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Research Article

Identify Distinct Prognostic Impact of ALDH1 Family Members by TCGA Database in Acute Myeloid Leukemia

Yi H, Deng R, Fan F, Sun H, He G, Lai S and Su Y*
Department of Hematology, General Hospital of Chengdu Military Region, China

***Corresponding author:** Su Y, Department of Hematology, General Hospital of Chengdu Military Region, Chengdu, 610083, China

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Abstract

Background: Acute myeloid leukemia is a heterogeneous disease. Identify the prognostic biomarker is important to guide stratification and therapeutic strategies.

Method: We detected the expression level and the prognostic impact of each ALDH1 family members in AML by The Cancer Genome Atlas (TCGA) database.

Results: Upon 168 patients whose expression level of ALDH1 family members were available. We found that the level of ALDH1A1correlated to the prognosis of AML by the National Comprehensive Cancer Network (NCCN) stratification but not in other ALDH1 members. Moreover, we got survival data from 160 AML patients in TCGA database. We found that high ALDH1A1 expression correlated to poor Overall Survival (OS), mostly in Fms-like Tyrosine Kinase-3 (FLT3) mutated group. HighALDH1A2 expression significantly correlated to poor OS in FLT3 wild type population but not in FLT3 mutated group. High ALDH1A3 expression significantly correlated to poor OS in FLT3 mutated group but not in FLT3 wild type group. There was no relationship between the OS of AML with the level of ALDH1B1, ALDH1L1 and ALDH1L2.

Conclusion: The prognostic impacts were different in each ALDH1 family members, which needs further investigation.

Keywords: Acute myeloid leukemia; ALDH1; Prognosis; TCGA database

Introduction

Acute Myeloid Leukemia (AML) is one of the most common leukemia in adults and it is a heterogeneous population [1,2]. Despite major improvements has been made in pathogenesis and therapeutics in AML, some types of AML eventually relapse and caused patients death [3,4]. Prognostic molecular markers and therapeutics are urgently needed. Recently larges of molecular alterations such as mutations or copy number variations have been discovered through next generation sequencing (NGS) approach. Some of the driver mutations or passenger mutations were distinguished through animal models [5-7]. Some of them are associated with overall survival rate, such as FLT3-ITD, ASXL1, et al. [8] However, thousands of genes are regulated by genomic or epigenomic mechanisms and also associated with overall survival [9,10]. Some of them were identified in the last decades, such as CXCR4 [11], EVI1 [11,12], DNMT3A [13], Gli1, et al. [14]. Whether the expression of other genes is associated with AML overall survival is still largely unknown.

Aldehyde Dehydrogenases (ALDH) are a group of enzymes that catalyze the oxidation of aldehydes [15]. Recently, several studies indicated that ALDH1 was associated with cancer progression [16,17]. Higher ALDH1 activities were found in cancer stem cells and ALDH1 had been identified as a marker of cancer stem cells in several cancers [18]. ALDH1 could also be as a predictor of poor outcome in clinics. Until now, at least six ALDH1 isoforms have been identified. They are ALDH1A1, ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1 and ALDH1L2. The impact of different isoenzymes on OS of cancer patients remains controversial. For instance, higher ALDH1A1 expression might correlate to poor OS or have no relationship with survival [19,20], ALDH1A2 was indicated with better OS [21] or poor OS [22,23]. ALDH1A3 might correlated to poor OS [24,25] or have no relationship with survival [21]. In AML, leukemia stem cells are enriched in CD34+CD38 - population that exhibit high ALDH1 activities. Inhibit ALDH1 activities could eradicate leukemia stem cell and sparing normal progenitors [26]. It is largely unknown which ALDH1 family member are contributing to ALDH1 activities in AML, also the OS impact of individual isoenzyme on AML are needed to be clarified.

Here we mined The Cancer Genome Atlas (TCGA) database from Natural Cancer Institute to distinguish the expression and the prognostic impact of each ALDH1 family member in AML.

Results

Until now, six ALDH1 family members in human were discovered and the tissue distribution and cellular location were reviewed before [27]. All the six isoenzymes were found in TCGA database.

We first determined the expression of each ALDH1 family member in TCGA. In TCGA database, all AML patients were stratified with NCCN guideline [28]. We grouped AML patients with NCCN stratification and compared the expression of each ALDH1 isoenzymes. The gene expression data of 168 patients was available. Figure 1 shows the expression of ALDH1A1, ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1 and ALDH1L2 with NCCN risk stratification.

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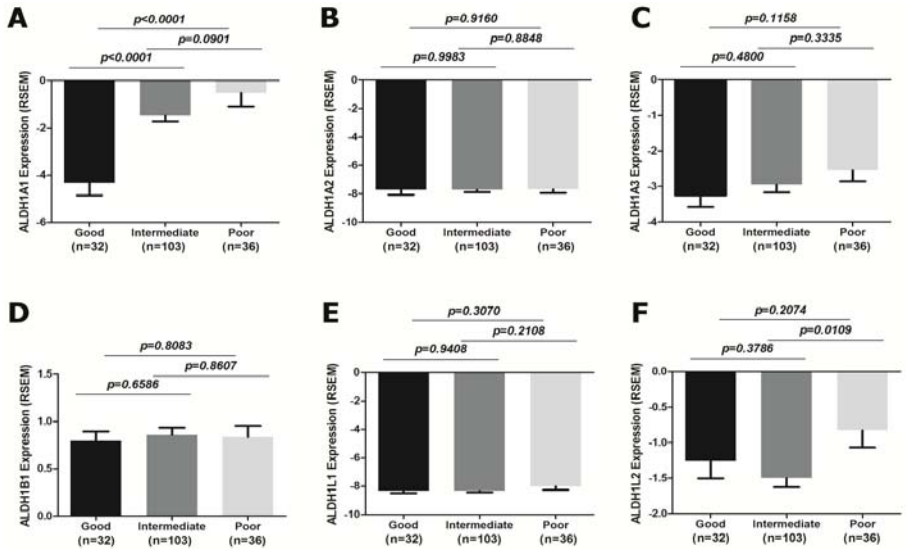

Figure 1: Expression level of different ALDH1 family members with NCCN stratification in TCGA database. Expression of each ALDH1 family member in 168 AML patients from TCGA dataset stratified by cytogenetic risk according to NCCN. The ordinate value indicated the expression level of each gene. It is represented by RSEM (RNA-Seq by Expectation Maximization). The differences between groups were analyzed by Unpaired Student's t-test. The expression level of ALDH1A1, ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1, ALDH1L2 were indicated in A-F, respectively.

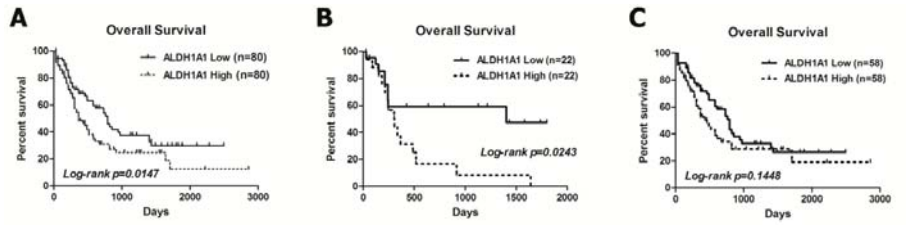

Figure 2: The prognostic impact of the expression level of ALDH1A1 in AML. A. Kaplan-Meier plots of OS of 160 AML patients whose OS values were available from TCGA database divided by ALDH1A1 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (B) and FLT3 wild type AML patients (C) divided by ALDH1A1 expression.

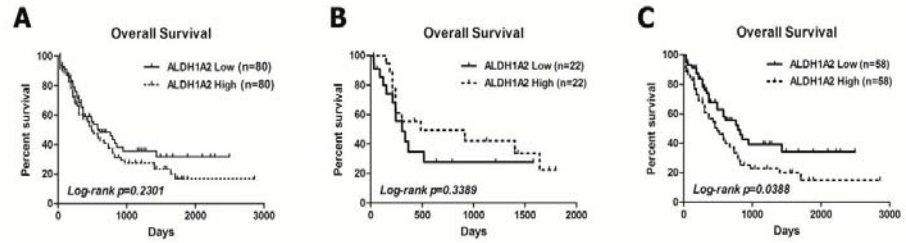

Figure 3: The prognostic impact of the expression level of ALDH1A2 in AML. (A) Kaplan-Meier plots of OS of 160 AML patients divided by ALDH1A2 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (n=44). (B) and FLT3 wild type AML patients (n=116). (C) divided by ALDH1A2 expression.

High expression level of ALDH1A1 was found to correlate to poor OS. In poor prognostic group, the relative expression value (RNA-Seq by Expectation Maximization, RSEM) is -0.2753 ± 0.5320, which was significantly higher than in favorable (-4.1870 ± 0.5155) and intermediate (-1.454 ± 0.2665) groups ($p<0.05$). Meanwhile, the expression level of ALDH1L2 was higher in poor group than in intermediate group ($p<0.05$). However, there was no relationship between gene expression of ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1 with NCCN risk stratification ($p>0.05$).

To investigate the prognostic impact of ALDH1 gene family, we collected all the survival data of 160 AML patients from TCGA dataset and analyzed by Kaplan-Meier approach. The median follow-up of this cohort is 557.4 days (0-2861 days). First, we evaluated the prognostic impact of ALDH1A1 on OS of AML patients. We equaled all the patients by ALDH1A1 mRNA level. ALDH1A1 high group (n=80, RSEM is set from -1.72 to 5.82) and ALDH1A1 low group (n=80, RSEM is set from -7.96 to -1.85). As shown in Figure. 1G, high ALDH1A1 expression was significantly correlated to shorter overall survival ($p<0.05$). As we know, AML patients who harboring the FLT3 mutation have poor prognosis. We did subpopulation test to figure out the impact of ALDH1A1 expression on FLT3 mutated patients

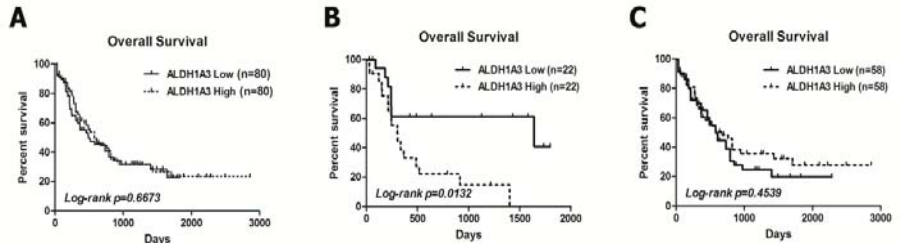

Figure 4: The prognostic impact of the expression level of ALDH1A3 in AML. (A) Kaplan-Meier plots of OS of 160 AML patients divided by ALDH1A3 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (n=44). (B) And FLT3 wild type AML patients (n=116) (C) divided by ALDH1A3 expression.

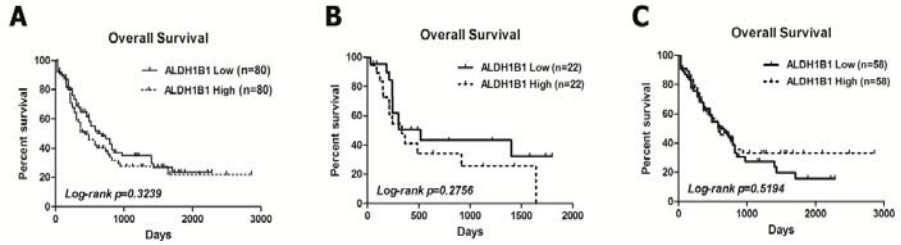

Figure 5: The prognostic impact of the expression level of ALDH1B1 in AML. (A) Kaplan-Meier plots of OS of 160 AML patients divided by ALDH1B1 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (n=44). (B) and FLT3 wild type AML patients (n=116) (C) divided by ALDH1B1 expression.

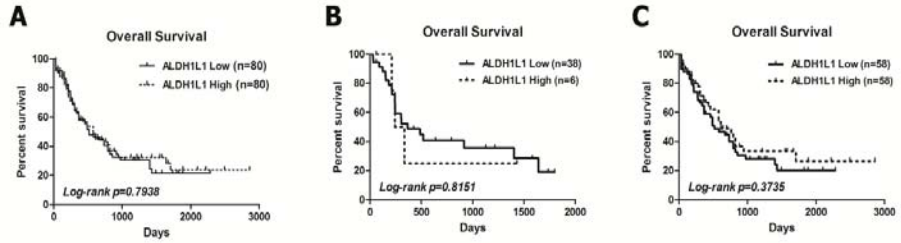

Figure 6: The prognostic impact of the expression level of ALDH1L1 in AML. (A) Kaplan-Meier plots of OS of 160 AML patients divided by ALDH1L1 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (n=44). (B) and FLT3 wild type AML patients (n=116). (C) divided by ALDH1L1 expression.

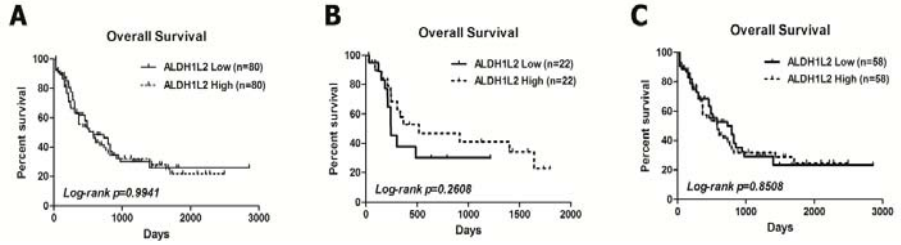

Figure 7: The prognostic impact of the expression level of ALDH1L2 in AML. (A) Kaplan-Meier plots of OS of 160 AML patients divided by ALDH1L2 expression. Survival curves were compared by log-rank test. Kaplan-Meier plots of OS of FLT3 mutated AML patients (n=44). (B) and FLT3 wild type AML patients (n=116) (C) divided by ALDH1L2 expression.

and FLT3 wild type patients. Figure 1H showed that in the group of FLT3 mutated AML, high ALDH1A1 expression significantly correlated with shorter OS ($p<0.05$). However, the correlation was not significant in FLT3 wild type group ($p>0.05$) (Figure 1C).

Then we determined the prognostic impact on ALDH1A2 expression. In figure 3A, high ALDH1A2 mRNA expression seemed correlated to poor OS in all patients, but the difference was not significant ($p>0.05$). The OS was no difference in FLT3 mutated patients based on ALDH1A2 expression ($p>0.05$) (Figure 3B). However, higher ALDH1A2 expression indicated poor OS in FLT3 wild type group ($p<0.05$) (Figure 3C).

Figure 4 showed that the prognostic impact of the expression level of ALDH1A3 in AML patients. We could not see the difference of OS based on ALDH1A3 expression in all patients ($p>0.05$) (Figure

4A) and in FLT3 wild type patients (p>0.05) (Figure 4C). However, when we focused on FLT3 mutated patients, lower ALDH1A3 mRNA level correlated to better OS (p<0.05) (Figure 4B).

Figure 5 to Figure 7 indicated the prognostic impact of the expression level of ALDH1B1, ALDH1L1 and ALDH1L2 in AML patients, respectively. All the curves were not separated based on ALDH1B1, ALDH1L1 and ALDH1L2 mRNA expression, no matter in FLT3 mutated or wild type patients groups.

Discussion

ALDH1 enzymes play an important role in normal hematopoietic differentiation and tumor progression [29,30]. Currently ALDH1 activity was measured by ALDEFLUOR approach and inhibited by diethylaminobenzaldehyde (DEAB) reagent. Selected ALDH1 positive cells have self-renew capacity and increased cancer cell regeneration in xenograft tumor model [31]. However, the function and prognostic impact of each ALDH1 family member in AML has not been identified yet. In this study, we mined AML mRNA sequencing and clinical dataset from TCGA and focused on the expression and prognosis of each ALDH1 member. ALDH1A1 is the most dominant enzyme of ALDH1 [32]. It is reported to be as an independent prognostic marker in triple negative breast cancer [33]. Here we showed that high expression of ALDH1A1 correlated to poor NCCN prognostic stratification, and ALDH1A1 was a prognostic marker in AML, especially in FLT3 mutated AML. The expression of ALDH1A2 and ALDH1A3 both have prognostic impact on defined group of patients. But ALDH1B1, ALDH1L1 and ALDH1L2 expression have no meaning on prognosis of AML.

ALDH1A1, ALDH1A2 and ALDH1A3 are highly conserved isoenzymes. They are participating in the synthesis of retinoic acid [34]. Recently all the ALDH1A family members were reported to participate in neuroblastoma progression and drug resistance [35]. ALDH1A family members were probably as potential tumor initiating cells markers and take part in tumor cell self-renewal. In AML, we found that all ALDH1A family members were associated with poor prognosis in defined group of patients, suggesting that they might contribute to leukemia stem cell capacity, result in drug resistance and shorter AML patients' survival. Interestingly, ALDH1A1 and ALDH1A3 both have poor OS indication in FLT3 mutated group of AML patients, suggesting that they might have crosstalk with FLT3 signaling in AML. As we know, FLT3 mutation indicated poor OS in AML. Aberrant FLT3 mutation caused ligand independent activation of FLT3 receptor and amplified cell proliferation signals. Moreover, FLT3 mutation could cause increased activated form of β-catenin [36], suggesting FLT3 signaling enhanced stemness signaling and increased cell self-renewal capacity. Whether ALDH1A1 and ALDH1A3 could be amplified by FLT3 signaling or other signaling has not been addressed yet. Our study indicated that if ALDH1A1 and ALDH1A3 were amplified in FLT3 mutated AML, the OS of AML patients was extremely poor. They were prospective targets in therapeutic strategy. How the regulation of FLT3 and ALDH1A1/ ALDH1A3 need further investigation. ALDH1B1, ALDH1L1 and ALDH1L2 were not important to AML patients' survival in our study. They have not been extensively discussed in the literature [34]. The functions of them in AML still need further investigation.

Taken together, our study demonstrated that ALDH1A1, ALDH1A2 and ALDH1A3 have prognostic impact in certain AML patients. ALDH1A isoenzymes could be measured in clinical samples and guide clinical strategy. Clinical trial depended on ALDH1 enzymes are urgently needed to assess the prognostic impact of each enzyme in real world in AML patients and provide better intervention strategy.

Methods

Clinical AML survival data and next generation sequencing data of transcriptome were available on http://tcga-data.nci.nih.gov/tcga/. Expression values between groups were compared by two-tailed Student's t-test. Overall survival curves were plotted by Kaplan-Meier methods and compared by log-rank test. P value were calculated and shown in the plots.

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