Fatal cardiac toxicity in two patients receiving same-day administration of cyclophosphamide and cytarabine as conditioning for hematopoietic stem cell transplantation

The reported incidence of cardiac toxicity caused by same-day administration of cytarabine and cyclophosphamide is varied. We performed autologous transplantation in 18 patients using a regimen consisting of etoposide/carboplatin/cyclophosphamide with/without cytarabine. Only the two patients who received same-day infusion of cytarabine and cyclophosphamide experienced fatal cardiac toxicity.

The dose-limiting factor of cyclophosphamide (CPA) is cardiac toxicity.[1] The maximum tolerated dose of CPA is approximately 200 mg/kg and fatal cardiac toxicity is rare at lower doses.[1] However, two groups reported that same-day administration of cytarabine (Ara-C) and CPA increased the incidence of fatal cardiac toxicity.[2,3] On the other hand, in the BEAC regimen, one of the most popular preparative schedules for autologous transplantation for lymphoma, Ara-C and CPA are administered on the same days and cardiac toxicity is not frequent.[4] In the combination of Ara-C, CPA and total body irradiation (CA/CY/TBI), a widely used regimen in Japan, Ara-C at 2 g/m^2 is infused on the same days with CPA and there have been no excessive cardiac toxicity.[5] However, two of our patients developed fatal cardiac toxicity, probably caused by same-day sequential infusion of CPA and Ara-C at lower doses.

From July 1996 to March 2000, 18 patients underwent autologous hematopoietic stem cell transplantation for non-Hodgkin's lymphoma. The conditioning regimen was a combination of etoposide, carboplatin, and CPA (E-CC) (Table 1). In addition to these, we added 500 or 1000 mg/m^2 of Ara-C twice daily for two days in six patients to evaluate the feasibility of the intensified regimen. Ara-C was added before E-CC (E-CCC1) in four patients and on the same day as CPA (E-CCC2) in two others. Informed consent was obtained from the patients before the conditioning regimen.

Both patients who received the same-day administration of CPA and Ara-C developed fatal cardiac toxicity (Table 2), whereas no cardiac toxicity was observed in the remaining patients. The two patients had diffuse large B-cell lymphoma in second remission. The first case had occasional premature ventricular contractions after the start of CPA and, on the last day of the regimen, she developed a high fever (39.5°) without any signs of infection. The second case developed transient paroxysmal supraventricular tachycardia on day –3, a fever (38.8°) without any signs of infection on day –2. Thereafter, the two cases followed a similar clinical course. We started combination antibiotics, but blood pressure decreased gradually. We considered septic shock and started a series of supportive therapies including catecholamines. Echocardiography showed impaired left ventricular function and electrocardiography revealed markedly low voltage. Neither patient responded to these therapies and both died in several hours. Autopsy was not permitted, thus, we could not establish definite causes of death. However, we considered that these patients had severe cardiac toxicity, because the levels of serum cardiac enzymes including creatinine kinase and lactate dehydrogenase were elevated and because of the changes in the echocardiographic and electrocardiographic findings. The high fever could be explained by myopericarditis due to CPA.[2]

Severe cardiac toxicity associated with CPA administration at a total dose around 120 mg/kg is uncommon. However, Peterson et al. reported dose-independent fatal cardiac toxicity caused by concurrent administration of Ara-C and relatively smaller doses of CPA.[3] They administered Ara-C continuously over 36 hours and two doses of CPA at 24-hour intervals during Ara-C administration. Trigg *et al.* reported three patients who developed fatal cardiac toxicity after receiving Ara-C at 3 g/m^2 twice daily for three days and CPA at 60 mg/kg for two doses on the second and third day of Ara-C administration. Ara-C was administered over 1 to 3 hours. On the other hand, in BEAC and CA/CY/TBI, Ara-C and CPA were administered on the same days and there were not excessive cardiac toxicity.[4,5] In these regimens, Ara-C was infused over shorter periods followed by the administration of CPA. According to these reports, we considered that the continuous infusion of Ara-C and/or its use at a very high-dose with CPA on the same days was responsible for the fatal cardiac toxicity.

However, we gave the E-CCC2 regimen, including a same-day sequential infusion of intermediate-dose Ara-C and CPA, to two

Table 1. Conditioning regimens. Etoposide (ETP) was given as a continuous infusion, whereas carboplatin (CBDCA), cyclophosphamide (CPA), and cytarabine (Ara-C) were administered over 2, 3, and 2 hours, respectively. CPA was administered 2 hours after the completion of the first Ara-C administration on each day.

E-CC		
ETP	400 mg/m^2/day	9 -8 -7 -6 -5 -4 -3 -2
CBDCA	400 mg/m^2/day	
CPA	50 mg/kg/day	
E-CCC1		
Ara-C	500-1000 mg/m^2 ×2/day	-9 -8 -7 -6 -5 -4 -3 -2
ETP	400 mg/m^2/day	
CBDCA	400 mg/m^2/day	
CPA	50 mg/kg/day	
E-CCC2		
ETP	400 mg/m^2/day	-9 -8 -7 -6 -5 -4 -3 -2
CBDCA	400 mg/m^2/day	
Ara-C	500-1000 mg/m^2×2/day	
CPA	50 mg/kg/day	

Table 2. Characteristics of the two patients.

	Case 1	Case 2
Age at transplant/sex	34/F	46/F
Anthracyclines	DOX 300 mg/m^2	DOX 424 mg/m^2
	MIT 16 mg/m^2	MIT 8 mg/m^2
FS before transplant	36%	33%
Clinical course	VPC (2 hours) tachycardia (6 hours) fever (16 hours) hypotention (24 hours) death (34 hours)	PSVT (6 hours) fever (36 hours) hypotention (50 hours) death (54 hours)

Anthracyclines:pretransplant cumulative dose of anthracyclines; DOX: doxorubicin; MIT: mitoxanthrone; FS: fractional shortening measured by echocardiography; VPC: premature ventricular contractions; PSVT:paroxysmal supraventricular tachycardia. The time in the clinical course denotes the interval from the start of cyclophosphamide to each episode.

patients and both developed fatal cardiac toxicity. When we administered the same doses of Ara-C and CPA on the different days (E-CCC1), no cardiac toxicity was observed in 4 recipients. Therefore, the same-day infusion of the two agents appeared to be responsible in this specific combination of E-CCC2. The use of etoposide or carboplatin might have reinforced the toxicity. Although we could not determine the reason why our combination enhanced cardiac toxicity, we considered it prudent to avoid such a combination when designing a new conditioning regimen.

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