

RESEARCH HIGHLIGHT

Intensive chemotherapy and sequential hematopoietic stem cell transplantation: Is it necessary for high-risk T-cell lymphoblastic lymphoma?

Ken H. Young 

Division of Hematopathology, Department of Pathology, Duke University Medical CenterDuke University Cancer Institute, Durham, NC 27710, USA

Correspondence:

Ken H. Young, MD, Ph.D., Professor and Director, Division of Hematopathology, Duke University Medical Center, Duke University Cancer Institute, Durham, NC 27710, USA.

Email: ken.young@duke.edu

Adult T-cell lymphoblastic lymphoma (T-LBL) is characterized by its rarity and poor prognosis, however, it is currently being treated without any internationally recognized therapies [1]. Acute lymphocytic leukemia (ALL)-like chemotherapy, such as the Berlin–Frankfurt–Muenster (BFM) regimen or the fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) regimen, is currently being widely used [2]. The former regimen is more intensive, while the latter regimen is relatively less toxic and better tolerated by patients. The BFM regimen has been associated with improved complete remission (CR) (83.6% vs.71.4%) and survival rate (5-year progression-free survival [PFS]: 67.4% vs. 36.4%; 5-year overall survival [OS]: 62.6% vs.31.8%) [3]. Regarding the treatment of T-LBL, there are still two key issues to be resolved. First, the optimal patient subgroup for the above two regimens has not yet been determined. Second, accurate screening of patients who might benefit from hematopoietic stem cell transplantation (HSCT) after the first CR is urgently required [4, 5].

We read with interest an innovative work by Tian et al [6] published in *Clinical Cancer Research*, whose study

seems to provide potential answers to the above questions, to some extent. In that study, using the data of 549 adult T-LBL patients from 27 medical centers, Tian et al constructed a four-CpG classifier (cg12373951, cg10323688, cg14569644, and cg01589972) through the Illumina 850K methylation microarray to predict the relapse risk of T-LBL patients. One of the interesting highlights of this work for clinicians is the construction and proposal of a nomogram which comprised of the four-CpG classifier and other factors such as Lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group performance status (ECOG-PS), central nervous system involvement, and NOTCH1/FBXW7 status. Strikingly, patients with a nomogram score of >138.5 who received HSCT after intensive chemotherapy had better relapse-free survival (RFS) and OS than those who did not. Among them, the BFM followed by HSCT group had significantly longer OS but comparable RFS than those who received hyperCVAD followed by HSCT.

Identifying risk indicators is particularly important in clinical decision-making, and Tian et al.'s series of studies are appreciated to enhance the precision therapy of T-LBL [7, 8]. For high-risk patients, intensive chemotherapy and early hematopoietic stem cell transplantation can be selected to reduce the relapse risk. For low-risk patients, early stem cell transplantation is not recommended, thereby minimizing potential treatment-related complications and reducing the financial burden. However, finding an indicator that combines satisfactory sensitivity and

Abbreviations: ALL, Acute lymphocytic leukemia; BFM, Berlin–Frankfurt–Muenster; CR, Complete remission; CVAD, Cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ECOG-PS, Eastern Cooperative Oncology Group performance status; FFPE, Formalin-fixed, paraffin-embedded; HSCT, Hematopoietic stem cell transplantation; LDH, Lactate dehydrogenase; OS, Overall survival; RFS, Relapse-free survival; T-LB, T-cell lymphoblastic lymphoma

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specificity is the key challenge that remains to be solved in the clinic.

In recent years, the exploration of DNA methylation markers has triggered wide interest [9]. DNA methylation is a stable but reversible epigenetic modification that regulates gene expression, and methylation values are applicable to various detection platforms [10, 11]. However, concerns regarding reproducibility and applicability prior to adoption in clinic exist. In this regard, Tian's study [6] found that the four-CpG classifier had high consistency in different types of tissues (i.e.: Formalin-fixed, paraffin-embedded [FFPE] tissue, fresh frozen tissue, and fresh effusion cells), indicating promising clinical application independent of tumor tissue type.

In summary, this study by Tian et al. [6] could be of great significance to support precision treatment in the field of T-LBL. Although this frontier study addressed several key questions regarding this devastating cancer on our march to moonshot, however, the molecular mechanism of how CpGs methylation affects the initiation and clonal evolution in T-LBL remains unclear, including the specific genes regulated by the CpGs or pathways activated in the process of functioning. Such questions still demand more in-depth studies.

AUTHORS' CONTRIBUTION

The author has read and approved the final manuscript.

ACKNOWLEDGMENTS

Not applicable.

COMPETING INTERESTS

The author declares no competing interests.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

FUNDING

Not applicable.

ORCID

Ken H. Young  <https://orcid.org/0000-0002-5755-8932>

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How to cite this article: Young KH. Intensive chemotherapy and sequential hematopoietic stem cell transplantation: Is it necessary for high-risk T-cell lymphoblastic lymphoma?. *Cancer Commun*. 2021;41:273–274. <https://doi.org/10.1002/cac2.12148>