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

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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, ele-

vated 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

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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. CIPS 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 transplantation^{1,5} 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 pruritus	18	223.7	—	—	—	—	no change	
2*	32/M	ALL	1	CA/CY/TBI	MA	uCB	CsA→FK	2nd relapse	leg pain pruritus	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 pruritus	15	263.8	CsA→FK	yes	—	positive	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/Flu/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 pruritus	2	18	—	—	—	positive	partially resolved	
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	Flu/CY/TBI	RIC	uCB	CsA+MTX	CR	leg pain	day-1, 47	500	—	day 47, yes	PSL	NA	partially resolved	5, 15
12	54/F	FL	1	Flu/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 lumbar pain	16	333.8	CsA→FK	yes	PSL	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	uCB	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 blastic 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)

Table 2. Clinical course of CIPS

The symptoms of CIPS	
Leg pain	9
Pruritus	2
Leg pain and pruritus	5
Median onset of CIPS (range)	Day 16 (–1~887)
Trough levels of CIs	
Above the target levels	8
Within the target levels	5
Below the target levels	2
Not applicable	1
Treatment	
Withdrawing the CIs	4
Reducing the CIs	2
Changing to the another CIs	7
Nothing	3
Outcome	
Resolved	13
Partially resolved	2
Not resolve	1
Median days of the resolution (range)	6 days (3~47)

Abbreviations: CIPS, calcineurin-inhibitor induced pain syndrome; CI, calcineurin inhibitor

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.

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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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