but low rates of early mortality and severe infection as well as faster recovery of tri-lineage hematopoiesis [21–26]. GVHD and severe cytokine release syndrome (CRS) were rare, and severe GVHD occurred in less than 1% of patients. In addition, MST has achieved favorable results in the post-remission therapy of young adults as well as improved outcomes of high-risk MDS and secondary AML [21]. MST studies for a small number of patients with relapsed or refractory AML, lymphoma and acute lymphoblastic leukemia, even a few immunosuppressed patients with acquired immunodeficiency syndrome (AIDS) (by modified MST), have also been reported [27–33].

Since its establishment in 2015, the International Microtransplant Interest Group has been committed to the study and refinement of MST worldwide and published the results of a multicenter, retrospective study of EAML patients in JAMA Oncology in 2018. Given the considerable clinical challenges, limited treatment options and the need for novel therapy for newly diagnosed EAML patients, we evaluated clinically-relevant publications including some single arm or randomized clinical trial data of MST in combination with new agents from January 1st, 2011 to November 30th, 2022 (see Supplementary file 1 for detailed search strategy), and referred to some guidelines of National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) [34–36]. Four major issues related to the treatment of EAML with MST were addressed, including therapeutic principle, indications, induction therapy, post-remission therapy and complication treatments.

2. Therapeutic principle of MST

Some forms of alloreactive immunotherapy produce anti-neoplastic effects without substantial engraftment or losing donor chimerism have been described [37–42]. Differently, MST is a novel and special form of alloreactive cell therapy that combines conventional chemotherapy or targeted agents with allogeneic donor cell infusion. The purpose of MST pre-conditioning is solely to eliminate leukemic or tumor cells to the greatest extent while avoiding damage to the immune function of the recipient. MST pre-conditioning therefore can use highly effective chemotherapeutic or targeted drugs to eliminate leukemia or tumor cells, however, immunosuppressive agents such as total body irradiation (TBI), fludarabine, and anti-lymphocyte/thymocyte globulin are avoided and GVHD prophylaxis is not required. Through infusion of GPBSCs from HLA-mismatched related or unrelated donors (infusion of unrelated cord blood stem cells has also occasionally been reported [32,43,44]), it is expected to establish transient or persistent donor microchimerism (<1% detectable donor cells), induce graft-*versus*-leukemia/recipient-*versus*-leukemia (GVL/RVL) effect and accelerate hematopoietic/immunologic recovery by promoting expansion of the host and/or donor T cells and stem or progenitor cells [45–49].

In addition to avoiding the use of immunosuppressive agents, it should be noted that MST emphasizes the formation of transient or persistent donor microchimerism and does not intend to form a high rate of donor chimerism or full donor chimerism (FDC) to avoid occurrence of GVHD. Similarly, MST also emphasizes the use of GPBSCs rather than donor lymphocyte infusion (DLI). Recent studies have proved that G-CSF mobilization can significantly promote the hematopoietic recovery and reduce the incidence of GVHD through increasing the number of $CD34^+$ cells in the peripheral blood and regulating the activity of T cells [50,51]. Although conventional DLI retains an anti-leukemic effect, it can significantly weaken and even inhibit the hematopoietic recovery, and increase the risk of GVHD. A recent study by Hu et al. reported that CR and survival rates of patients with fewer HLA-matching loci with unrelated MST donors were similar or even better than those with more HLA-matching loci with related DLI donors [52]. Confirmation of these findings will require a prospective, likely randomized study with larger patient cohorts. The following five issues should be carefully considered in the application of MST.

2.1. Donor screening

Requirements of donor screening and physical examination for MST are the same as those for traditional allo-HSCT. Donor evaluations include high-resolution HLA typing and killer cell immunoglobulin-like receptor (KIR) genotyping and donor-specific *anti*-HLA antibody [53]. Among eligible donors, we prefer HLA-mismatched related donors, but do not exclude HLA-fully mismatched related or unrelated donors as candidates [52]. Avoiding donors who are homozygous for HLA loci that are shared with the recipient is also suggested due to increased risk of GVHD [22].

2.2. Infusion and collection of donor GPBSCs

Qualified consenting donors undergo peripheral blood mononuclear cell mobilization with G-CSF and the cells are collected according to standard protocols [20–22]. Mononuclear cells (MNC) are counted using flow cytometry for $CD34^+$, $CD3^+$, $CD4^+$, $CD8^+$, $CD3^-CD16^+CD56^+$ (NK), $CD3^+CD16^+CD56^+$ (NKT) and γ-δ T cells. The donor GPBSC infusion is usually administered within 24–72 h after cessation of the last dose of cytotoxic drugs and can be delayed to 96 h or longer in special circumstances. The recommended number of infused donor cells is MNC $2.5 \pm 25\% \times 10^8$/kg and/or $CD3^+$ $1 \pm 25\% \times 10^8$/kg. The remaining GPBSCs after the first infusion can be cryopreserved for subsequent use. If the number of cells collected does not meet the needs of full post-remission cycles, replacement with another donor is allowed. The procedures and standards for screening, mobilization and collection of cells are the same as those used for the original donor.

2.3. Supportive care and management of complications

Transfusion of blood products and supportive care should be given according to protocols at each treating center. Most centers consider it a standard of care that all blood products are irradiated before transfusion. The prophylaxis and treatment of bacterial and fungal infections are handled according to the standards of each center. The administration of G-CSF for neutropenia after MST can promote hematopoietic recovery, and each center can choose the type, dosage and duration of these growth factors following their own standards.

Previous studies have shown that GVHD rarely occurs after MST [20–23,52,54]. We therefore do not recommend GVHD prophylaxis after MST. However, if the patient develops high fever, skin rash, diarrhea, and/or liver dysfunction including rapid elevation of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase and/or elevated cytokines including but not limited to IL-2, IL-8, IL-10, IL-6, IL-12, IFN-α and IFN-γ within 5–30 days after GPBSC infusion, the possibility of acute GVHD should be considered, and levels of donor engraftment and other relevant examinations should be performed promptly. If a diagnosis of GVHD is confirmed, treatment with agents such as corticosteroids and other standard agents according to local guidelines should be initiated as soon as possible.

2.4. Concomitant medication

Given the low risk of GVHD, immunosuppressive agents are not recommended before or after induction and consolidation therapy of MST. It is also not recommended to give total body or lymphatic irradiation. There have been no clinical reports of MST resulting in cytomegalovirus (CMV) viremia or pneumonia to date. Therefore, primary prevention of CMV reactivation or disease is not recommended. For those with targetable molecular biology and genetic abnormalities (such as BCR/ABL transcripts, IDH1/2 or FLT3 mutation et al.), the combination of targeted drugs before and after MST is commonly employed and encouraged, but ideally each agent would be better studied in combination with MST to ensure safety and efficacy of the combination. MST incorporated with immunomodulatory agents such as lenalidomide may also get benefit [55]. Those who have concomitant diseases treated with other medications should be treated with those medications as clinically indicated, but MST should be avoided in patients who require uninterrupted immunosuppressive medications such as those used for autoimmune disease.

2.5. Laboratory examination

Routine laboratory examinations including blood cell, bone marrow aspiration cytogenetic, molecular, and immunophenotypic data are necessary. Measurable residual disease (MRD) examinations, immune function studies involving T cells, B cells, NK cells and cytokine monitoring should be performed in accordance with the standards of each center. GVL/RVL effects detected by the pentamer are also recommended, if possible. Many studies have reported that donor microchimerism could be persistent for days to years after MST therapy in hematological diseases and immunosuppressed patients with AIDS [20,21,31]. Recently, Li et al. assessed donor microchimerism by the next-generation sequencing and demonstrated the persistence of donor microchimerism (median 10.5 months) is closely related to outcomes of MST therapy on the AML patients [56]. Although the relationship between the proportion and duration of donor microchimerism and clinical efficacy needs to be further clarified [57–59], the importance of microchimerism analysis of donor cells should still be emphasized. The donor microchimerism detection including fluorescence in situ hybridization (FISH), chromosome analysis, short tandem repeat-polymerase chain reaction (STR-PCR), indel-based PCR, flow cytometry testing, single nucleotide polymorphism (SNP), deletion insertion polymorphisms (DIP) and next-generation sequencing et al. should carry out in accordance with standards of each center.

3. Candidates for MST

The best approach to treat EAML remains controversial. Increasing age is an independent adverse risk factor in patients with EAML. Many studies demonstrated that EAML patients, especially those older than 75 years old, have poor tolerance to standard-dose induction chemotherapy with slower hematopoietic recovery, inferior CR rate and survival times [3–6]. The current guidelines (NCCN and ELN) attach considerable importance to the physical fitness assessment and scoring of EAML patients, establishing criteria that may be more critical than age in determining whether to receive intensive therapy [60–63]. Patients who belong to the fit or unfit group are likely to tolerate intensive or reduced-intensity chemotherapy with aggressive supportive care. Recent studies showed that

EAML patients aged 60–74 years who received MST with appropriate intensity of induction chemotherapy can also obtain higher CR and survival rates without increasing early mortality compared to chemotherapy alone [22]. Therefore, for the EAML patients younger than 74 years of age, especially for the fit group, MST should be considered, including induction and post-remission therapy. In addition, the results published by the Microtransplant Interest Group in JAMA Oncology showed that in EAML patients who received reduced-intensive induction and post-remission chemotherapy-based MST, the CR rate, early mortality and hematopoietic recovery speed were not significantly different between the age groups of 75–85 and 60–74 years [22]. These results indicate that EAML patients, including the 75–85 years age group with good physical status, may benefit from MST including a favorable CR rate and acceptable hematopoietic recovery. Hence, the application of MST based on adjusting chemotherapy doses for these patients is worthy of a consideration. Special attention should also be given to improving supportive care.

The molecular characteristics of EAML are critical in determining prognosis. According to the genetic features at diagnosis, ELN recommendations divide AML patients into three risk groups. In older patients, AML frequently evolves from antecedent MDS, is enriched for high-risk cytogenetic abnormalities, and is often resistant to conventional chemotherapy. These patients have a poor response and tolerance to conventional induction chemotherapy, high risk of bleeding, infection complications, and slow hematopoietic recovery, leading to relatively high early mortality and lower CR and survival rates. However, results from the Microtransplant Interest Group showed that among patients in the 60–85 age group, the CR rate was 66.7% in those with high-risk features including chromosomal or molecular abnormalities and secondary MDS receiving MST-based induction remission therapy, although this is still significantly lower than 82.1% of the standard risk group. Studies from Sung and Punwani also had similar results [54,64]. More importantly, early mortality and speed of hematopoietic recovery of this group were not significantly different from those in the standard-risk group, indicating may benefit from MST in this subgroup. In addition, considering that patients in this group tend to have a higher relapse rate, it should be considered to appropriately increasing the intensity of induction chemotherapy or with targeted therapy based on the MST platform to further improve LFS. However, for EAML patients at relapsed and/or refractory stage, although a few studies have reported that MST can improve CR and survival rates, an adequately large number of patients is lacking [27,32,43,64–66] and this consensus does not make a clear recommendation.

4. MST induction therapy in newly diagnosed EAML

Induction chemotherapy regimens for newly diagnosed EAML have been recommended by the international expert panel of NCCN and ELN according to the patient's age, prognosis and physical status [35,67]. For patients under 75 years of age and in fit and unfit groups, MST combined with standard intensive or reduced intensity induction chemotherapy is recommended. For patients older than 75 years of age in poor physical condition, low dose targeted therapy or clinical trials focusing on best supportive care may be considered. In addition, several new drugs such as CPX-351, venetoclax and hypomethylating agents have shown favorable outcome in the treatment of EAML. In a phase 3 trial of 309 EAML patients, compared with those in the DA induction regimen group, both the CR rate and survival of patients in the CPX-351 group were improved [68]. The effect of venetoclax is also promising. According to published results, the CR rate of venetoclax combined with azacitidine in the treatment of AML was 36.7%, and the CR + CRi rate was 66.4% [15]. The limitation of this treatment is that hematopoietic recovery is slow in some patients, and long-term survival is awaiting longer follow up. In view of this, we may consider recommending the combination of targeted drugs and MST as an alternative, although the final safety and efficacy of venetoclax with hypomethylating agents (HMA) based on MST has not yet been determined in a large number of patients. Recommended MST-based induction chemotherapy regimens for newly diagnosed EAML (excluding acute promyelocytic leukemia) according to guidelines of the ELN and NCCN [34–36] are as follows.

4.1. "Fit" patients

1. Standard induction chemotherapy: daunorubicin 60 mg/m^2, or idarubicin 12 mg/m^2, or mitoxantrone 12 mg/m^2 IV d1-3; cytarabine 100–200 mg/m^2 IV d1-7.
2. Venetoclax + HMA: venetoclax 100 mg d1, 200 mg d2, and 400 mg d3-28 PO; azacitidine 75 mg/m^2 IV d1-7 (alternatively d1-5 + d8-9) or decitabine 20 mg/m^2 d1-5.
3. CPX-351 100 U/m^2 (daunorubicin 44 mg/cytarabine 100 mg) IV d1, 3, 5.

4.2. "Unfit" patients

1. Venetoclax + HMA: venetoclax 100 mg d1, 200 mg d2, and 400 mg d3-28 PO; azacitidine 75 mg/m^2 IV d1-7 (alternatively d1-5) or decitabine 20 mg/m^2 d1-5.
2. Reduced intensive chemotherapy: daunorubicin 45–60 mg/m^2, or idarubicin 8–12 mg/m^2, or mitoxantrone 8–12 mg/m^2 IV d1-3; cytarabine 75–100 mg/m^2 IV d1-7 (alternatively d1-5).

4.3. "Frail" patients

Clinical trials (venetoclax, decitabine or azacitidine) or best supportive care.

In the above regimen, GPBSCs should be infused within 24–48 h after completion of chemotherapy agents (cytarabine, decitabine or azacitidine). If necessary, the GPBSC infusion can be delayed up to 96 h. For those not in complete remission (CR or CRi) after the first induction chemotherapy, a second induction chemotherapy with the same regimen and GPBSC infusion should be administered.

Patients who do not achieve CR or CRi after either of the two induction chemotherapies are considered treatment failure and may be suitable for other clinical trials or protocols.

5. MST post-remission therapy for EAML

In addition to allo-HSCT, post-remission therapies, including intermediate and high-dose cytarabine, may be beneficial for prolonging LFS and OS in selected EAML [67]. Considering that EAML patients have less chance to receive allo-HSCT, the post-remission treatment is even more important. There is limited experience and evidence on how many courses of post-remission treatment should be given for EAML patients. Results from the Microtransplant Interest Group showed that the 2-year OS and LFS were 61.3% and 47.5%, respectively, for those who received 2–3 courses of MST with intermediate cytarabine or reduced-intensive chemotherapy as consolidation therapy, and were significantly higher than patients who received only one or no course of MST consolidation therapy (11.1%, $P < 0.001$ and 7.8%, $P < 0.001$, respectively). The treatment-related mortality and early mortality did not differ between the two cohorts [22]. This study provided important evidence of benefit of MST for post-remission treatment of EAML patients, and two or three courses of consolidation are associated with better outcome. Although these data are not from a randomized controlled study, the results suggest that at least two courses of intermediate-dose cytarabine combined with MST or standard-dose idarubicin or daunorubicin with standard-dose cytarabine for a total of 4–6 cycles based on MST as post-remission treatment for EAML patients who achieved CR are beneficial. Patients in the high-risk EAML group have a higher incidence of relapse and may benefit from more courses of post-remission MST treatment.

It has not been determined whether further maintenance therapy, including targeted novel drugs or cell therapy alone, is needed after MST consolidation therapy. Treatment selection should be made by each center according to MRD and individual disease characteristics [69,70]. It should be emphasized that the physical status should be reassessed after achieving CR because patients who were scored as “unfit” at the time of diagnosis may be reevaluated as “fit” following the leukemia remission and hematopoietic recovery. It should be noted that patients with EAML who have achieved CR and are able to receive allo-HSCT should be given priority for allo-HSCT as post-remission therapy [71–78]. The recommended post-remission therapy regimens based on MST and referred to some guidelines of ELN and NCCN are as follows [34–36].

5.1. *“Fit” patients*

1. Intermediate-dose cytarabine: cytarabine 500–1000 mg/m^2 q12 h d1-3 for 3–4 cycles.
2. Standard chemotherapy: daunorubicin 60 mg/m^2, or idarubicin 12 mg/m^2, or mitoxantrone 12 mg/m^2 IV d1-3; cytarabine 100–200 mg/m^2 IV d1-7 for a total of 4–6 cycles.

5.2. *“Unfit” patients*

1. Venetoclax + HMA: venetoclax 100 mg d1, 200 mg d2, and 400 mg d3-28 PO; azacitidine 75 mg/m^2 IV d1-7 (alternatively d1-5 + d8-9) or decitabine 20 mg/m^2 (d1-5) for 8–12 cycles.
2. Intermediate-dose cytarabine: cytarabine 500–1000 mg/m^2 q12 h d1-3 for 3–4 cycles.

In the above regimen, GPBSCs should be infused within 24–48 h after completion of chemotherapy agents (cytarabine, decitabine or azacitidine). If necessary, the infusion can be delayed up to 96 h. In the above regimens, the first consolidation chemotherapy should be administered after hematopoietic recovery (about 4–6 weeks after completion of induction chemotherapy). The following consolidation chemotherapy courses should be administered approximately 8–12 weeks (for intermediate-dose cytarabine and standard chemotherapy) and 4–6 weeks (for venetoclax + HMA) after the first day of the previous consolidation treatment.

6. Conclusions

MST may provide a safe and effective therapeutic alternative for EAML. Although this consensus group has made recommendations on therapies to be considered for EAML patients, the limitations of these recommendations are that the data are derived from single-arm trials and clinical studies or randomized controlled studies with small cohort of cases. In addition, there are nuanced or controversial problems dealing with EAML therapy that are not covered in this consensus. We encourage multicenter randomized controlled studies comparing MST with hematopoietic stem cell transplantation in appropriate age and disease groups and studies combining MST with novel targeted therapies in order to better define the role of MST in the treatment of EAML. We also look forward to more mechanistic studies of MST, including evaluations of molecular immune mechanisms, microchimerism detection and novel cell efficiency modification technologies. We look forward to adopting this consensus to further standardize the MST therapeutic protocol, improve outcomes for EAML and facilitate international collaboration to generate meaningful clinical outcome data.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Abbreviations

AML	acute myeloid leukemia
allo-HSCT	allogeneic hematopoietic stem cell transplantation
EAML	elderly AML
MDS	myelodysplastic syndrome
TRM	transplant-related mortality
GVHD	graft-versus-host disease
OS	overall survival
MST	microtransplant
GPBSC	G–CSF–mobilized peripheral blood stem cells
CR	complete remission
LFS	leukemia-free survival
CRS	cytokine release syndrome
AIDS	acquired immunodeficiency syndrome
NCCN	National Comprehensive Cancer Network
ELN	European LeukemiaNet
TBI	total body irradiation
GVL	graft-versus-leukemia
RVL	recipient-versus-leukemia
FDC	full donor chimerism
DLI	donor lymphocyte infusion
KIR	killer cell immunoglobulin-like receptor
MNC	mononuclear cells
CMV	cytomegalovirus
MRD	measurable residual disease
FISH	fluorescence in situ hybridization
STR-PCR	short tandem repeat-polymerase chain reaction
SNP	single nucleotide polymorphism
DIP	deletion insertion polymorphisms
HMA	hypomethylating agents
CRi	complete remission with incomplete hematological recovery

Appendix A. Supplementary data

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