Letter to the editor

Title

Novel stratification for newly diagnosed AML treated with Venetoclax-based therapy in the real world: Hokkaido Leukemia Net Study

Authors

Naoki Miyashita[1)], Masahiro Onozawa[1)], Toshihiro Matsukawa[1)], Akio Mori[2)], Daisuke Hidaka[3)], Koichiro Minauchi[4)], Akio Shigematsu[5)], Junichi Hashiguchi[6)], Tetsuyuki Igarashi[7)], Yasutaka Kakinoki[8)], Yutaka Tsutsumi[9)], Makoto Ibata[10)], Kentaro Wakasa[11)], Katsuya Fujimoto[12)], Toshimichi Ishihara[13)], Hajime Sakai[14)], Satoshi Iyama[15)], Tatsuo Oyake[16)], Takeshi Kondo[2)], Takanori Teshima[1)]

1) Department of Hematology, Hokkaido University Faculty of Medicine, Graduate school of Medicine, Sapporo, Japan
2) Blood Disorders Center, Aiiku Hospital, Sapporo, Japan
3) Department of Hematology, Sapporo Hokuyu Hospital, Sapporo, Japan
4) Department of Hematology, Sapporo City General Hospital, Sapporo, Japan
5) Department of Hematology, Kushiro Rosai Hospital, Kushiro, Japan
6) Department of Internal Medicine, Kitami Red Cross Hospital, Kitami, Japan
7) Department of Hematology, Tenshi Hospital, Sapporo, Japan
8) Department of Hematology, Asahikawa City Hospital, Asahikawa, Japan
9) Department of Hematology, Hakodate Municipal Hospital, Hakodate, Japan
10) Department of Hematology, Sapporo Kosei General Hospital, Sapporo, Japan
11) Department of Hematology, Obihiro Kosei Hospital, Obihiro, Japan
12) Department of Hematology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan
13) Department of Hematology, Kin-ikyo Chuo Hospital, Sapporo, Japan
14) Department of Hematology, Teine Keijinkai Hospital, Sapporo, Japan
15) Department of Hematology, Sapporo Medical University, Sapporo, Japan
16) Department of Hematology and Oncology, Iwate Medical University, Yahaba, Japan

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Corresponding author
Masahiro Onozawa, MD, PhD
Department of Hematology, Hokkaido University Faculty of Medicine, Graduate School of Medicine, Sapporo, Japan
Kita 15, Nishi 7, Kita-ku, Sapporo, JAPAN 0608638
Phone: +81-11-706-7214
Fax: +81-11-706-7823
E-mail: onozawa@med.hokudai.ac.jp

MAIN TEXT

Venetoclax (VEN) was approved in Japan in March 2021 for treatment of acute myeloid leukemia (AML), and VEN-based regimens have been widely used as initial therapy predominantly for elderly and unfit patients. The prognostic risk classification of AML has been subdivided according to chromosomal abnormalities and genetic mutations. The National Comprehensive Center Network (NCCN) and European LeukemiaNet (ELN) continue to revise their prognostic risk classifications for AML,[1-7] but it is not known whether the currently used NCCN and ELN risk classifications can be used to stratify the prognosis of patients treated with VEN-based therapy. We prospectively followed newly diagnosed AML patients who were initially treated by a VEN-based regimen and analyzed the relationships between gene mutations and outcomes in our regional cohort.

A total of 89 AML cases were initially treated by VEN-based therapy (Supplementary Fig. 1A). Patients' characteristics are shown in Table 1. The median overall survival (OS) period for all patients was 367 days (range, 12-636 days) (Supplementary Fig. 1B). The complete remission (CR) + CR with incomplete hematologic recovery (CRi) rate for all patients was 61% (Supplementary Fig. 1C), which is comparable to clinical trial results (64.7% and 67%, respectively).[8,9]

Patients who achieved CR, CRi, morphologic leukemia-free state (MLFS), or partial remission (PR) during the observation period and had no relapse were designated as Group 1, those who relapsed were designated as Group 2, and those in whom the disease became stable disease (SD) or progressive disease (PD) were designated as Group 3. Cytogenetics and mutational status of each patient are shown in Fig. 1A. Patients with *FLT3*-ITD were relatively few (8/89, 9%) whereas patients with *TP53* mutation were enhanced (24/89, 27%) reflecting the older age of the cohort. *IDH2* mutations were significantly more frequent in Group 1 (P=0.010), and *NPM1* mutations tended to be more frequent in Group 1 and Group 2 (P=0.064). Complex karyotypes tended to be more frequent in Group 3 (P=0.056) and were correlated with *TP53* mutations (P<0.001). Among the genetic mutations that were detected in two or more patients, patients with mutations in *DNMT3A*, *IDH1*, *IDH2*, and *NPM1* showed a CR+CRi ratio of more than 80%. We defined these muations as “VEN-sensitive mutations”. NCCN2017 risk category correlated to CR+CRi ratio (90.9% in the favorable risk group, 65.5% in the intermediate risk group, and 51.0% in the poor risk group; P=0.040) (Fig. 1A, Supplementary Table 1). However, NCCN2017 risk stratification did not stratify the outcome for patients in this cohort (P = 0.26, Fig. 1B).

In multivariate analyses including age, sex, “VEN-sensitive mutation” and “CK/*TP53*mt” group, “VEN-sensitive mutation” and “CK/*TP53*mt” group were strongly favorable (HR, 0.23, p=0.0019) and poor (HR, 2.32, p=0.032) prognostic factor, respectively (Supplementary Table 2). The cases with both CK/*TP53*mt and VEN-sensitive mutation showed significantly better survival compared to those with CK/*TP53*mt without VEN-sensitive mutation (Supplementary Fig. 1D). Depending on these findings, we propose the novel stratification. Patients with VEN-sensitive mutations were defined as VEN-sensitive mutation group even if they had bystander poor prognostic biomarker such as complex karyotype, *TP53*, or *RUNX1*. Then we defined complex karyotype and/or *TP53* mutation (CK/*TP53*mt) group who lack VEN-sensitive mutation. Finally, we defined others who lack both VEN-sensitive mutation and CK/*TP53*mt. The patient characteristics such as age, sex, performance status, and WBC count were not statistically different in these three groups (Supplementary Table 3). Based on these subcategories, we can successfully stratify the prognosis of the AML patients who were treated with a Venetoclax-based regimen (Fig. 1C, Supplementary Fig. 1E).

Currently, the NCCN and ELN prognostic classifications are widely used to predict the prognosis of AML. These stratifications were mainly based on results obtained in younger patients who were intensively treated. We previously showed the NCCN2017 effectively divided the prognosis of elderly cohort (≥65 year) [10]. However, NCCN2017 did not stratified AML patients who were initially treated by VEN-based therapy. A newly developed molecular-targeted agent could change the significance of a certain risk factor; for example, the introduction of an upfront FLT3 inhibitor abrogated the poor prognostic impact of *FLT3*-ITD.[11,12]

Most of the patients in the NCCN2017 favorable risk group were classified as patients in the VEN-sensitive mutation group and many patients in the NCCN2017 intermediate risk group were classified as patients in the others group in the new classification, while almost half of the patients in the NCCN2017 poor risk group were re-classified as patients in either the VEN-sensitive mutation group or the others group (Fig. 1D). The novel stratification successfully extracts a better prognostic group especially from the NCCN2017 poor risk group (Fig. 1E-G).

According to a report of a subanalysis of the open-label, non-randomized phase 1b trial (NCT02203773) and the confirmatory VIALE-A phase 3 randomized trial (NCT02993523), prognostication using the ELN2017 classification was shown to be

ineffective for patients who received VEN-based therapy.[8,9] Molecularly defined stratification including *FLT3*-ITD, *NRAS*/*KRAS*, and *TP53* were proposed for VEN-based therapy[13], however patients with *FLT3*-ITD showed better survival compared to those without *FLT3*-ITD in our cohort (Supplementary Fig.2A). In this study period, gilteritinib and quizartinib were available in Japan, which might ameliorate poor prognostic impact of *FLT3*-ITD. Recently, Mayo clinical published stratification depends on the scoring system.[14] Their stratification divided the overall survival and event-free survival beautifully in our cohort (Supplementary Fig. 2B). However, their scoring system is not available at the onset of the disease, because they included "treatment response" itself into the scoring system (Supplementary Fig. 2B). Our scoring is simple and immediately available at the onset of the disease.

Our results are consistent with the results of several previous studies showing that patients with *DNMT3A*, *IDH1*, *IDH2*, and *NPM1* mutations respond to VEN and that patients with *TP53* mutations do not or transiently respond to VEN.[15,16] The prognostic model depending on these VEN-sensitive mutations would be useful. The mechanisms underlying VEN-sensitive mutation overcoming the poor prognostic impact of CK/*TP53*mt need to be clarified. Because our data is derived from a relatively small cohort and short observation, the stratification needs to be validated in a larger cohort of patients.

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AUTHOR CONTRIBUTIONS

Naoki Miyashita and Masahiro Onozawa designed the study, analyzed the data and wrote the manuscript; Naoki Miyashita performed the molecular analysis. Toshihiro Matsukawa, Shinsuke Hirabayashi, Akio Mori, Daisuke Hidaka, Koichiro Minauchi, Akio Shigematsu, Junichi Hashiguchi, Tetsuyuki Igarashi, Yasutaka Kakinoki, Yutaka Tsutsumi, Makoto Ibata, Kentaro Wakasa, Katsuya Fujimoto, Toshimichi Ishihara, Hajime Sakai, Satoshi Iyama, Tatsuo Oyake and Takeshi Kondo contributed to the data collection and provided critique to the manuscript. Takanori Teshima revised and approved the manuscript; All authors read and approved the final manuscript.

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CONPETING INTERESTS

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The datasets for the cohort study generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

This study was part of a prospective observational study (Hokkaido Leukemia Net, UMIN000048611). It was conducted in compliance with ethical principles based on the Helsinki Declaration and was approved by the institutional review board of Hokkaido University Hospital (#015-0344).

Table

Table 1. Patients' characteristics

Figure legends

Fig. 1.

A. Cytogenetic and genetic mutation profile of patients in each group according to response to treatment. For each genetic mutation, the number of positive cases and the CR + CRi ratio are shown in the right panel.
B. Stratification according to NCCN 2017.
C. Stratification according to novel stratification for VEN-based treatment. VEN-sensitive mt: VEN-sensitive mutation; CK/TP53 mt: complex karyotype and/or TP53 mutation
D. Alluvial diagram showing comparison between NCCN2017 classification and novel stratification for VEN-based treatment. VEN-sensitive mt: VEN-sensitive mutation; CK/TP53 mt: complex karyotype and/or TP53 mutation

E-G. Reclassification of NCCN2017 category according to the novel stratification for VEN-based treatment. The novel stratification successfully extracts a better prognostic group from the NCCN2017 poor risk group.

Supplementary information

Supplementary Document

Supplementary Fig. 1

A. Age distribution and choice of the initial therapy for our AML cohort

B. Overall survival of the patients who were initially treated by VEN-based treatment (n=89)

C. Best response by VEN-based treatment

D. Survival of CK/*TP53* mt with or without VEN-sensitive mutation

E. EFS divided by our stratification

Supplementary Fig. 2

A. Döhner's stratification

B. Mayo's stratification

Supplementary Table 1 Patients' characteristics by risk status according to the NCCN guidelines 2017

Supplementary Table 2 Patients' characteristics by risk status according to novel stratification for VEN-based treatment

Supplementary Table 3 Univariate and multivariate analyses for overall survival

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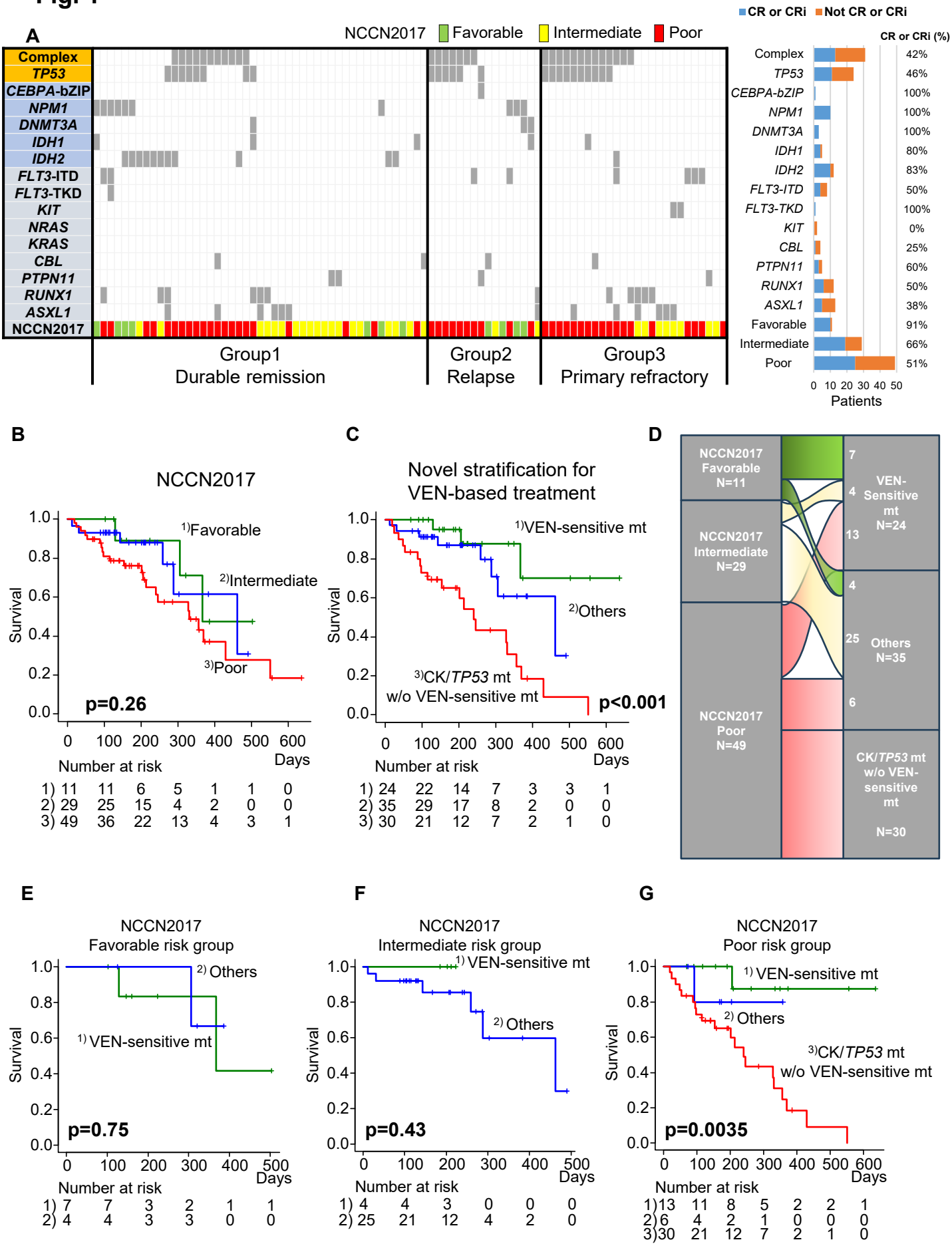
Table 1. Patients' characteristics (N=89)

		N (%)
Age	Median, (range)	75 (57-90)
Gender	Male	49 (52.5)
	Female	40 (47.5)
Performance status	0-1	67 (75.2)
	2-4	22 (24.8)
WBC at diagnosis	Median, (range) (/μL)	2,415 (400-210,740)
FAB classification	M4 or M5	13 (14.6)
	Others	48 (54.0)
	Unknown	28 (31.4)
Karyotype	Normal	32 (36.0)
	Complex	31 (34.8)
	Others	26 (29.2)
NCCN 2017	Favorable	11 (12.4)
	Intermediate	29 (32.6)
	Poor	49 (55.0)
Regimen	VEN+azacitidine	85 (95.5)
	VEN+cytarabine	4 (4.5)
Antifungal agent	Yes	75 (84.3)
Febrile neutropenia	Yes	47 (52.8)
CR+CRi	Yes	54 (60.9)
Relapse	Yes	24 (27.0)
Underwent Allo-SCT	Yes	4 (4.5)

Abbreviation, VEN: venetoclax; CR: complete remission; CRi: CR with incomplete hematologic recovery; Allo-SCT: allogeneic hematopoietic stem cell transplantation

Fig. 1


A
NCCN2017 Favorable Intermediate Poor
CR or CRi Not CR or CRi
CR or CRi (%)
Complex 42%
TP53 46%
CEBPA-bZIP 100%
NPM1 100%
DNMT3A 100%
IDH1 80%
IDH2 83%
FLT3-ITD 50%
FLT3-TKD 100%
KIT 0%
CBL 25%
PTPN11 60%
RUNX1 50%
ASXL1 38%
Favorable 91%
Intermediate 66%
Poor 51%
0 10 20 30 40 50
Patients
Group1 Durable remission
Group2 Relapse
Group3 Primary refractory
B
NCCN2017
1)Favorable
2)Intermediate
3)Poor
p=0.26
Survival
Days
Number at risk
1) 11 11 6 5 1 1 0
2) 29 25 15 4 2 0 0
3) 49 36 22 13 4 3 1
C
Novel stratification for VEN-based treatment
1)VEN-sensitive mt
2)Others
3)CK/TP53 mt w/o VEN-sensitive mt
p<0.001
Survival
Days
Number at risk
1) 24 22 14 7 3 3 1
2) 35 29 17 8 2 0 0
3) 30 21 12 7 2 1 0
D
NCCN2017 Favorable N=11
NCCN2017 Intermediate N=29
NCCN2017 Poor N=49
7
4
13
4
25
6
VEN-Sensitive mt N=24
Others N=35
CK/TP53 mt w/o VEN-sensitive mt N=30
E
NCCN2017
Favorable risk group
2) Others
1) VEN-sensitive mt
p=0.75
Survival
Days
Number at risk
1) 7 7 3 2 1 1
2) 4 4 3 3 0 0
F
NCCN2017
Intermediate risk group
1) VEN-sensitive mt
2) Others
p=0.43
Survival
Days
Number at risk
1) 4 4 3 0 0 0
2) 25 21 12 4 2 0
G
NCCN2017
Poor risk group
1) VEN-sensitive mt
2) Others
3)CK/TP53 mt w/o VEN-sensitive mt
p=0.0035
Survival
Days
Number at risk
1)13 11 8 5 2 2 1
2)6 4 2 1 0 0 0
3)30 21 12 7 2 1 0