ELSEVIER

Blood 142 (2023) 6495–6496

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Daprodustat, a Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor, Improves Hematological Insufficiency without Progression of Myelodysplastic Syndrome with Chronic Kidney Disease

Ryujiro Hara[1,2,3], *Toshihiko Kitahara*[2], *Hiroki Numata*[2], *Shigeki Watanabe*[2], *Eri Kikkawa*[4], *Makoto Onizuka, MD PhD*[4], *Hiroshi Kawada, MDPhD*[4]

[1] Department of Hematology/Oncology, TOKAI UNIVERSITY SCHOOL OF MEDICINE, KANAGAWA, Japan
[2] Ebina General Hospital, Ebina, Japan
[3] Ozawa Hospital, Odawara, Japan
[4] Department of Hematology/Oncology, Tokai University School of Medicine, Isehara, Japan

Introduction

Hematological insufficiency is a critical issue in the treatment of myelodysplastic syndrome (MDS). The current standard treatment for cytopenia in MDS involves blood transfusion and the administration of erythropoiesis stimulating agents (ESAs). However, ESAs are only effective in certain patients with low erythropoietin levels; patients who are not suitable candidates for allogeneic hematopoietic stem cell transplantation (allo-HSCT) require lifelong blood transfusions. As a result, there is a growing demand for new treatments for cytopenia in MDS, and researchers have been exploring various molecular-targeted drugs in recent years. One promising option is the hypoxia-inducible factor -prolyl hydroxylase inhibitor (HIF-PHi). This inhibitor stabilizes HIF1α, which in turn normalizes endogenous erythropoietin production and iron metabolism, leading to improved renal anemia. It is believed that HIF-PHi could potentially enhance MDS-related anemia by increasing erythropoietin levels. However, despite some case reports, there have been no comprehensive clinical studies evaluating the effectiveness and safety of HIF-PH inhibitors for MDS. Moreover, it is essential to address concerns related to HIF1α overexpression, which has been associated with exacerbating various malignant tumors, including MDS. To assess the safety and effectiveness of HIF-PHi for MDS, we conducted a prospective clinical trial evaluating an oral HIF-PHi called daprodustat.

Methods

The study included MDS patients with chronic kidney disease (CKD) stage $\geq$ 3, considering daprodustat's approval in Japan, at Ebina General Hospital. Patients with MDS who were treated with deoxyribonucleic acid methylation inhibitors and/or who underwent allo-HSCT were excluded. Participants were administered daprodustat at the approved dose for renal anemia and underwent regular blood sampling and bone marrow examination. The primary and secondary endpoints were the leukemia rate within 1 year after HIF-PHi administration and hematological improvement (HI), respectively. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Institutional Review Board of the Ebina General Hospital (approval number: JMA-388). Written informed consent was obtained from all participants.

Results

Seventeen patients with MDS, with a median age of 81years, were included in the analysis. Revised International Prognostic Scoring System scores (IPSS-R) were very low, low, intermediate, high, and very high in 1, 11, 3, 1, and 1 patients, respectively. Five cases were changed from ESA treatment. Within 1 year after HIF-PHi administration, no patients developed leukemia, and both peripheral blood Wilms tumor 1 protein concentrations and bone marrow myeloblast counts remained unchanged from pre-treatment levels. HI was observed in 8 patients within 6 months, and the median dose was 6 (range, 2-12) mg for HI achievement. On univariate analysis, pretreatment transferrin saturation (TSAT, $P = 0.002$, Figure 1) and ferritin concentration ($P = 0.016$) were inversely associated with HI achievement. However, pretreatment hepcidin concentration, erythropoietin concentration, previous ESA use, and IPSS-R were not associated with HI achievement. Notably, when a TSAT cutoff of $<$ 45% was used, achieving HI showed a sensitivity and specificity of 87.5% and 100.0%. Moreover, patients with TSAT $<$ 45% showed significant improvement in anemia after 3 months and beyond (Figure 2). No significant differences were observed in neutrophil and platelet counts between the two groups. Throughout the study, eleven adverse events occurred, including 6 infections, and 1 case each of myocardial infarction, eosinophilia, erythema multiforme, organizing pneumonia, and spinal fracture.

Conclusion
HIF-PHi administration did not lead to MDS progression. Notably, in MDS patients with CKD, low TSAT was a predictor for achieving HI by HIF-PHi.

Disclosures No relevant conflicts of interest to declare.

OffLabel Disclosure: Daprodustat is a drug for renal anemia, but we will discuss its effectiveness for MDS.

Figure 1

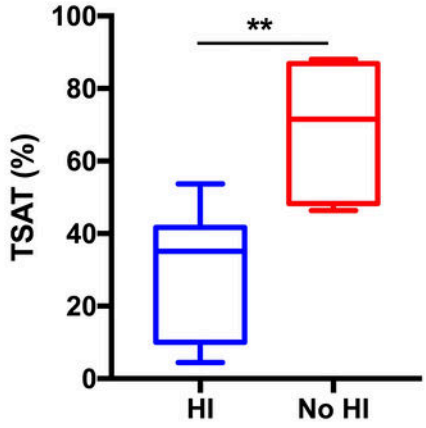

Figure 2

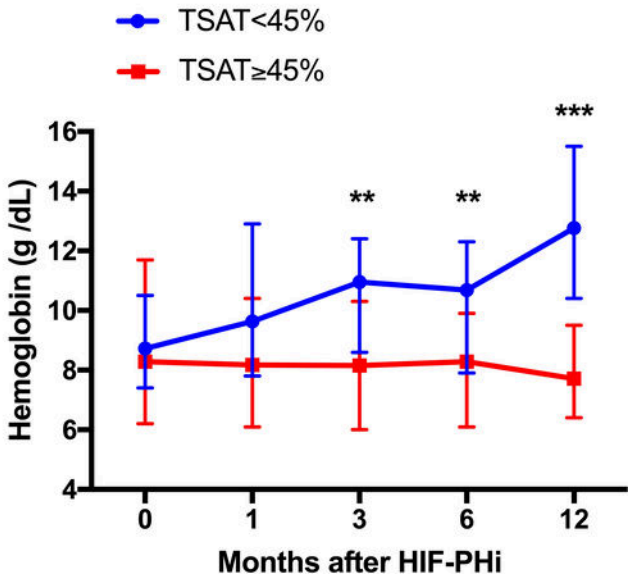

Figure 1

https://doi.org/10.1182/blood-2023-182991