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Case report

Successful management of acute graft-versus-host disease with ibrutinib during cord blood transplantation for germline *DDX41*-mutated acute myeloid leukemia

Ayana Uchimura [a], Hajime Yasuda [a,*], Hiroko Onagi [b], Tadaaki Inano [a], Shuichi Shirane [a], Midori Ishii [a], Yoko Azusawa [e], Yasuharu Hamano [a], Hidetaka Eguchi [c], Masami Arai [d], Jun Ando [a,e], Miki Ando [a]

[a] *Department of Hematology, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[b] *Department of Human Pathology, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[c] *Diagnostics and Therapeutics of Intractable Diseases, Intractable Disease Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[d] *Department of Clinical Genetics, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[e] *Division of Cell Therapy & Blood Transfusion Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*

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ABSTRACT

Background: Acute graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) with significant morbidity and mortality, and efficacy of currently available therapeutics are limited. Acute and chronic GVHD are similar in that both are initiated by antigen presenting cells and activation of alloreactive B-cells and T-cells, subsequently leading to inflammation, tissue damage, and organ failure. One difference is that acute GVHD is mostly attributed to T-cell activation and cytokine release, whereas B-cells are the key players in chronic GVHD. Ibrutinib is an irreversible inhibitor of the Bruton's tyrosine kinase (BTK), which is part of B-cell receptor signaling. Ibrutinib is currently used for treating chronic GVHD, but its efficacy towards acute GVHD is unknown. Besides BTK, ibrutinib also inhibits interleukin-2 inducible T-cell kinase (ITK), which is predominantly expressed in T-cells and a crucial enzyme for activating the downstream pathway of TCR signaling. ITK activates PLCγ2 and facilitates signaling through NF-κB, NFAT, and MAPK, leading to activation and proliferation of T-cells and enhanced cytokine production. Therefore, the TCR signaling pathway is indispensable for development of acute GVHD, and ITK inhibition by ibrutinib would be a rational therapeutic approach.

Case presentation: A 56-year-old male acute myeloid leukemia patient with Myeloid neoplasms with germline DEAD-box RNA helicase 41 (*DDX41*) mutation underwent cord blood transplantation and developed severe gastrointestinal (GI) acute GVHD which was refractory to steroids and mesenchymal stem cell therapy. While acute GVHD accommodated by multiple life-threatening GI bleeding events persisted, chronic cutaneous GVHD developed, and ibrutinib 420 mg/day was initiated from day 147 of transplant. Although ibrutinib was commenced targeting the chronic GVHD, unexpected and abrupt remission of acute GVHD along with remission of chronic GVHD was observed.

* Corresponding author.
E-mail address: hyasuda@juntendo.ac.jp (H. Yasuda).

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Conclusion: Ibrutinib is a promising therapeutic for treating acute GVHD, and further studies are warranted.

1. Introduction

Graft-versus-host disease (GVHD) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Although different pathological conditions, acute and chronic GVHD are similar in that both are initiated by antigen presenting cells and activation of alloreactive B-cells and T-cells, subsequently leading to inflammation, tissue damage, and organ failure. One difference is that acute GVHD is mostly attributed to T-cell activation and cytokine release, whereas B-cells are the key players in chronic GVHD [1].

Ibrutinib is an irreversible inhibitor of the Bruton's tyrosine kinase (BTK). BTK is part of B-cell receptor signaling, which is crucial for B-cell survival, proliferation, and migration [2]. A phase 1b/2 study involving 42 patients with steroid-dependent or steroid-refractory chronic GVHD demonstrated that ibrutinib administration achieved a best overall response rate of 69 % and complete response rate of 31 %, leading to FDA approval of ibrutinib at a daily dose of 420mg for treatment of chronic GVHD in 2017 [2,3]. Besides BTK, ibrutinib also inhibits interleukin-2 inducible T-cell kinase (ITK), which is in turn part of T-cell receptor (TCR) signaling. TCR signaling is crucial for T-cell activation, proliferation, and cytokine release [2]. Therefore, in theory, ibrutinib may not only be effective for treating chronic GVHD, but also acute GVHD as well. A pre-clinical study utilizing a well-established acute GVHD mouse model demonstrated that recipients treated with ibrutinib showed a significant improvement in acute GVHD clinical scores compared to vehicle controls throughout an 80-day monitoring period [4]. However, information on ibrutinib efficacy for treating acute GVHD in humans are lacking. We report a patient achieving complete response (CR) to steroid-refractory acute GVHD with ibrutinib after cord blood transplantation (CBT) for myeloid neoplasms (MN) with germline DEAD-box RNA helicase 41 (*DDX41*) mutation.

2. Case

A 56-year-old male with a history of schizophrenia presented to our department for progressive pancytopenia. His father, grandfather, and cousin had a history of either myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Peripheral blood tests showed a white blood cell count of 1.8×10^9/L (neutrophils 58 %, lymphocytes 32 %, monocytes 7.5 %, eosinophils 2.0 %, basophils 0.5 %), hemoglobin of 12.9 g/dL, and platelet count of 117×10^9/L. Bone marrow examination revealed hypoplasia, micromegakaryocytes, and an increased blast count of 20 %. Myeloperoxidase staining showed approximately 10 % of blasts to be

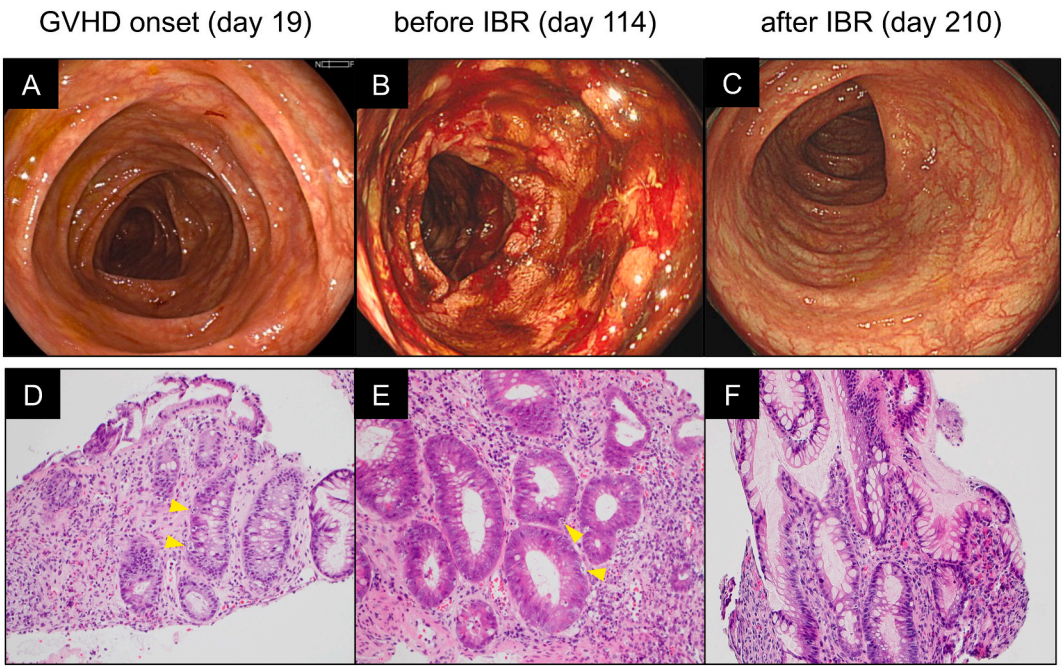

Fig. 1. Endoscopic and pathological findings (hematoxylin-eosin staining, original magnifications × 200) at onset of acute GVHD (A) (D), before ibrutinib administration (B) (E), and after ibrutinib administration (C) (F). Yellow arrows indicate apoptotic bodies. Abbreviations: IBR: ibrutinib. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

positive, and flow cytometry revealed blasts to be positive for HLA-DR, CD34, CD38 and CD117. Cytogenetic analysis showed 47, XY, +8 [3]/46, XY [17]. Next generation sequencing (NGS) identified c.1088_1090del (p.Ser363del) in the *DDX41* gene of the proband, which is an in-frame variant, and segregation studies showed that his father suffering from MDS harbored an identical variant whereas it was absent in his mother who carried no MN. The findings were compatible with their phenotypes, and the *DDX41* mutation was considered to be germline. The patient's initial condition of schizophrenia was unstable after informing him of AML, and he was judged ineligible for intensive induction therapy. Instead, two courses of venetoclax and azacitizine therapy were carried out, and he achieved a complete remission. By this time, his mental status had significantly recovered, and allo-HSCT was planned. A database search of the Japan Marrow Donor Program found no HLA-matched donor available, and family members were not considered as candidates due to the hereditary predisposition for MN. Thus, CBT with reduced-intensity conditioning (fludarabine 30 mg/m^2 on days −7 to −3, melphalan 70 mg/m^2 on days −2 and −1, and total body irradiation 4Gy/2fr on day −2) accompanied by GVHD prophylaxis with tacrolimus and mycophenolate mofetil was carried out. He developed acute gastrointestinal (GI) GVHD [lower GI stage 2, grade III, based on the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria] on day 19 of CBT (Fig. 1A and D). As his acute GVHD was resistant to 1mg/kg/day of methylprednisolone, mesenchymal stem cell (MSC) therapy was added and continued for 12 administrations, and although diarrhea transiently improved, he developed bloody stool. Lower GI endoscopy on day 114 revealed multiple ulcers throughout the total colon and terminal ileum, and biopsies revealed crypt apoptosis (Fig. 1B and E). Pathology revealed no signs of cytomegalovirus enteritis. His acute GVHD was judged to have progressed to lower GI stage 4, grade IV by the MAGIC criteria. He suffered from four life-threatening events of massive lower GI bleeding, but these were managed with red blood cell transfusions and transcatheter arterial embolization. On day 133, while acute GI GVHD was still active, he developed lichen planus-like skin lesions and biopsies were indicative of chronic cutaneous GVHD. Topical steroids were administered, but the lesions progressed to score 3 on the NIH consensus skin criteria, and ibrutinib was initiated at 420 mg/day from day 147. Ibrutinib led not only to complete response (CR) of cutaneous chronic GVHD on day 167, but also unexpected abrupt improvement of the lingering acute GI GVHD leading to rapid tapering of systemic steroids and discontinuation after day 162. Parenteral nutrition was discontinued and oral feeding was resumed from day 173. CR of acute GI GVHD was confirmed on day 194, and lower GI endoscopy done on day 210 showed remarkable improvement of colon lesions and deep ulcers were no longer observed (Fig. 1C and F). The patient remains well with ibrutinib continuation, no adverse events have been observed, and the *DDX41*-mutated AML has not recurred as of day 266. There are no firm recommendations concerning the optimal timing of ibrutinib tapering and termination for either acute or chronic GVHD at time of reporting, and ibrutinib is planned to be continued in the patient until more data are available [3].

3. Discussion

The presented patient experienced life-threatening grade IV acute GI GVHD which was refractory to steroids and MSC therapy. Ibrutinib administration, which was originally targeted towards cutaneous chronic GVHD, brought about remarkable and abrupt remission of protracted acute GI GVHD. Ibrutinib is known for its efficacy towards chronic GVHD, but this report is the first to demonstrate clinical efficacy towards acute GVHD. Acute GVHD remains a major complication of allo-HSCT associated with significant morbidity and mortality. The cumulative 100-day incidence of acute GVHD has been reported to be 49 % in patients undergoing allo-HSCT in a multicenter trial. As for mortality, one-year overall survival of patients with grade III-IV acute GVHD was reported to be 40 %. Systemic steroids remain the standard first-line treatment, but infectious complications are frequent and response rates are reported to be around 50 % [5]. The JAK2 inhibitor ruxolitinib was approved for steroid-refractory acute GVHD by the FDA in 2019 based on the phase II study, REACH1 [6]. REACH1 led to REACH2, a phase III study comparing ruxolitinib versus best available treatment in patients with steroid-refractory or steroid-dependent acute GVHD and reported overall response rates of 62 % and 39 %, respectively. However, in REACH2, the durable response rate of the ruxolitinib arm on day 56 was low at 39.6 %, and there is an unmet need for treating steroid-refractory acute GVHD [7].

The potential ibrutinib holds for treating acute GVHD is supported by its mechanisms of action in conjunction with the mechanisms by which acute GVHD occurs. Acute GVHD is initiated by activation of host antigen presenting cells (APCs) by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), which are released because of damage caused by conditioning chemotherapy and radiotherapy. Subsequently, host APCs activate donor alloreactive CD4$^+$ and CD8$^+$ T-cells, leading to host tissue damage and acute GVHD. Host tissue damage is mediated by pro-inflammatory cytokines such as INFγ and TNF by donor alloreactive CD4$^+$ T-cells, whereas induction of apoptosis is the main mechanism of tissue damage by doner alloreactive CD8$^+$ T-cells [5]. Besides BTK, ibrutinib also inhibits ITK, which is predominantly expressed in T-cells and a crucial enzyme for activating the downstream pathway of TCR signaling [1]. ITK activates PLCγ2 and facilitates signaling through NF-κB, NFAT, and MAPK, leading to activation and proliferation of T-cells and enhanced cytokine production. Therefore, the TCR signaling pathway is indispensable for development of acute GVHD, and ITK inhibition by ibrutinib would be a rational therapeutic approach [1].

Another novel aspect is that this is the first report of successful CBT for MN with germline *DDX41* mutation, which is an autosomal dominant hereditary MDS/AML syndrome with unique features such as male predominance, late life onset, tendency of indolent disease course, and less pronounced cytopenias compared to other MDS/AML. The risk of developing AML in *DDX41*-mutated individuals is negligible before the age of 40, but rises to 25 % at age 70 and 49 % at age 90, resulting in a life-time risk of AML of around 50 %. Screening for *DDX41* mutations in patients with MN is important because it affects donor selection (family members may not be appropriate) and monitoring relatives for development of MN may also be an important option to be considered [8]. Allo-HSCT is the only potentially curative therapy for MN with germline *DDX41* mutation, but application of allo-HSCT has recently become a subject of debate due to the unique high rates of severe acute GVHD and non-relapse mortality (NRM). In a retrospective analysis of 86 germline *DDX41*-mutated AML patients eligible for allo-HSCT, 35 patients underwent allo-HSCT in first CR. Allo-HSCT in first CR was associated

with significantly prolonged relapse-free survival, but not with longer overall survival (OS) [9]. Another retrospective study of 29 patients with *DDX41*-mutated MDS/AML demonstrated a trend towards shorter OS in the 13 patients undergoing allo-HSCT, and the authors recommended to defer allo-HSCT until disease progression or relapse [10]. Both studies reported high NRM rates of 31 % and 44.8 %, respectively, and GVHD significantly contributed to NRM. However, cure may still be an important goal, especially for younger patients as the presented case, and some investigators advocate allo-HSCT for MN with germline *DDX41* mutation with utilization of enhanced GVHD prophylaxis measures including posttransplant cyclophosphamide [11].

4. Conclusion

Acute GVHD is a major life-threatening complication of allo-HSCT. Efficacy of currently available therapeutics including ruxolitinib are limited, and there is an unmet need for treating acute GVHD. We report a case with protracted severe acute GVHD that was successfully treated with ibrutinib. Ibrutinib inhibits not only BTK but also ITK, which is indispensable for TCR signaling and development acute GVHD. Ibrutinib is a promising treatment approach for acute GVHD, and further studies are warranted. This is also the first report of successful CBT in a patient with MN with germline *DDX41* mutation. Because family members may not always be appropriate donor candidates for allo-HSCT due to the hereditary nature of MN with germline *DDX41* mutation, the experience with CBT we share will be of valuable information for treating future cases.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report.

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Data availability statement

Data will be made available on reasonable request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Ayana Uchimura: Writing – original draft, Conceptualization. **Hajime Yasuda:** Writing – review & editing, Conceptualization. **Hiroko Onagi:** Investigation. **Tadaaki Inano:** Supervision. **Shuichi Shirane:** Supervision, Conceptualization. **Midori Ishii:** Supervision. **Yoko Azusawa:** Writing – review & editing. **Yasuharu Hamano:** Supervision. **Hidetaka Eguchi:** Investigation. **Masami Arai:** Investigation. **Jun Ando:** Supervision, Project administration, Conceptualization. **Miki Ando:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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