THE PROGNOSTIC SIGNIFICANCE OF MISSENSE MUTATIONS IN THE KAT DOMAIN OF CREBBP GENE IN 14;18+ FOLLICULAR LYMPHOMA

A. SMOLYANINOVA[1], I. BOLSHAKOV[1], Y. SIDOROVA[1], B. BIDERMAN[1], E. GEMDZHIAN[1], HUNAN JULHAKYAN[1], A. SUDARIKOV[1], E. ZVONKOV[1], E. PAROVICHNIKOVA[1]

1. National Medical Research Center for Hematology, 125167, Moscow, Russia

Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin's lymphoma. This tumor is distinguished by genetic variations, as well as pronounced clinical heterogeneity, ranging from indolent forms to cases that progress within 24 months with transformations (POD24/transf.) or progress within 12 month (POD12) with an extremely poor prognosis [1]. Currently, the relationship between CREBBP gene mutations and prognosis in FL is not well understood [2,3].

Objectives

To determine the CREBBP gene mutations profile in FL 14;18+ grades 1–3A and its prognostic significance, depending on therapy (conventional therapy (CT) and high-dose chemotherapy with autologous steam cell transplantation (ASCT)).

Methods

In a retrospective study tumor samples from untreated patients with FL were examined over the period from 2013 to 2024. Exons 22–30 of the CREBBP gene were analyzed by NGS in 62 samples of patients with FL 14;18+ grades 1–3A. Of these 31 (50%) patients received CT (R-CHOP/BR), 25(39%) patients received ASCT, and 6 patients received unconventional therapy.

Results

CREBBP gene mutations were detected in 32 (50%) patients. Single missense mutations in KAT domain (KATmiss+) were found in 20/32 (63%) cases. In 12/32 (37%) patients nonsense, in-frame shift or multiple CREBBP mutations were found. In group KATmiss+ the 5-year overall survival (OS) was 100% in all therapy groups (Fig.1 b,d). In CT group the 5-year event free survival (EFS) in KATmiss− vs KATmiss+ was 32% and 49% (median follow-up 37 months) (Fig.1a).

In the ASCT group 5-year EFS was higher in patients KATmiss- (Fig. 1 c). The 5-year EFS and OS in KATmiss− group who received ASCT and CT was 86% vs 33%(p=0.05) and 94% vs 77% (p=0.08) (Fig.1e). POD12 in KATmiss+ and KATmiss− groups was 7% and 38% (p=0.05). In 6/13 (46%), repeat biopsies confirmed the transformation. Of these, there were 5 cases of POD24/transf. that occurred in KATmiss− group who received CT/unconventional therapy. In ASCT group no cases of transformation were recorded.

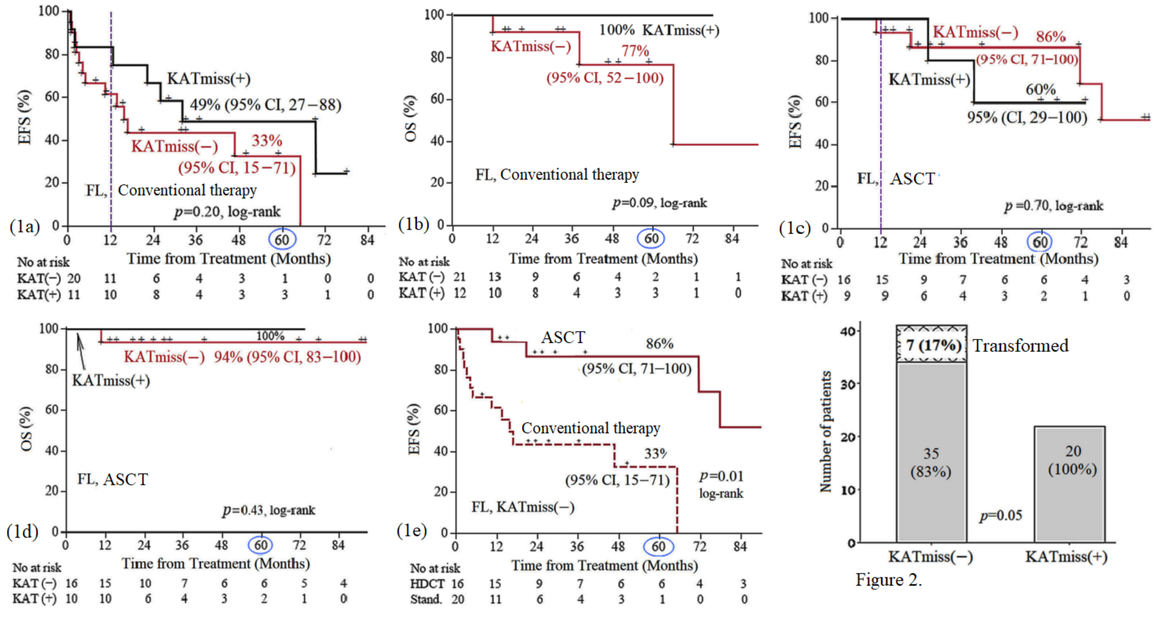


Figure 2.

Figure 1. Comparison of 5-year survival rates among FL subgroups. EFS (1a) and OS (1b) according to the KATmiss status in conventional therapy group; comparison of EFS (1c) and OS (1d) according to the KATmiss status in ASCT group; comparison of EFS according to the therapy type in KATmiss(−) group (1e).

Figure 2. Groups of patients with and without KATmiss mutation.

Summary

Detection of a single missense mutation in the KAT domain of the CREBBP gene can be considered a discriminatory feature that separates FL with a favorable prognosis from FL of high risk with POD24/transf. and POD12. Patients with FL KATmiss− require more intensive treatment regimens as a first line therapy

References

1.Casulo C., et al. Clin Lymphoma Myeloma Leuk. 2023;23(1):40–8. DOI:10.1016/J.CLML.2022.09.003.
2. Dreval K., et al. Blood. 2023;142(6):561. DOI:10.1182/BLOOD.2022018719.
3.Green M.R.,, et al. Proc Natl Acad Sci U S A. 2015;112(10):E1116–25. DOI:10.1073/PNAS.1501199112/-/DCSUPPLEMENTAL.