Therapeutic Advances in Hematology Case Series

Experiences of allogeneic hematopoietic cell transplantation following non-myeloablative conditioning regimen in severely comorbid patients with myelofibrosis: case series with a patient presenting with extensive extramedullary hematopoiesis

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***Abstract*:** We have performed allogeneic hematopoietic cell transplantation (allo-HCT) using a reduced intensity conditioning regimen for curative management of advanced myelofibrosis (MF). However, allo-HCT is rarely considered for elderly or patients with severe comorbidities due to high transplantation-related mortality. In those patients, an alemtuzumab-based non-myeloablative (NMA) conditioning regimen followed by stem cell transplantation could be a possible treatment that has been tried in sickle cell anemia showing stable mixed chimerism and improvement of the disease. However, it is uncertain whether this regimen can provide durable donor-dominant chimerism also in patients with MF. We planned a two-stage allo-HCT in four patients – initially aimed at mixed chimerism with NMA conditioning and then reinforced with additional stem cell infusion if graft failure occurred. In one case with extensive extramedullary hematopoiesis, causing blindness and paraplegia, we achieved stable complete donor-chimerism and complete molecular response with disappearance of bone marrow fibrosis after allo-HCT. Although this NMA regimen failed to achieve durable donor-chimerism, additional stem cell infusion showed a possible role for stable long-term chimerism with good clinical outcomes. Although it leaves room for further improvement, allo-HCT using an NMA conditioning regimen may be worth consideration for advanced MF patients with severe comorbidity, otherwise no appropriate treatment option is available.

Keywords: allogeneic, hematopoietic cell transplantation, myelofibrosis, non-myeloablative conditioning

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative treatment for advanced myelofibrosis (MF), but substantial risk of transplantation-related mortality (TRM) is a considerable obstacle, especially in elderly patients or in patients with severe comorbidity.[1] Although recent data showed a benefit of allo-HCT even in lower-risk groups, and some reduced-intensity conditioning (RIC) regimens showed promising outcomes, we still confront severe complications after allo-HCT.[2–5] We have also used RIC regimens that consisted of fludarabine (30 mg/m^2 for 5 days) and busulfan (3.2 mg/kg for 2 days) with 400 cGy of total body irradiation (TBI) as curative treatment of advanced MF. However, patients

with severe comorbidity, or elderly patients, cannot even tolerate this RIC allo-HCT. To avert this, therefore, we are forced to use non-myeloablative (NMA) conditioning regimens, and found an idea from a regimen that consisted of alemtuzumab (1 mg/kg) plus low-dose TBI (400 cGy) and graft-versus-host disease (GVHD) prophylaxis with sirolimus, which was previously introduced for the treatment of sickle cell anemia.[6] This regimen was associated with extremely low TRM, which made us to consider an NMA conditioning regimen for severely comorbid or elderly patients with advanced MF ineligible for RIC allo-HCT. This NMA regimen could provide stable mixed chimerism, which proved sufficient for production of donor-type blood cells and reversion of the sickle cell disease phenotype in the absence of GVHD. However, mixed chimerism itself may not be sufficient for complete reversion of bone marrow (BM) fibrosis, and a considerable proportion of patients could not discontinue immunosuppressive drugs even after 1 year because of decreased donor T-cell chimerism (<50%). Therefore, we initially aimed to achieve mixed chimerism using the NMA conditioning regimen upon consideration of patient's comorbidity and/or advanced age, and then tried to reinforce donor chimerism with an additional stem cell infusion after total nodal irradiation of 500 cGy if there is evidence of declining chimerism. Four patients, all of whom with severe comorbidity (Table 1), received peripheral blood stem cells following the NMA conditioning regimen; three of them from a matched sibling donor (MSD), whereas one had a matched unrelated donor (MUD, CASE #1). Regarding poor engraftment or graft failure after NMA regimen, an additional second stem cell infusion from the same donor was planned. For monitoring engraftment status, we checked complete blood count (CBC) and whole blood (WB) and T-cell chimerism, and additional stem cell infusion was planned when the WB mixed chimerism fell under 50% at any time post-HCT from the two consecutive samples checked at least 3 months apart. Regardless of WB chimerism, if T-cell chimerism fell under 50% at 1 year or later post-HCT, an additional second stem cell infusion was also planned.

Case #1

A 67-year-old female patient with hypertension, grade 3 Eastern Cooperative Oncology Group (ECOG) performance status (PS), and a score of 4 on the HCT-comorbidity index (CI) received stem cells from MUD, resulting in neutrophil recovery at D + 10. Also, a 99% WB donor chimerism with negative *JAK2*V617F mutation was observed at 1 month post-HCT. However, she suffered from fungal sinusitis and toxic hepatitis and died due to progressive sepsis at 2 months. During the infection management before her death, we identified complete loss of chimerism with positive conversion of *JAK2*V617F mutation.

Case #2

A 56-year-old male patient with kidney injury and poor pulmonary function with pleural effusion had an ECOG PS of grade 3 and HCT-CI score of 6. Neutrophil recovery was observed at D + 10, and a 1-month WB donor chimerism was 90%, but *JAK2*V617F mutation was positive. Except for anemia, blood counts were stable until 7 months post-HCT, at which time WB chimerism was 88%. At 10 months post-HCT, while preparing an additional second stem cell infusion, peripheral blast count increased to 59% and BM exam showed transformation to secondary acute myeloid leukemia with *NPM1, IDH2, ASXL1*, and *SB2B3* mutation detected by next generation sequencing. Because of improved PS, we decided to proceed with intensive chemotherapy instead of a second stem cell infusion.

Case #3

A 66-year-old female patient with *CALR*-positive post-ET MF received stem cells from MSD. She presented poor ECOG performance grade 3–4 and her HCT-CI score was 5. Compared with previous cases, she received a lower dose of $CD34^+$ stem cells but neutrophil and platelet counts did not decrease to nadir. A 1-month WB donor chimerism was 95% but *CALR* mutation was still positive. Anemia and thrombocytopenia developed 6 months after transplantation and we found WB donor chimerism decreased to 40%, which was managed by additional stem cell infusion at 8 months and 20 months. During that period, the patient's PS surprisingly recovered to ECOG grade 1. However, we could not obtain stable engraftment with eventual graft loss occurred at 29 months (WB chimerism and donor T-cell chimerism, 22% and 70%, respectively), and we decided on a second allo-HCT from an unrelated donor. Because of improved condition

Table 1. Characteristics of MF patients treated with NMA conditioning regimen.

UPN	Age/sex	Diagnosis/ mutation/DIPSS-plus	Comorbidity/ ECOG/HCT-CI/ Time to HCT	Cell dose (× 10^6/kg) 1st infusion: $CD34^+/CD3^+$ 2nd infusion: $CD34^+/CD3^+$	Donor/GF type /GF treatment	Initial chimerism/mutation Worst chimerism/mutation Final chimerism/mutation	GVHD/survival status
#1	67/F	PMF/*JAK2*V617F/ INT-2	Old age, Hypertension/ECOG 3/CI 4/45 months	11.4/154.0	MUD/Late GF/Not done	WB 99% T 99%/Negative. at 1 month WB 0% T 0%/Positive at 2 months WB 0% T 0%/Positive at 2 months	None/Died (2 months) due to fungal sinusitis
				Not done			
#2	56/M	PMF/*JAK2*V617F/ High	Renal insufficiency Chronic lung disease/ECOG 3/CI 6/27 months	15.5/98.4	MSD/mixed chimerism /Not done	WB 90% T 77%/Positive at 1 month WB 88% T 51%/Positive at 7 months WB 79% T 29%/Positive at 12 months	None/progressed to AML (12 months) Alive (16 months)
				Not done			
#3	66/F	Post-ET MF/*CALR Type I*/ INT-2	Old age/ECOG 3–4/ CI 5/6 months	5.3/632.0	MSD/Late GF/2nd infusion (8, 20 months) RIC allo-HCT (35 months)	WB 95% T 91%/Positive at 1 month WB 40% T 25%/Positive at 6 months WB 100% T 98%/Negative at 36 months	None/Alive (42 months) after 2nd allo-HCT
				2.5/147.0			
#4	45/F	Post-PV MF/*JAK2* exon12/ INT-2	Extramedullary mass Blind, paraplegia/ECOG 4/ CI 4/45 months	18.9/843.0	MSD/mixed chimerism/Second infusion (19 months)	WB 86% T 89%/Negative at 1 month WB 37% T 41%/Positive at 18 months WB 99% T 99%/Negative at 45 months	Mild oral GVHD/ Alive (53 months) after 2nd infusion
				11.0/230.0			

Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CBC, complete blood count; CI, comorbidity index; DIPPS, dynamic international prognostic scoring system; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocytosis; GF, graft failure; GVHD, graft-*versus*-host disease; INT-2, intermediate-2; MF, myelofibrosis; NMA, non-myeloablative; PMF, primary MF; PV, polycythemia vera; RIC, reduced intensity conditioning; T, donor T-cell chimerism; WB, whole blood chimerism.

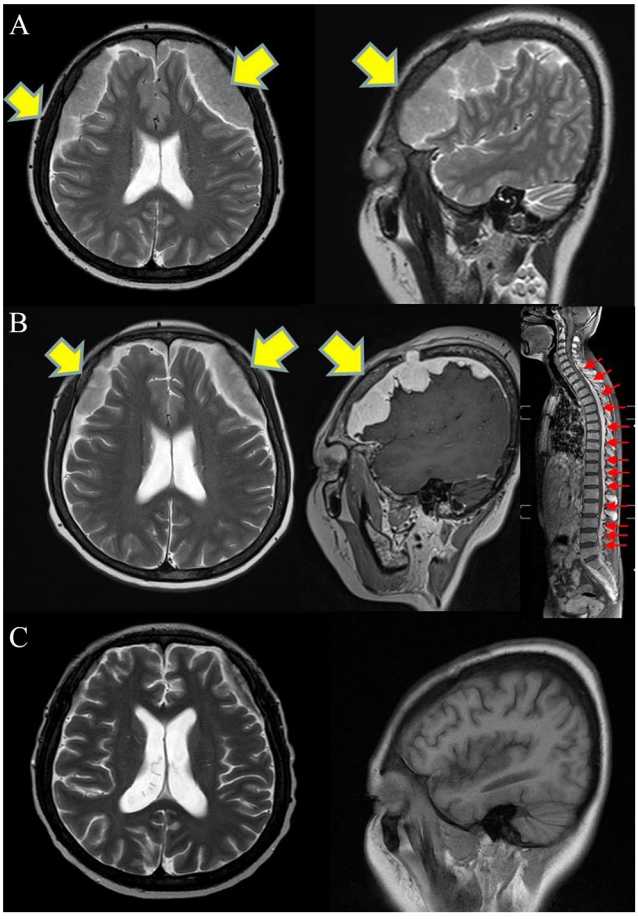

Figure 1. (A) Pachymeningeal thickening along parietotemporal regions caused by extramedullary hematopoiesis at dura mater (large arrows). (B) Although partial response was shown in meningeal involvement after radiation therapy on whole brain, progressive extramedullary hematopoiesis developed along the posterior aspect of spinal canal from C5 to S5, which caused diffuse cord compression (small arrows). (C) Previously involved lesions were dramatically improved in brain MRI checked at 6 months post-HCT.
HCT, hematopoietic cell transplantation; MRI, magnetic resonance imaging.

after previous transplantation, we were able to apply RIC regimen for second transplantation at 35 months after previous allo-HCT.

Case #4

The remaining case was a 45-year-old female patient who presented with extensive extramedullary hematopoiesis, which aggravated severe neurological complications such as blindness and paraplegia, with ECOG performance grade 4 and HCT-CI score 4. The patient was diagnosed as polycythemia vera (PV) with *JAK2* exon 12 mutation accompanying splenomegaly in 2002, and treated with intermittent phlebotomy until 2007. Progressive thrombocytopenia and huge splenomegaly with a longest diameter of 25 cm was identified in 2012, and a follow-up BM study showed MF-3 fibrosis with normal karyotype. Splenectomy was conducted in 2014 due to severe pain. After splenectomy, thrombocytopenia and constitutional symptoms improved transiently but she complained of intermittent headache and diplopia at 5 months after splenectomy. Brain MRI showed diffuse meningeal thickening along parietotemporal regions (Figure 1A), and dura biopsy revealed an increased number of hematopoietic precursors of all lineages. Diplopia was aggravating, with visual disturbance, and back pain and paraplegia developed despite radiation therapy (Figure 1B). We planned a RIC allo-HCT but the patient's performance status was getting worse due to progressive paraplegia and development of pneumonia. Although we explained that she was not a proper candidate for allo-HCT due to the high expectation

of fatality, we finally decided to conduct allo-HCT using NMA conditioning regimen with patient consent and willingness. The patient received a $CD34^+$ stem cell infusion of 18.9 x 10^6/kg from her younger brother on September 2015. CBC recovered on day 13 and the patient discharged without early complications. Although herpes zoster infection occurred, no GVHD developed, follow-up BM showed improved fibrosis with MF-2 grade, and meningeal lesions on follow-up MRI totally disappeared at 6 months post-HCT (Figure 1C). Despite improved performance status with stable blood counts, WB and donor T-cell chimerism declined progressively; 66% and 62% at 6 months, and 37% and 41% at 18 months post-HCT, respectively. Mutation of *JAK2* exon 12 became undetectable at 6 months post-HCT, but re-appeared at 11 months post-HCT. She was scheduled for additional stem cell infusion when the chimerism fell to 47% at 14 months post-HCT, and infusion was conducted at 19 months post-HCT ($CD34^+$ and $CD3^+$, 11.0×10^6/kg and 230.0×10^6/kg, respectively). At 8 months after second stem cell infusion, both WB and T-cell chimerism became 99% and she is alive with full donor chimerism and no evidence of BM fibrosis at 52 months post-HCT. However, her neurological complications still remain. She experienced only mild oral GVHD, which was soon resolved with low dose of prednisolone.

Patients with MF frequently exhibit accompanying extramedullary hematopoiesis within the liver, spleen, or any sites at advanced stage.[7] However, involvements in vital organs, such as cardiovascular system or central nervous system (CNS), are rare manifestations and can sometimes be fatal.[8,9] Although these manifestations are not included as an adverse-risk parameter in a prognostic scoring system, uncontrolled extramedullary hematopoiesis might be an emergency complication and should be treated by urgent radiation therapy or with allo-HCT in progressive cases.[10] Although RIC regimens allow allo-HCT for patients ineligible for a myeloablative conditioning regimen, we still confront high TRM after transplantation.[11] Therefore, we should cautiously consider NMA conditioning regimens for MF with progressive extramedullary hematopoiesis that aggravates a patients' comorbidities. Among several NMA regimens, low dose TBI plus alemtuzumab for sickle cell anemia showed stable mixed-donor chimerism with reversal of hemoglobinopathy without significant GVHD and TRM.[12,13] Our experience also showed this NMA regimen can be applied safely in MF patients with severe comorbidity, without producing acute or chronic complications. However, severe viral or fungal infection due to alemtuzumab and poor graft function are the problems most expected, and these should be considered and closely monitored for survival outcome. Thus, a meticulous search for potential focus of infection should be performed prior to HCT. We think the critical difference in treatment outcome between patient #3 and #4 may be the difference in the number of infused stem cells ($CD34^+$, 10.9×10^6/kg and 2.5×10^6/kg, respectively). In addition, our experience also suggested that the time and appropriate procedure for additional stem cell infusion should be studied more, and that NMA conditioning regimen followed by stem cell infusion from unrelated or mismatched donor should be tried cautiously due to poor immune reconstitution and infectious complications. We expect that MF patients with severe comorbidity might be treated successfully with alemtuzumab-based NMA regimen from MSD followed by additional stem cell infusion without significant fatalities.

Author contributions

Jae-Ho Yoon contributed to reviewing patients and writing the manuscript; Gi June Min, Sung-Soo Park, Silvia Park, Sung-Eun Lee, Byung-Sik Cho, Yoo-Jin Kim supported the treatment course of those patients; patients and the manuscript was critically reviewed by Hee-Je Kim, Chang-Ki Min, Seok-Goo Cho, Jong Wook Lee and Seok Lee. Ki-Seong Eom is corresponding author, was mainly in charge of those patients, and wrote the manuscript

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Conflict of interest statement

The authors declare that there is no conflict of interest.

Consent for publication

We confirm that all patients provided written informed consent for the publication of patient information in the present manuscript.

Ethics approval and consent to participate

This research was conducted in accordance with the Institutional Review Board guidelines of the Catholic Medical Center (KC16ZISE0397).

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