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604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

NGS Profile and the Mathematical Prediction Model for Venetoclax Combination Therapy in HM-Screen-Japan 02 Study

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[Introduction]
Azacitidine and venetoclax combination therapy (Aza/Ven) is a novel strategy for acute myeloid leukemia (AML). Although this regimen is widely used as a first line treatment not only for unfit/elderly patients but also for fit/young patients in the real-world situation, appropriate patient selection is an important issue. HM-SCREEN-Japan 02 (UMIN-CTR UMIN000046371) is a Japanese multicenter prospective observational study to evaluate the clinical utility of targeted sequencing. In this study, we performed the sub-analysis of newly diagnosed AML patients who received Aza/Ven as a 1 st line treatment to elucidate the genetic background of AML. Furthermore, we proposed a novel mathematical model to predict the response of Aza/Ven.

[Methods]
AmoyDx® Myeloid Blood Cancer Panel for acute myeloid leukemia was used for the targeted sequencing. We performed linear discriminant analysis to predict complete response patients by Aza/Ven based on clinical information before treatment. We utilized three clinical quantities for the analysis: Wilms Tumor-1 (WT1) mRNA expression level, the number of "favorable mutations", and that of "unfavorable mutations". Favorable and unfavorable mutations were defined as *IDH1, IDH2, NPM1*, and *CEBPA* mutations, and *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2* and *TP53* mutations, respectively, based on the previous reports (NEJM 2019, Blood 2022). The data were standardized and utilized for the linear discriminant analysis. Statistical analyses were performed using R version 4.2.3 software (R Foundation for Statistical Computation, Vienna, Austria).

[Results]
Total 158 patients were enrolled in our study. Among 48 patients who received Aza/Ven as a 1 st line therapy, NGS analyses were performed prior to treatment in 38 patients. Their median age was 70.5 (39-92) years old. AML with myelodysplasia-related changes was the major subtype (71%) and 37 percent of the cases had high risk cytogenetic abnormalities at diagnosis. After 1 st line Aza/Ven treatment, complete remission (CR)/ CR with incomplete blood count recovery (CRi) was achieved in 63% of the cases while the remaining 37% were non-CR. There was a trend that patients with *NPM1* and *IDH1/2* mutations achieved CR/CRi, while patients with *RUNX1* mutation were not tended to achieve CR (Figure 1).

Next, we performed linear discriminant analysis of treatment response using three pretreatment clinical factors. Linear discriminant analysis found a linear combination of prognostic factors that best separates two classes in the group of patients. Thirty-seven patients were employed to determine the discriminant function D, given by $D = 0.638 \times x - 0.76 \times y + 0.68 \times z + 0.145$. Here x, y, and z represented the WT1 quantity in peripheral blood, the number of "favorable mutations", and that of "unfavorable mutations" after standardization, respectively. Using this model, 81.1% of cases were correctly classified, and so were 75.7% of cases with leave-one-out cross validation method (Table 1).

[Discussions]

As previously reported (NEJM 2019, Blood adv 2020), IDH1/2 and NPM1 mutations tended to be sensitive to Aza/Ven in our cohort. However, it would be hard to predict the response of Aza/Ven by a single gene mutation because multiple gene mutations were co-existed in most of the cases (Figure 1) and clinical factors including tumor markers might also affect the outcome. Our mathematical model, involving gene mutations and WT1, could efficiently predict the response of Aza/Ven, which may support the selection of 1 st line treatment. In conclusion, our study revealed the genetic landscape of real-world Aza/Ven therapy and provided a potential prognostic model.

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Figure 1

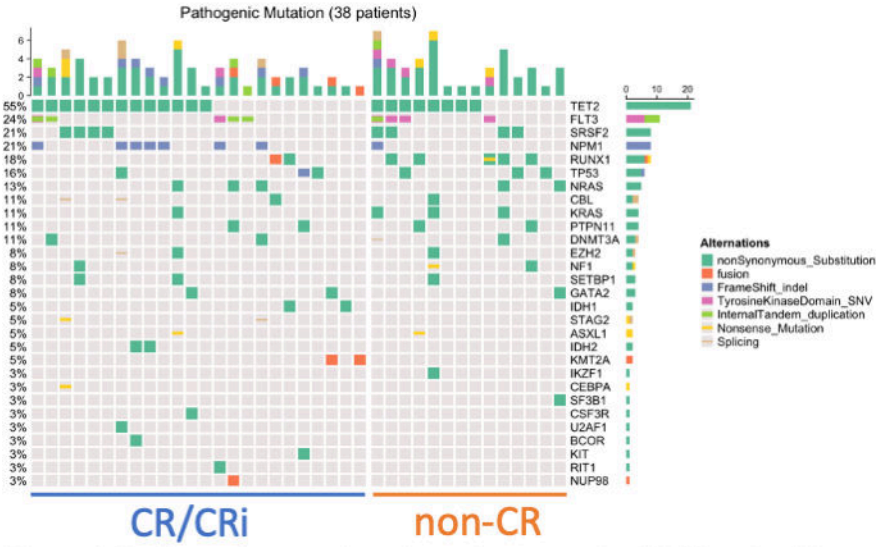

Figure 1: Pathogenic mutations in patients received 1st line Aza/Ven

Each column shows the results of targeted NGS performed before 1st line Aza/Ven. Twenty-four patients(63%) achieved CR/CRi after 1 cycle of Aza/Ven, while 14 patients (37%) were non-CR.

Table 1

CR/CRi or non-CR	Predicted patient number	Matched patient number	Total predictive accuracy
Total	37	30	81.10%
CR/CRi	26	21	
non-CR	11	9	
Leave one out cross validation			
Total	37	28	75.70%
CR/CRi	24	19	
non-CR	13	9	

Table 1: The results of the mathematical prediction model

CR/CRi or non-CR could be classified with 81.1% of the accuracy that were validated by leave-one-out cross validation method.

Figure 1

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