

# Tolerance and efficacy of total body irradiation and cladribine prior to allogeneic hematopoietic cells transplantation in patients with acute myeloid leukemia and myelodysplastic syndromes – synopsis of clinical study

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## Abstract

**Introduction:** Allogeneic hematopoietic cell transplantation (allo-HCT) is a standard of care for patients with acute myeloid leukemia (AML) and patients with intermediate and high-risk myelodysplastic syndrome (MDS). Despite many years of experience there is still no standard for conditioning regimen. The aim of this study is to analyse the efficacy and safety of a conditioning treatment with cladribine in combination with total body irradiation (TBI).

**Material and methods:** A group of 40 adult patients referred for allo-HCT due to AML and MDS are to be enrolled in the study. The inclusion criteria are: informed consent, chemo-sensitivity for cladribine treatment regimens (when used in induction therapy), age 18–60, and performance status 0–2 according to World Health Organization. The conditioning regimen consists of cladribine and TBI at a total dose of 12 Gy in three fractions given over three consecutive days. The goal of the study is to assess the tolerability and efficacy of the regimen.

**Results:** Our results may stimulate further investigation in this field i.e. phase III trials to compare this regimen to others.

**Conclusion:** A myeloablative conditioning regimen consisting of total body irradiation in combination with cladribine may contribute to improved outcomes after allo-HCT for AML and MDS patients.

**Key words:** allo-HCT, myeloablative regimen, transplantation, cladribine, total body irradiation, TBI

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## Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a standard of care for patients with acute myeloid leukemia (AML) and patients with intermediate and high-risk myelodysplastic syndrome (MDS). Most patients up to 60 years old qualify for transplantation with a myeloablative regimen which traditionally involves the use of high doses

of alkylating agents alone, or in combination with total body irradiation (TBI). An advantage of one over the other has not been proven. A German group showed that TBI can be used with the purine analog fludarabine instead of the previously used cyclophosphamide. This contributes to reduced toxicity while maintaining high efficacy [1, 2].

In AML and MDS, the evidence from clinical trials, including those conducted by the Polish Adult Leukemia

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Group (PALG), indicates that cladribine is more effective than fludarabine. Using it in the conditioning regimen may therefore contribute to increasing the effectiveness of the allo-HCT procedure, i.e. to reducing the risk of disease relapse. The results of studies comparing the efficacy of cladribine to fludarabine in the first-line treatment of AML patients indicate a similar tolerability of both drugs. It is therefore assumed that the conditioning regimen with cladribine will not increase the toxicity [3–5].

## Current research

Our project assumes that the use of TBI in combination with another purine analog, cladribine, could be even more favorable. Cladribine is produced in Poland based on an original synthesis process. This assumption is based on the results of the PALG studies. It was proven that the addition of cladribine to daunorubicin and cytarabine during induction treatment increases the chance of achieving complete remission and the probability of overall survival in patients with AML, including AML preceded by MDS. This effect with fludarabine was not seen. Both drugs increase Ara-CTP levels in leukemia blasts. However, only cladribine showed direct cytotoxic and hypomethylating activity, which justifies the observed differences in efficacy [5]. The initial experience of our clinical practice indicates good tolerance of TBI and cladribine as part of the allo-HCT preparation protocol.

This study is led by the Department of Bone Marrow Transplantation and Oncohematology in Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRIO), Gliwice Branch, Poland. The partner of the study is PALG.

## Material and methods

The study population consists of 40 patients undergoing allo-HCT due to high-risk MDS and AML. The criteria for patient inclusion in the study are: diagnosis of AML in the first with complete remission from the group of intermediate or high cytogenetic risk, AML in the second or subsequent complete remission, or high-risk MDS. Patients have to be 18 to 60, with clinical condition of a 0–2 level according to the World Health Organization (WHO) scale. All type of donors are allowed: human leukocyte antigen (HLA)-compliant family donor, matched or mismatch unrelated donor, or haploidentical donor. The patient signed informed consent to participate in the study.

The conditioning regimen consists of cladribine in a dose of 5 mg/m<sup>2</sup> of patient per day for five consecutive days. After that, TBI is performed in a total dose of 12 Gy in three fractions of 4 Gy each for three consecutive days. The source of hematopoietic cells is bone marrow or peripheral blood. Immunosuppressive therapy depends on HLA matching. In transplantation from matched donors, a combination of cyclosporin A and methotrexate is used.

In this type of donor, ATG is also used. The dose depended on the type of donor (sibling vs unrelated). In the case of HLA, mismatch and haploidentical donors post-transplant cyclophosphamide and tacrolimus with mycophenolate mofetil are used.

Patients are referred for transplant eligibility from PALG partner centers. These centers are responsible for the proper preparation of patients. The final qualification of the patient for allo-HCT as well as for a clinical trial takes place within the transplant center, i.e. the study lead.

The main goal of the study is to assess the tolerability and efficacy of the regimen. The probability of progression-free survival (PFS) after 24 months was the primary study end-point. Secondary endpoints include: rates of adverse events, the probability of overall survival (OS) at 24 months, relapse incidence (RI) at 24 months, non-relapse mortality (NRM) at 24 months, the incidence of acute and chronic graft-versus-host disease, and the time of neutrophil and platelet engraftment.

The duration of the study is 56 months from the date of signing the contract for the implementation of the clinical trial. During its duration, 24 months are set aside for recruiting patients, with a 24-month observation period.

## Discussion

Research by the PALG has confirmed the improved effectiveness of induction therapy by adding cladribine to daunorubicin and cytosine arabinoside. A randomized trial comparing the DA, DAF, and DAC regimens has further demonstrated a benefit in OS and PFS in patients treated with a DAC induction regimen. This scheme has been included as a standard of care in the recommendations of the National Comprehensive Cancer Network (NCCN) [5, 6].

TBI-based protocols formed the conditioning regimen in patients prior to allo-HCT. The combination of cyclophosphamide with TBI (referred to as the Cy-TBI regimen) was used in pioneering transplants by Thomas in 1971. Currently, 12 Gy is the most common myeloablative dose of TBI. Recent years have brought about the combination of irradiation with less toxic chemotherapeutic agents such as fludarabine.

Cladribine alone in conditioning treatment has already been described in small groups of patients, mainly in reduced intensity and nonmyeloablative conditioning [7–9]. To date, no clinical trial has been conducted describing its therapeutic effect at this stage of treatment, especially in treatment with myeloablative potential. Also, the combination of cladribine with radiotherapy has not yet been analyzed.

The myeloablative conditioning regimen consisting of TBI in combination with cladribine may contribute to improved outcomes after allo-HCT for AML and MDS patients. Results may stimulate further investigation in this field, i.e. phase III trials to compare this regimen to others.

## Conclusions

The good experience of the PALG group in the use of cladribine in the treatment of AML and MDS, and of the German group in using the combination of TBI with fludarabine in conditioning treatment, raise hopes that the study conditioning regimen will be more effective.

## Authors' contributions

MSK, SG – design of study, manuscript writing, revision and approval.

## Conflict of interest

None.

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## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) for experiments involving humans: EU Directive 2010/63/EU for animal experiments: Uniform requirements for manuscripts submitted in biomedical journals.

## References

1. Stelljes M, Bornhauser M, Kroger M, et al. Cooperative German Transplant Study Group. Conditioning with 8-Gy total body irradiation and fludarabine for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia. *Blood*. 2005; 106(9): 3314–3321, doi: [10.1182/blood-2005-04-1377](https://doi.org/10.1182/blood-2005-04-1377), indexed in Pubmed: [16020510](https://pubmed.ncbi.nlm.nih.gov/16020510/).
2. Bornhäuser M, Kienast J, Trenschele R, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol*. 2012; 13(10): 1035–1044, doi: [10.1016/s1470-2045\(12\)70349-2](https://doi.org/10.1016/s1470-2045(12)70349-2).
3. Holowiecki J, Grosicki S, Robak T, et al. Polish Adult Leukemia Group (PALG). Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study. *Leukemia*. 2004; 18(5): 989–997, doi: [10.1038/sj.leu.2403336](https://doi.org/10.1038/sj.leu.2403336), indexed in Pubmed: [14999298](https://pubmed.ncbi.nlm.nih.gov/14999298/).
4. Hołowiecki J, Grosicki S, Kyrz-Krzemien S, et al. Daunorubicin, cytarabine and fludarabine (DAF) for remission induction in relapsed or refractory acute myeloid leukemia. Evaluation of safety, tolerance and early outcome—Polish Adult Leukemia Group (PALG) pilot study. *Ann Hematol*. 2008; 87(5): 361–367, doi: [10.1007/s00277-007-0421-4](https://doi.org/10.1007/s00277-007-0421-4), indexed in Pubmed: [18074133](https://pubmed.ncbi.nlm.nih.gov/18074133/).
5. National Comprehensive Cancer Network. Bone Cancer (Version 3.2021). [http://www.nccn.org/professionals/physician\\_gls/pdf/bone.pdf](http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf) (March 02, 2021).
6. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol*. 2012; 30(20): 2441–2448, doi: [10.1200/JCO.2011.37.1286](https://doi.org/10.1200/JCO.2011.37.1286), indexed in Pubmed: [22508825](https://pubmed.ncbi.nlm.nih.gov/22508825/).
7. Markova M, Barker JN, Miller JS, et al. Fludarabine vs cladribine plus busulfan and low-dose TBI as reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation: a prospective randomized trial. *Bone Marrow Transplant*. 2007; 39(4): 193–199, doi: [10.1038/sj.bmt.1705556](https://doi.org/10.1038/sj.bmt.1705556), indexed in Pubmed: [17220905](https://pubmed.ncbi.nlm.nih.gov/17220905/).
8. Saito T, Kanda Y, Nakai K, et al. Immune reconstitution following reduced-intensity transplantation with cladribine, busulfan, and anti-thymocyte globulin: serial comparison with conventional myeloablative transplantation. *Bone Marrow Transplant*. 2003; 32(6): 601–608, doi: [10.1038/sj.bmt.1704205](https://doi.org/10.1038/sj.bmt.1704205), indexed in Pubmed: [12953133](https://pubmed.ncbi.nlm.nih.gov/12953133/).
9. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood*. 2001; 97(3): 631–637, doi: [10.1182/blood.v97.3.631](https://doi.org/10.1182/blood.v97.3.631), indexed in Pubmed: [11157478](https://pubmed.ncbi.nlm.nih.gov/11157478/).