CORRESPONDENCE

Growing adoption of pharmacologic maintenance therapy after allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a survey on behalf of the EBMT acute leukemia working party

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TO THE EDITOR:

Disease recurrence in acute myeloid leukemia (AML) is the primary cause of failure in allogeneic hematopoietic cell transplantation (allo-HCT). The risk of relapse post-transplant is influenced by several factors, including the AML genomic profile, disease status at transplant, conditioning regimen, and measurable residual disease (MRD) presence before allo-HCT [1]. To mitigate relapse risk, prophylactic pharmacologic and cellular interventions have been explored [2] to maintain remission and enhance the graft-versus-leukemia (GVL) effect without causing significant toxicity. Recent studies on hypomethylating agents (HMAs), and FLT3 inhibitors for post-allo-HCT maintenance therapy have shown promising leukemia-free survival (LFS) improvements [3–8]. Therefore, transplant physicians are increasingly adopting these interventions post-allo-HCT, supported by evidence of efficacy and tolerability [9–11]. However, skepticism persists due to challenges in proving efficacy through large randomized trials and concerns about long-term toxicities.

The study aimed to survey European Society for Blood and Marrow Transplantation (EBMT)- affiliated centers to identify the current clinical practices regarding maintenance treatment post-allo-HCT in AML patients.

After approval of the Acute Leukemia Working Party (ALWP), a questionnaire-based survey was emailed to all EBMT-affiliated centers in January 2023, with two reminders between January and June 2023. The questionnaire included 10 questions addressing maintenance treatment indications, drug types, and treatment duration (supplementary file). No specific demographics, or center-level transplant data were collected. Descriptive statistics analyzed responses. All methods were performed in accordance with the relevant guidelines and regulations.

SURVEY RESULTS

A total of 115 out of the 424 centers from 31 countries responded (27.1%). The top 11 countries by number of responses: Italy ($n = 19$), Germany ($n = 13$), Turkey ($n = 13$), Spain ($n = 10$), France ($n = 8$), Poland ($n = 8$), Switzerland ($n = 5$), United Kingdom ($n = 5$), Netherlands ($n = 4$), China ($n = 3$) and Czech Republic ($n = 3$).

Overall, 102 out of 115 (88.7%) responding centers confirmed using maintenance strategies, including pharmacological or cellular therapies (i.e. donor lymphocyte infusion [DLI]) post-allo-HCT in AML. Among these, the majority of transplant centers ($N = 67$; 65.7%) use it based on a personalized decision, the others use it either routinely on all patients ($N = 17$; 16.7%), or rarely ($N = 18$; 17.6%) (Fig. 1a).

Regarding the indication, all centers that implement maintenance responded to this specific question. The majority of the centers recommend maintenance treatment for AML patients in second remission or beyond, and for those transplanted in active disease ($N = 64$, 62.7%) or in AML patients in first remission with a high risk of relapse based on cytogenetic or molecular data ($N = 61$, 59.8%). Thirty-four (33.3%) centers use it for *FLT3*-mutant AML, of which 20 (19.6%) centers use it exclusively in *FLT3* mutant AML. Finally, 11 (10.8%) centers recommend it for all patients regardless of the risk of disease (Fig. 1b).

Most centers ($N = 77$, 75.5%) use a combination of pharmacologic and cellular therapies, and 23 (22.5%) centers use only pharmacologic therapies.

Among the centers utilizing pharmacologic therapies ($N = 100$), 64 centers (64.0%) employ HMAs as a core component of their maintenance regimen. In 53 (82.8%) of these, 5-azacitidine is the preferred HMA, while decitabine is used in 6 (9.4%) centers. Furthermore, a notable number of centers incorporate HMAs in combination with other therapeutic agents: 38 (59.4%) centers combine HMAs with DLI, and 28 (43.8%) centers pair HMAs with venetoclax. Additionally, 43 (67.2%) centers utilize other combination of modalities (Fig. 1c).

Among the centers where HMAs are employed, 40 (62.5%) centers provided responses regarding whether their implementation was prophylactic or pre-emptive. Most centers ($N = 35$; 87.5%) use it pre-emptively, either MRD driven or chimerism driven, whereas 22 (55%) centers use it prophylactically. Most centers ($N = 37$, 59.7%) continue HMA treatment for one year, 15 (24.2%) for two years and only 10 (16.1%) continue indefinitely or until disease recurrence or toxicity.

As for the use of FLT3 inhibitors as maintenance, out of 100 responding centers, 94 (94.0%) are implementing this strategy. The most common choice was sorafenib in 83 (88.3%) centers, gilteritinib in 31 (30.0%), and midostaurin in 28 (29.8%) (Fig. 1d). Among 68 centers providing indication data, 55 (80.9%) use FLT3 inhibitors as prophylaxis whereas 28 (41.1%) use a pre-emptive approach. The preferred maintenance duration was for two years in 51 (54.8%) centers, followed by one year in 30 (32.3%) centers, continuous until disease relapse or toxicity in 9 (9.7%) centers, and for five years in only 3 (3.2%) centers.

Novel agents are used in 70 (70%) centers, with venetoclax ($n = 53$, 75.7%) and enasidenib ($n = 14$, 20%) being the most commonly used agents.

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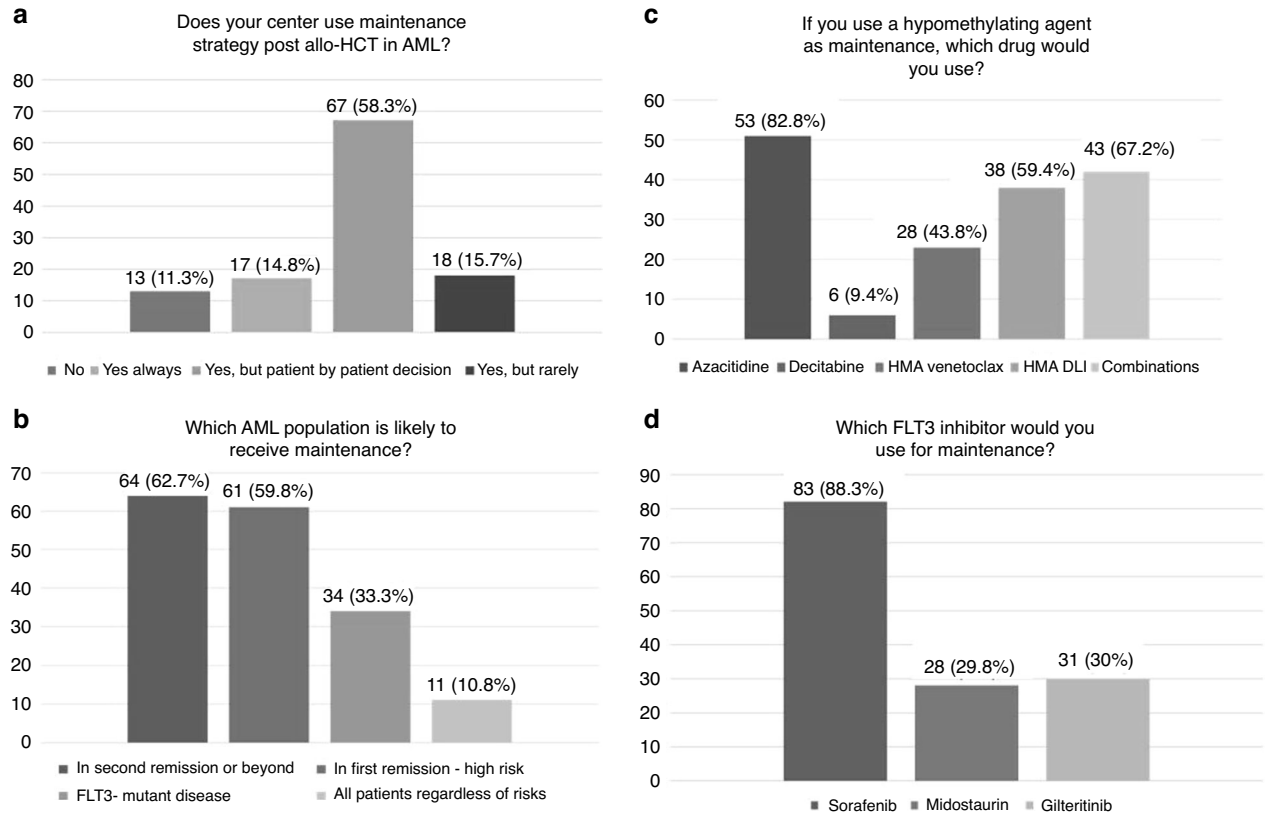

Fig. 1 Histogram representation of questionnaire results on the use of maintenance treatment post-allogeneic transplant by EBMT centers. a Use of maintenance strategies post-transplant in AML. **b** AML patient populations most likely to receive maintenance therapy. **c** Choice of hypomethylating agent for maintenance therapy. **d** Preferred FLT3 inhibitor for maintenance use.

Regarding practice patterns among centers, 32 (29.6%) of 108 responding centers claim that maintenance treatment is part of their routine practice for all patients, 46 (42.6%) only for FLT3 mutant AML. Others are not routinely implementing maintenance because they are still skeptical ($N = 8$), whereas six centers have concerns regarding tolerability, and 16 (14.8%) cannot implement because of regulatory restrictions or lack of access whether availability or affordability.

The survey highlights widespread adoption of maintenance treatments post-allo-HCT in AML as 88.7% of centers confirmed their use, reflecting an evolving therapeutic landscape beyond the allo-HCT. The diverse geographical representation provides a comprehensive overview of current clinical practices encompassing different regulatory and health systems. Personalized approaches predominate (66%), reflecting nuanced understanding of patient-specific factors like disease status and genetic mutations (e.g., FLT3).

The survey confirms that FLT3 inhibitors are the most used pharmacologic treatments (94%), with sorafenib being the predominant choice, supported by evidence of synergistic effects with the allo-immune environment and improved relapse-free survival (RFS).

Similarly, HMAs, particularly 5-azacitidine, are being widely used by 63.9% of responding centers. The benefit of HMAs lies in their broad applicability across all AML subtypes, irrespective of genetic mutations. They also serve as a cornerstone for numerous potential combination therapies, including those with DLI or targeted agents. Despite the lack of extensive robust data on these combinations as maintenance therapy post-allo-HCT, a considerable number of centers in our survey (52.4% for venetoclax, 59.4% for DLI when used with 5-azacitidine) have adopted this approach, underscoring a proactive approach to exploring novel therapies despite limited robust data [12].

The duration of maintenance therapy varies, with many centers opting for one or two years of treatment, similar to what has been reported, with a smaller number continuing indefinitely or until disease recurrence [10]. This variability underscores the need for research to establish optimal durations that balance efficacy, quality of life, and safety.

Despite growing enthusiasm, some centers remain skeptical, citing the need for more robust evidence from randomized clinical trials. Concerns about long-term toxicities, regulatory barriers, and costs also hinder the universal implementation of these strategies. These challenges highlight the ongoing need for high-quality research to provide definitive evidence on the benefits and risks of maintenance treatments.

Selection bias may overestimate maintenance therapy use, as centers employing such strategies might be more likely to respond. However, these survey results underscore the necessity of continued research to refine maintenance strategies and establish standardized guidelines. Further studies, particularly randomized trials, are crucial to determine the most effective therapies and their durations, and to address the concerns about long-term safety.

In conclusion, this survey reveals that maintenance treatments post-allo-HCT in AML are widely adopted across EBMT-affiliated centers, with a predominant focus on personalized approaches and targeted therapies such as HMAs and FLT3 inhibitors, particularly sorafenib. While enthusiasm is evident, ongoing research is essential to optimize implementation and address challenges. This study provides a foundation for advancing post-transplant care and improving AML patient outcomes.

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DATA AVAILABILITY

The dataset represents the results of the survey. One or multiple answers were permitted from each center depending on the question. No personal data are included. The dataset remains the property of the EBMT. The results of the survey are available upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

Contribution: I.A wrote the manuscript with input from the coauthors. I.A., M.L., I.K. contributed in survey questionnaire design, distribution, data collection and analysis. M.L. performed the statistical analysis of the data. I.A., M.M, and A.B., designed the study. All authors (M. L., I. K., F. B., E. B., G. B., J. E., S. G., N.-C. G., F. L., A. N., Z. P., S. P., A. R., J. S., B. S., C. S., R. S., A. S., J. V., F. C., A. B., and M. M.) participated in the discussion, intellectual content, and have reviewed and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the principles of the Declaration of Helsinki. The survey obtained permission from the participating centers to answer the questions. Individual consent was not required, as no personal data were collected. No ethical board committee was needed for the approval of the survey.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-025-02576-4.

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