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POSTER ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Venetoclax-Based Therapy before Allogeneic Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

Chika Kato[1], Yuho Najima, MDPhD[2], Daichi Sadato, PhD[3], Chizuko Hirama[3], Kana Kato, MD[4], Kaori Kondo, MD[4], Yasutaka Sadaga[4], Satoshi Sakai, MD[4], Yasuhiro Kambara, MD[4], Yoshimi Nabe, MD[4], Ko Teshima, MD[4], Kazuya Asano, MD[4], Kazuya Kurihara, MD[4], Atsushi Jinguji, MD[4], Masashi Shimabukuro, MD[4], Fumihiko Ouchi, MD[4], Kazuki Inai, MD[4], Satoshi Koi, MD[4], Naoki Shingai, MD PhD[4], Takashi Toya, MDPhD[4], Hiroaki Shimizu, MDPhD[4], Kyoko Haraguchi, MD PhD[5], Takeshi Kobayashi, MD PhD[4], Hironori Harada, MD PhD[4,6], Yoshiki Okuyama, MD PhD[5], Yuka Harada, MD PhD[3], Noriko Doki, MD PhD[4]

[1] Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Bunkyo-Ku, Japan
[2] Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[3] Clinical Research Support Center, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[4] Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[5] Division of Transfusion and Cell Therapy, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan
[6] Lab. Oncology, Tokyo University of Pharmacy & Life Sciences, Tokyo, Japan

Introduction

The BCL-2 inhibitor venetoclax (VEN) is effective in older patients with untreated acute myeloid leukemia (AML). Few reports exist on the use of VEN as a bridging therapy for allogeneic hematopoietic cell transplantation (HCT) for AML. Previous studies have shown that *NPM1* and *IDH2* gene mutations are associated with high response rates to VEN therapy. We performed a retrospective cohort study to analyze the efficacy of VEN-based bridging therapy before HCT.

Methods

We included 46 patients who were eligible for HCT and received bridging therapy combined with VEN between April 2021 and June 2023 at our center. We evaluated response rates to VEN and HCT outcomes. None of the patients received VEN prior to the study. The response rate to VEN was evaluated using the 2022 European LeukemiaNet (ELN) criteria. We estimated overall survival (OS) using the Kaplan-Meier method, log-rank test, and Gray's test for univariate analysis of cumulative incidence of relapse (CIR) and non-relapse mortality (NRM). We used the Cox proportional hazards model for a multivariate analysis of OS. We extracted DNA from the bone marrow or peripheral blood, and analyzed gene mutations using next-generation sequencing (NGS), targeting 70 genes known to be recurrently mutated in myeloid malignancies.

Results

Of the 46 patients, 32 had *de novo* AML, 7 had *de novo* MDS/AML, 5 had secondary AML, 1 had secondary MDS/AML, and 1 had myeloid sarcoma. The median age was 59 (21-70) years. Nineteen were women and 7 had a history of HCT. The regimens combined with VEN were azacitidine in 39 cases and low-dose cytarabine in 7. According to the 2022 ELN risk classification by genetics at diagnosis, 7 were favorable, 11 were intermediate, and 27 were at adverse risk. Nine patients were in hematological complete remission (CR) / CR with incomplete count recovery (CRi) while 37 were not, when VEN was initiated. The maximum response rates among the patients who started VEN treatment in the non-CR group were: 18 with CR/CRi (49%) and no response in 19 (51%). The median time from the first dose of VEN to HCT was 70 (27-315) days. Forty-one patients underwent HCT and 19 (43%) were in CR/CRi at HCT. The reasons for discontinuation of VEN were HCT in 34 cases, failure in 9, and adverse events in 4 (hematological toxicity in 3 cases and infection in 1). Sixteen patients died due to primary disease (n=9), infection (n=5), thrombotic microangiopathy (n=1), and multi-organ failure (n=1). The median post-HCT observation period of survivors was 156 (25-775) days, and at 1-year after HCT, OS was 49.6% (95% CI: 28.0-67.9), CIR was 40.6% (95% CI: 24.1-56.6) and NRM was 15.2% (95% CI: 5.5-29.5). At 1-year after HCT, outcomes of the patients who were in CR/CRi at HCT was better than that of those who were not (OS, 80.8% vs. 26.4%, p=0.002; CIR, 13.4% vs. 61.8%, p<0.01; NRM, 0% vs. 26.7%, p<0.05). In 35 of the patients who underwent the first HCT, the 1-year OS was 88.9% in those who were in CR and 36.5% in those who were not (p=0.015). Thirty cases were non-CR at the start of the VEN regimen prior to their first HCT. This group had a 1-year

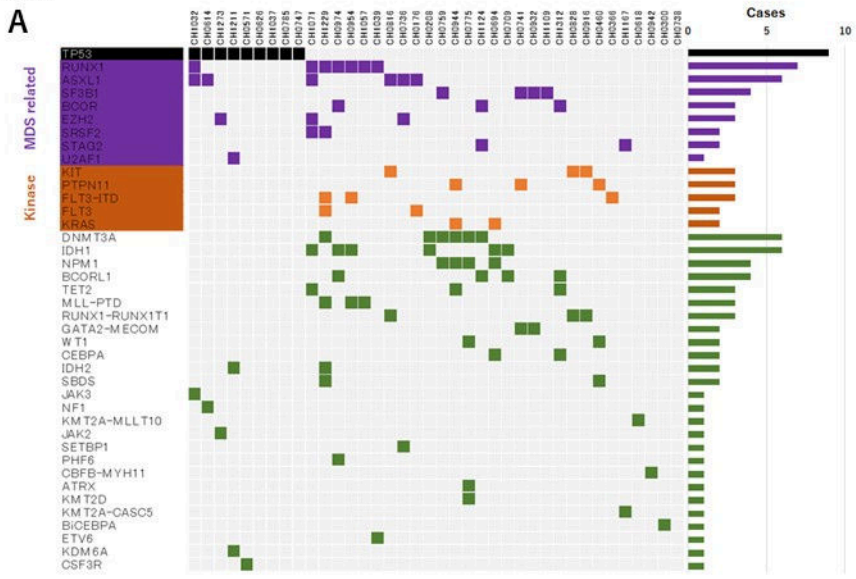
OS of 57.8% (95% CI, 27.4-79.3). In 11 patients who achieved CR before HCT and 18 others who did not, the 1-year OS rates were 83.3% and 39.9%, respectively (p=0.10).
Genetic analysis was performed by NGS in 37 patients before starting VEN, revealing mutations in *TP53* (n=9), *RUNX1* (n=7), *IDH1* (n=6), *ASXL1* (n=6), and *DNMT3A* (n=6) (Fig. 1A). Alterations in MDS-related genes (n=20) and kinase-related genes (*KIT*, *PTPN11*, *FLT3*, *KRAS*, n=11) were frequent. Among the patients receiving their first HCTs, the 1-year OS was 0% in the group with *TP53* mutations, and 63.9% in the wild-type *TP53* group (p=0.04). The OS was worse in patients with mutated *TP53* or kinase-related genes (n=19) than those without either mutation (n=15) (Fig. 1B, 1-year OS 28.7% vs. 72.9%, p=0.029). A multivariate analysis of OS revealed that patients who were not in CR at HCT (HR, 25.01 [95% CI, 2.406-259.9], p=0.007), those who previously underwent HCT (HR, 36.81 [95% CI, 4.599-294.7], p=0.035), and those with *TP53* or kinase-related gene mutations (HR, 6.311 [95% CI, 1.137-350.0], p=0.035) had significantly lower OS rates. There was no significant difference in OS between the different ELN risk categories.

Conclusions

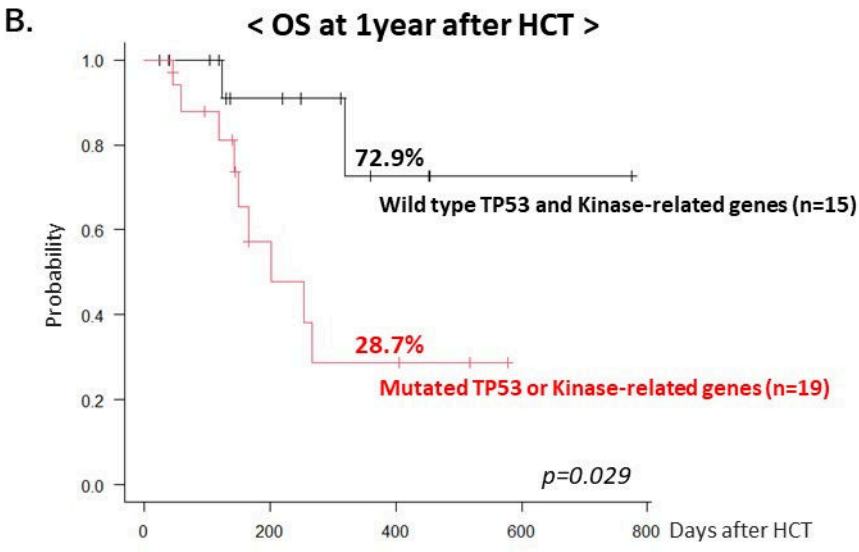
Non-CR at the time of HCT, a history of HCT, and mutations in *TP53* or kinase-related genes were found to be independent poor prognostic factors for OS after VEN-based bridging treatment followed by HCT.

Disclosures Najima: *Astellas Pharma Inc.:* Consultancy, Speakers Bureau; *CSL Behring K.K.:* Speakers Bureau; *Chugai Pharmaceutical Co., Ltd.:* Speakers Bureau; *Bristol-Myers Squibb K.K.:* Speakers Bureau; *Amgen Inc.:* Speakers Bureau; *Otsuka Pharmaceutical Co., Ltd.:* Speakers Bureau; *Nippon Shinyaku Co., Ltd.:* Speakers Bureau; *Sumitomo Pharma Co., Ltd.:* Speakers Bureau; *AbbVie GK:* Speakers Bureau; *Kyowa Kirin Co., Ltd.:* Speakers Bureau; *Janssen Pharmaceutical K.K.:* Speakers Bureau; *Daiichi Sankyo Co. Ltd.:* Consultancy, Speakers Bureau; *Takeda Pharmaceutical Company Limited.:* Speakers Bureau; *Novartis Pharma K.K.:* Speakers Bureau. **Harada:** *Novartis Pharma K.K.:* Speakers Bureau. **Doki:** *Janssen Pharmaceutical K.K.:* Honoraria; *Novartis Pharma K.K.:* Honoraria.

Fig.1



The landscape of gene mutations before VEN-based therapy.



The mutation profile before VEN-based therapy predicted OS after HCT.

Figure 1

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