Clinical characteristics of calcineurin inhibitor-induced pain syndrome (CIPS) after allogeneic hematopoietic stem cell transplantation

Noriko Doki1, Kazuhiko Kakihana1, Masahiro Ashizawa2, Masahiro Onoda3, Chikako Ohwada4, Sumiko Kobayashi5, Moritaka Gotoh6, Shin Fujisawa7, Shinichiro Okamoto8, for the Kanto Study Group for Cell Therapy

1Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
2Division of Hematology, Jichi Medical University, Saitama Medical Center, Omiya, Japan
3Internal medicine, Chiba Aoba Municipal Hospital, Chiba, Japan
4Department of Hematology, Chiba University Hospital, Chiba, Japan
5Department of Hematology, Tokyo Metropolitan Gerontology Hospital, Tokyo, Japan
6Department of Hematology, Tokyo Medical University, Tokyo, Japan
7Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan
8Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

Calcineurin inhibitor (CI)-induced pain syndrome (CIPS) is a rare complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, because of its rarity, the optimal management of this complication remains unknown.

We analyzed the clinical features and treatment outcomes of the patients who developed CIPS after allo-HSCT. The study included patients who underwent allo-HSCT between January 2003 and December 2014 at the hospitals participating in the KSGCT. Sixteen patients developed CIPS. The most common symptom was leg pain, which was observed in 9 patients, followed by leg pain associated with pruritus in five, and pruritus only in two. The median time from allo-HSCT to CIPS was 16 days. CIPS occurred within 30 days of starting CIs in 14 patients (87.5%). CI was discontinued in four patients; the dose of CI was reduced in two patients, and seven patients were switched to another CI. The symptoms in all of those 13 patients with intervention resolved within 6 days from the onset of CIPS.

The possibility of CIPS must be considered when patients who have undergone allo-HSCT develop intolerable leg pain and/or pruritus. Our findings suggest that withdrawal/dose reduction of the CI or substitution with another CI is an effective treatment for CIPS. (Journal of Hematopoietic Cell Transplantation 6(2): 115–119, 2017.)

Introduction

Calcineurin inhibitor (CI)-induced pain syndrome (CIPS) was first described in an organ transplant recipient in 1991,1 and has been subsequently reported among patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT).2–4 The characteristic clinical features of CIPS include severe pain localized in the bilateral lower limbs, elevated CI trough levels at the onset, lack of response to common analgesics, bone marrow edema as seen with magnetic resonance imaging, and increased uptake as seen with bone scintigraphy.2,5 However, few studies have analyzed the clinical course and complications in patients with CIPS after allo-HSCT. Therefore, we conducted a retrospective study to elucidate the clinical features and outcomes of patients with CIPS after allo-HSCT at the institutions of the Kanto Study Group.
Group for Cell Therapy (KSGCT).

Patients and methods
The study included patients who underwent allo-HSCT between January 2003 and December 2014 at the hospitals participating in the KSGCT. Detailed clinical information was obtained by retrospective chart review. CIs was defined as severe, disabling, bilateral leg pain and/or intolerable dermal pruritus without a skin rash. Cyclosporine (CsA) and tacrolimus (FK) were administered beginning 1 day before the transplant for the prophylaxis of graft-versus-host disease (GVHD). CI was administered by continuous infusion except for some institutions where CsA was given intravenously over 10 hours. The CIs were given orally when patients were able to eat.

Results

Patient Characteristics (Table 1)
Sixteen patients developed CIPS. The clinical characteristics of those 16 patients at the onset of CIPS are shown in Table 1. The median age was 37.5 years (range: 18–59 years), and 8 patients (50%) were male. The primary diseases included acute myeloid leukemia (n = 3), acute lymphoblastic leukemia (n = 5), myelodysplastic syndrome (n = 5), chronic myelogenous leukemia (n = 2), and follicular lymphoma (n = 1). Two patients developed CIPS after their second HSCT. Twelve patients underwent myeloablative transplants for hematological malignancies. The sources of stem cells were related bone marrow (n = 3), unrelated bone marrow (n = 7), related peripheral blood (n = 1), and unrelated cord blood (n = 5). Nine patients were given CsA, and seven patients received FK. Acute GVHD developed in seven patients at the onset of CIPS, and six patients had been treated with CIs and steroids. Bone scintigraphy was performed in six patients, and four patients showed increased uptake in the ankles, knees, and/or elbows.

Clinical presentation of CIPS after allo-HSCT (Table 2)
Sixteen patients developed CIPS at a median of 16 days (range: −1 to 887 days) after HSCT. Fourteen patients (87.5%) had an onset of CIPS within 30 days of starting CIs, whereas two patients developed CIPS more than 10 months after HSCT. Regarding the trough levels of CIs, the level was above the therapeutic range (200–300 ng/mL for CsA, and 10–15 ng/mL for FK) in 8 patients (50%), below in two, and within the range in five. The first symptom of CIPS was bilateral leg pain in 9 patients, pruritus only in two patients, and leg pain associated with pruritus in five patients.

Intervention and outcome
CIs were discontinued in four patients, the dose of CI was reduced in two patients, and the CI was changed to another CI in seven patients. Three patients did not receive intervention. Symptoms in all of 13 patients with intervention resolved. The median time to the resolution of symptoms was 6 days (range: 3–47 days). Two patients developed acute GVHD after withdrawal of CIs, and one patient died from acute GVHD. Among the three patients without intervention, two patients showed minimal resolution of symptoms, and symptoms in one patient did not resolve. Analgesics such as morphine, pentazocine, flurbiprofen, and fentanyl were administered to 7 patients at the onset of CIPS. However, none of those analgesics were effective for relieving pain.

Discussion
This multicenter observational retrospective study analyzed the clinical characteristics of CIPS with the largest number of patients reported so far. This syndrome affects about 5% of patients who undergo organ transplantation or allo-HSCT.6 We could not precisely analyze the incidence of CIPS. However, more than 2,000 allo-HSCTs were performed at the participating institutions during this study period, and thus, the incidence of CIPS appears to be less than 1%.

Regarding the day of onset, most patients developed CIPS within 30 days after allo-HSCT. The onset in our series was earlier than in previous reports of organ transplantation5 in which CIPS occurred several months after transplantation.2 At the onset of CIPS, the trough levels of CIs were higher following organ transplantation6 than HSCT. In addition, the trough level in 8 patients (50%) was above the therapeutic range, but the levels were within or below the range in the other patients in this study. These discrepancies suggest a different etiology for CIPS after allo-HSCT compared to that after organ transplantation. Similar to previous reports,2,8 the symptoms of CIPS in the current series were leg pain (9 patients, 56%), leg pain and pruritus (five patients, 31%), and only pruritus without leg pain (two patients, 13%).

Regarding the treatment, commonly used analgesics failed to relieve pain in all of 7 patients. Calcium channel blockers
### Table 1. Patient characteristics

| Patient no | Age/gender | Underlying disease | Times of HSCT | Conditioning regimen | MA/RIC | Type of HSCT | GVHD prophylaxis | Disease status at HSCT | Symptoms | Disease onset (days after HSCT) | CIs trough level at disease onset | Intervention of CIs | GVHD at disease onset | Use of systemic steroids | Bone scintigraphy outcome | Days to resolution |
|------------|------------|--------------------|---------------|----------------------|--------|-------------|----------------|-------------------|----------|-------------------------------|-------------------------|----------------|----------------|------------------------|---------------------|---------------------|
| 1*         | 18/F       | AML               | 2             | Flu/Mel/TBI          | RIC    | uCB         | CsA+MTX        | 1st relapse       | leg pain      | 18                           | 233.7                   | —                 | —                | —                      | no change           |                     |
| 2*         | 32/M       | ALL               | 1             | CA/CY/TBI            | MA     | uCB         | CsA→FK        | 2nd relapse      | leg pain      | 12                           | 8.8                     | Discontinuation | yes              | PSL                  | resolved            | 5                   |
| 3*         | 51/M       | MDS               | 1             | BU/CY                | MA     | uBM         | FK+MTX        | MDS              | leg pain      | 302                          | 10.7                    | Discontinuation | —                | PSL                  | positive resolved   | 11                  |
| 4*         | 19/F       | MDS               | 1             | BU/CY                | MA     | uBM         | FK+MTX        | MDS              | leg pain      | 887                          | NA                      | Discontinuation | yes              | PSL                  | NA resolved          | 6                   |
| 5           | 29/M       | CML-BC            | 1             | CY/TBI               | MA     | rPB         | CsA+MTX        | CML 2nd CP      | leg pain      | 15                           | 263.8                   | CsA→FK          | yes              | —                      | resolved            | 7                   |
| 6           | 24/F       | MDS               | 1             | BU/CY                | MA     | uBM         | FK+MTX        | MDS              | pruritus      | 11                           | 9.4                     | FK→CsA          | yes              | —                      | NA resolved          | 3                   |
| 7           | 32/M       | MDS               | 2             | CY/Fu/TBI            | RIC    | rBM         | CsA+MTX        | Engraftment failure | leg pain      | 2                            | 419                     | Discontinuation | —                | —                      | negative resolved   | 14                  |
| 8           | 43/F       | CML-BC            | 1             | CA/CY/TBI            | MA     | uBM         | FK+MTX        | CML 2nd CP      | pruritus      | 1                            | 18.3                    | FK→CsA          | —                | —                      | NA resolved          | 3                   |
| 9           | 43/M       | ALL               | 1             | CA/CY/TBI            | MA     | uBM         | FK+MTX        | CR               | leg pain      | 2                            | 18                      | —                 | —                | —                      | positive resolved   | 2                   |
| 10          | 59/F       | MDS               | 1             | BU/CY                | MA     | uBM         | FK+MTX        | MDS              | leg pain      | 23                           | 21.6                    | FK→CsA          | yes              | —                      | NA resolved          | 3                   |
| 11          | 24/M       | AML               | 1             | Fu/TBI               | RIC    | uCB         | CsA+MTX        | CR               | leg pain      | day-1, 47                     | 500                     | —                 | —                | day 47, yes          | PSA partially resolved | 5, 15               |
| 12          | 54/F       | FL                | 1             | Fu/Mel               | RIC    | rBM         | CsA+MTX        | nonCR           | pain         | 19                           | 380                     | Discontinuation | —                | —                      | negative resolved   | 22                  |
| 13          | 47/F       | AML               | 1             | CA/CY/TBI            | MA     | rBM         | CsA+MTX        | CR               | leg pain      | 16                           | 333.8                   | CsA→FK          | yes              | PSLS                 | NA resolved          | 2                   |
| 14          | 28/M       | ALL               | 1             | CY/TBI               | MA     | uBM         | CsA+MTX        | CR               | leg pain      | 21                           | 509                     | CsA→FK          | —                | —                      | NA resolved          | 15                  |
| 15          | 44/F       | ALL               | 1             | CY/TBI               | MA     | uBM         | CsA+MTX        | CR               | finger pain  | 8                            | 135.5 (10h)               | Discontinuation | —                | —                      | NA resolved          | 47                  |
| 16          | 44/M       | ALL               | 1             | CY/TBI               | MA     | uCB         | FK+MMF        | CR               | leg pain      | 21                           | 20.5                     | FK→CsA          | —                | mPSL                  | positive resolved   | 5                   |

Abbreviations: HSCT, hematopoietic stem cell transplantation; MA, myeloablative; RIC, reduced intensity conditioning; GVHD, graft versus host disease; CIs, calcineurin inhibitors; M, male; F, female; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML-BC, chronic myelogenous leukemia blast crisis; FL, follicular lymphoma; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; CA, cytosine arabinoside; CY, cyclophosphamide; BU, busulfan; uCB, unrelated cord blood; rPB, related peripheral blood; uBM, unrelated bone marrow; rBM, related bone marrow; CsA, cyclosporine; MTX, methotrexate; FK, tacrolimus; MMF, mycophenolate mofetil; CP, chronic phase; CR, complete remission; PSL, prednisolone; NA, not applicable. ": previously reported cases (reference 4)
have been reported to be effective for CIPS after organ transplantation.5,9,10 Those reports suggest that the effects of calcineurin inhibition on vascular tone play an important role in the development of CIPS.8 However, only one patient received diltiazem in our study, and thus, we could not assess the efficacy of calcium channel blockers for CIPS in the setting of allo-HSCT. This study confirmed that discontinuation, dose reduction, or switching to another CI is effective for management of CIPS. However, we should also consider the possibility of exacerbation of GVHD when the dose of CIs is adjusted to treat CIPS. Although our observation did not specifically address this issue, switching to another CI may be better when GVHD is not completely resolved or soon after GVHD remission is obtained.

A previous report showed that some patients with human herpes virus-6 (HHV-6) associated with encephalitis/myelitis show CIPS-like symptoms.11 In the present study, we excluded the patients who were diagnosed with HHV-6 encephalopathy at the onset of CIPS. We should use PCR to test the CSF for HHV-6 for the differential diagnosis of HHV-6 encephalopathy in patients with CIPS.

This study revealed that patients who underwent allo-HSCT from any stem cell source and who were given either CsA or FK may develop CIPS. Interestingly, one patient developed CIPS twice, at the beginning of the CIs and on day 47 after allo-HSCT. Although the pathogenesis of CIPS is poorly understood, this condition is hypothesized to result from calcineurin-induced vascular changes that disrupt bone perfusion and permeability, leading to intraosseous vasoconstriction and bone marrow edema.2,12 Our experience clearly shows the necessity of examining a larger series of patients undergoing allo-HSCT to clarify the etiology of CIPS after allo-HSCT.

Our analysis has some limitations. First, this was a retrospective study. Second, there were some differences in terms of the incidence of CIPS among the participating institutions. Because CIPS is diagnosed after the exclusion of other diseases, to consider the possibility of CIPS throughout allo-HSCT would lead to the diagnosis. However, our study showed that CIPS was a very rare complication, and there were typical patients who were diagnosed as CIPS by specialists among many participating institutions.

In summary, although CIPS is a rare complication after allo-HSCT, it is associated with severe pain. The possibility of CIPS must be considered when patients who have undergone allo-HSCT develop intolerable leg pain and/or pruritus. We should withdraw, reduce, or change to another CI in such patients. At the same time, we should also distinguish HHV-6 encephalopathy from CIPS.

Acknowledgements

We wish to thank all the staff in the participating institutions of the Kanto Study Group for Cell Therapy.

Author’s Contributions

ND, KK, MA, MO, CO, SK, MG, and SF contributed to the data collection of the patients. SO supervised the project. ND and SO wrote the manuscript.

Conflict of interest disclosure

All authors declare that there are no competing interests associated with the publication of this report.

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