At least 2 days after cortisol administration, individualized doses of docetaxel were diluted in 250 mL of 5% glucose or 0.9% saline and administered by 1-hour intravenous infusion at 9 AM to each patient. The doses of docetaxel in subsequent cycles of treatment were unchanged, and no prophylactic premedication to protect against docetaxel-related hypersensitivity reactions was administered in either of the treatment arms.

PK Study

Blood samples for PK studies were obtained from all of the patients during the initial treatment cycle. An indwelling cannula was inserted in the arm opposite that used for the drug infusion, and blood samples were collected into heparinized tubes. Blood samples were collected before the infusion; 30 minutes after the start of the infusion; at the end of the infusion; and 15, 30, and 60 minutes and 3, 5, 9, and 24 hours after the end of the infusion. All blood samples were centrifuged immediately at 4,000 rpm for 10 minutes, after which the plasma was removed and the samples were placed in polypropylene tubes, labeled, and stored at −20°C or colder until analysis.

PK parameters were estimated by the nonlinear least squares regression analysis method (WinNonlin, Version 1.5; Bellkey Science Inc, Chiba, Japan) with a weighting factor of 1 per year.[2] Individual plasma concentration-time data were fitted to two- and three-compartment PK models using a zero-order infusion input and first-order elimination. The model was chosen on the basis of Akaike's information criteria.[31] The peak plasma concentration (C_{max}) was generated directly from the experimental data. AUC was extrapolated to infinity and determined based on the best-fitted curve; this measurement was then used to calculate the absolute CL (L/h), defined as the ratio of the delivered dosage (in milligrams) and AUC.

To assess PD effect of docetaxel, the percentage decrease in ANC was calculated according to the following formula: % decrease in ANC = (pretreatment ANC − nadir ANC)/(pretreatment ANC) × 100.

Measurements

The concentration of urinary 6-β-OHF was measured by reversed phase high-performance liquid chromatography with UV absorbance detection according to previously published methods.[30,32,33]

Docetaxel concentrations in plasma were also measured by solid-phase extraction and reversed phase high-performance liquid chromatography with UV detection according to the previously published method.[30,34] The detection limit corresponded to a concentration of 10 ng/mL.

Statistical Analysis

Fisher's exact test or χ^2 test was used to compare categoric data, and Student's t test was used for continuous variables. The strength of the relationship between the estimated docetaxel CL and the observed docetaxel CL was assessed by least squares linear regression analysis. The interpatient variability of AUC for each arm was evaluated by determining the SD and was compared by F test. Biases, or the mean AUC value in each arm minus the target AUC (2.66 mg/L · h), were also compared between the arms by Student's t test.

A two-sided P value of ≤ .05 or less was considered to indicate statistical significance. All statistical analyses were performed using SAS software version 8.02 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Between October 1999 and May 2001, 59 patients were enrolled onto the study and randomly assigned to either the BSA-based arm (n = 30) or the individualized arm (n = 29). All 59 patients were assessable for PK and PD analyses. The pretreatment characteristics of the 59 patients are listed in Table 1. The baseline characteristics were well balanced between the arms except for three laboratory parameters: ALB, AAG, and ALP. These three parameters were not included in the eligibility criteria. The majority of patients (95%) had a performance status of 0 or 1. Twenty (67%) and 16 (55%) patients had been treated with platinum-based chemotherapy in the BSA-based arm and individualized arm, respectively. Only two patients in the individualized arm had liver metastasis, and most of the patients had good hepatic functions.

Individualized Dosing of Docetaxel

In the individualized arm, the total amount of 24-hour urinary 6-β-OHF after cortisol administration (total 6-β-OHF) was 9,179.6 ± 3,057.7 μg/d (mean ± SD), which was similar to the result of our previous study.[30] The estimated docetaxel CL was 21.9 ± 3.5 L/h/m^2 (mean ± SD), and individualized dose of docetaxel ranged from 37.4 to 76.4 mg/m^2 (mean, 58.1 mg/m^2; Fig 1).

PK

Docetaxel PK data were obtained from all 59 patients during the first cycle of therapy, and PK parameters are listed in Table 2. Drug levels declined rapidly after infusion and could be determined to a maximum of 25 hours. The concentration of docetaxel in plasma was fitted to a biexponential equation, which was consistent with previous reports.[30,35-38] The mean alpha and beta half-lives were 9.2 minutes and 5.0 hours in the BSA-based arm and 9.2 minutes and 7.4 hours in the individualized arm, respectively.

In the BSA-based arm, docetaxel CL was 22.6 ± 3.4 L/h/m^2 (mean ± SD), and AUC averaged 2.71 mg/L · h (range, 2.02 to 3.40 mg/L · h). In the individualized arm, docetaxel CL was 22.1 ± 3.4 L/h/m^2, and AUC averaged 2.64 mg/L · h (range, 2.15 to 3.07 mg/L · h). The least squares linear regression analysis showed that the observed docetaxel CL was well estimated in the individualized arm (r^2 = 0.821; Fig 2).

The SDs of AUC in the BSA-based arm and in the individualized arm were 0.40 and 0.22, respectively, and the ratio of SD in the individualized arm to that in the BSA-based arm was 0.538 (95% CI, 0.369 to 0.782). The biases from the target AUC in the BSA-based arm and in the individualized arm were 0.047 (95% CI, −0.104 to 0.198) and −0.019 (95% CI, −0.102 to 0.064), respectively, with no significant difference. The interpatient variability of

Table 1. Patient Characteristics

Characteristic	BSA-Based Arm No. of Patients	%	Individualized Arm No. of Patients	%	P
Enrolled	30		29		
Eligible	30	100	29	100	
Age, years					.62
Median	61		62		
Range	52-73		45-73		
Sex					
Male	25	83	19	66	.14
Female	5	17	10	34	
ECOG PS					
0	7	23	1	3	.08
1	22	73	26	90	
2	1	3	2	7	
Prior treatment					
None	4	13	4	14	.99
Surgery	11	37	9	31	.65
Radiotherapy	13	43	10	34	.49
Chemotherapy	21	70	18	62	.52
Platinum-based regimens	20	67	16	55	.37
Site of disease					
Lung	23	77	28	97	.10
Liver	0	0	2	7	.24
Pleura	8	27	12	41	.23
Bone	7	23	9	31	.71
Extrathoracic lymph nodes	0	33	10	34	.93
Laboratory parameters					
ALB, g/L					.02
Median	38		35		
Range	26-45		24-44		
AAG, g/L					.04
Median	1.00		1.25		
Range	0.28-2.15		0.64-2.54		
AST, U/L					.67
Median	21		22		
Range	10-40		7-41		
ALT, U/L					.88
Median	18		18		
Range	6-54		4-45		
ALP, U/L					.03
Median	249		324		
Range	129-540		185-986		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status, ALB, serum albumin; AAG, alpha-1-acid glycoprotein; ALP, serum alkaline phosphatase.

AUC was significantly smaller in the individualized arm than in the BSA-based arm ($P < .01$; Fig 3).

PD

In both arms, neutropenia was the predominant toxicity related to docetaxel treatment, and 28 of 30 (93%) patients in the BSA-based arm and 25 of 29 (86%) patients in the individualized arm had grade 3 or 4 neutropenia.

Table 2. Docetaxel PK Parameters

Parameters	BSA-Based Arm (n = 30)	Individualized Arm (n = 29)
C_{max}, μg/mL	0.36-2.70	0.99-2.41
$t_{1/2}$ alpha*, minutes	9.2 ± 3.3	9.2 ± 2.7
$t_{1/2}$ beta*, hours	5.0 ± 4.8	7.4 ± 11.7
CL* L/h	37.6 ± 6.3	34.8 ± 7.1
CL* L/h/m²	22.6 ± 3.4	22.1 ± 3.4
AUC		
Mean mg/L · h	2.71	2.64
Range mg/L · h	2.02-3.40	2.15-3.07
Median	2.65	2.66
SD	0.40	0.22

Abbreviations: PK, pharmacokinetic; BSA, body-surface area; CL, clearance; AUC, area under concentration-time curve; SD, standard deviation.
*Data represent mean ± SD.

Nonhematologic toxicities, such as gastrointestinal and hepatic toxicities (ie, hyperbilirubinemia, aminotransferase elevations), were mild in both arms.

PD effects shown as the percentage decrease in ANC are listed in Table 3. The percentage decrease in ANC for the BSA-based arm and individualized arm were 87.1% (range, 59.0 to 97.7%; SD, 8.7) and 87.5% (range, 78.0 to 97.2%; SD, 6.1), respectively, suggesting that the interpatient variability in the percentage decrease in ANC was slightly smaller in the individualized arm than in the BSA-based arm (Fig 4). The response rates between the two arms were similar; five of 30 (16.7%) and four of 29 (13.8%) patients

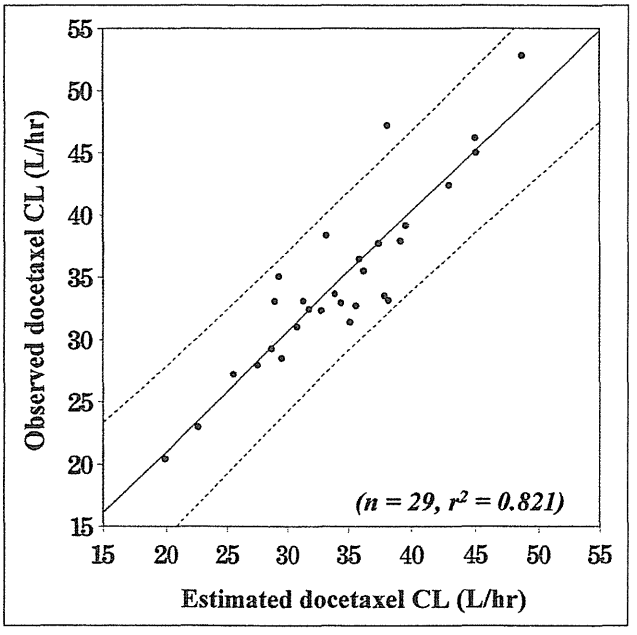

Fig 2. Correlation between the estimated and observed docetaxel clearance (CL) in the individualized arm (n = 29). (—) Linear regression line (r^2 = 0.821); (– – –) 95% CIs for individual estimates.

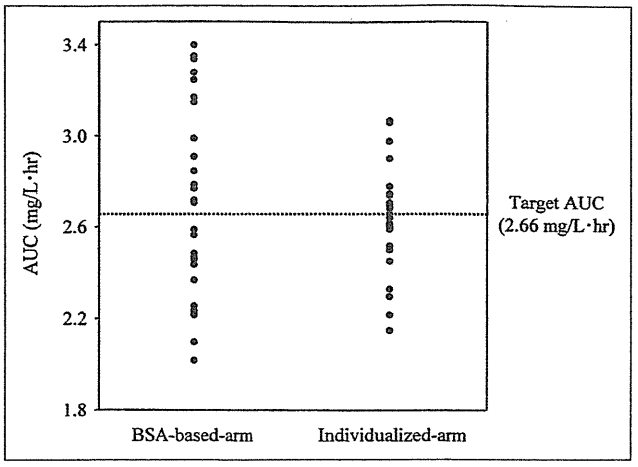

Fig 3. Comparison of area under the concentration-time curve (AUC) variability between the arms ($P < .01$; F test). BSA, body-surface area.

achieved a partial response in the BSA-based arm and individualized arm, respectively.

DISCUSSION

In oncology practice, the prescribed dose of most anticancer drugs is currently calculated from BSA of individual patients to reduce the interpatient variability of drug exposure. However, PK parameters, such as CL of many anticancer drugs, are not related to BSA.[2,39-43] Although PK parameters of docetaxel are correlated with BSA, individualized dosing based on individual metabolic capacities could further decrease the interpatient variability.[43]

CYP3A4 plays an important role in the metabolism of many drugs, including anticancer agents such as docetaxel, paclitaxel, vinorelbine, and gefitinib. This enzyme exhibits a large interpatient variability in metabolic activity, accounting for the large interpatient PK and PD variability. We have developed a novel method of estimating the interpatient variability of CYP3A4 activity by urinary metabolite of exogenous cortisol. That is, the total amount of 24-hour urinary 6-β-OHF after cortisol administration was highly correlated with docetaxel CL. We conducted a prospective randomized PK and PD study of docetaxel to evaluate whether the application of our method to individualized dosing could decrease PK and PD variability compared with BSA-based dosing.

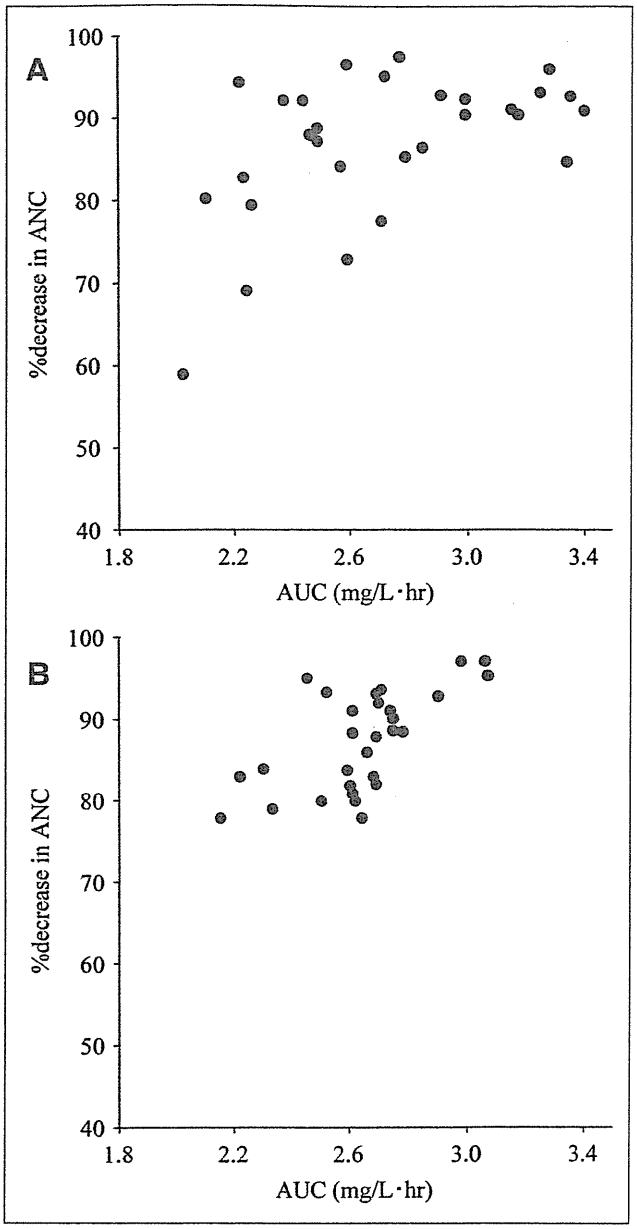

Fig 4. Correlation between area under the concentration-time curve (AUC) and percentage decrease in absolute neutrophil count (ANC) in each arm. (A) body-surface area–based arm; (B) individualized arm.

Table 3. Percentage Decrease in ANC

Parameters	BSA-Based Arm (n = 30)	Individualized Arm (n = 29)
Percentage decrease in ANC, %		
Mean	87.1	87.4
Range	59.0-97.7	78.0-97.2
Median	89.7	88.4
SD	8.7	8.1

Abbreviations: ANC, absolute neutrophil count; BSA, body-surface area; SD, standard deviation.

The study by Hirth et al[28] showed a good correlation between the result of the erythromycin breath test and docetaxel CL, and the study by Goh et al[29] showed a good correlation between the midazolam CL and docetaxel CL. In our study, we prospectively validated the correlation between docetaxel CL and our previously published method using the total amount of urinary 6-β-OHF after

cortisol administration in the individualized arm. As shown in Fig 2, the observed docetaxel CL was well estimated, and the equation for the estimation of docetaxel CL developed in our previous study was found to be reliable and reproducible. The target AUC in the individualized arm was set at 2.66 mg/L · h. This value was the mean value from our previous study, in which 29 patients were treated with 60 mg/m^2 of docetaxel. Individualized doses of docetaxel ranged from 37.4 to 76.4 mg/m^2 and were lower than expected.

The SD of AUC in the individualized arm was about 46.2% smaller than that in the BSA-based arm, a significant difference; this result seems to indicate that the application of our method to individualized dosing can reduce the interpatient PK variability. Assuming that the variability of AUC could be decreased 46.2% by individualized dosing applying our method, overtreatment could be avoided in 14.5% of BSA-dosed patients by using individualized dosing (Fig 5, area A), and undertreatment could be avoided in another 14.5% of these patients (Fig 5, area B). We considered that neutropenia could be decreased with patients in area A by individualized dosing. However, it is unknown whether the therapeutic effect of docetaxel could be improved in the patients in area B by individualized dosing because no significant positive correlation has been found between docetaxel AUC and antitumor response in patients with non–small-cell lung cancer.[43] In this study, seven of 30 (23.3%) and two of 30 (6.7%) patients in the BSA-based arm were included in area A and B, respectively (Figs 3 and 5).

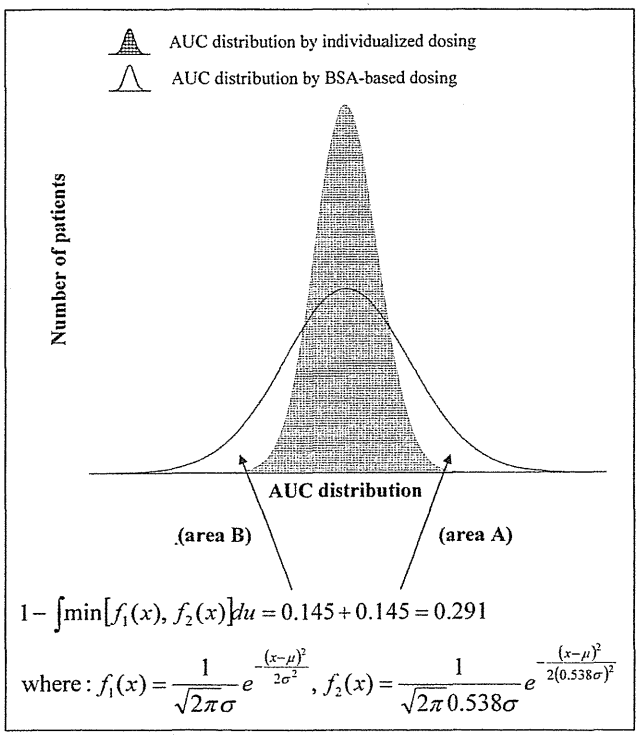

Fig 5. Simulated comparison of area under the concentration-time curve (AUC) distribution between body-surface area (BSA) –based dosing and individualized dosing when the variability of AUC is decreased 46.2% by individualized dosing applied using our method.

As shown in Figure 4, the percentage decrease in ANC was well correlated with AUC in both arms, which was similar to previous reports.[37,43] It was also indicated that the interpatient variability in the percentage decrease in ANC was slightly smaller in the individualized arm than in the BSA-based arm; however, this difference was not significant. The response rates between the two arms were similar. Although the interpatient PK variability could be decreased by individualized dosing in accordance with our method, the interpatient PD variability such as toxicity and the antitumor response could not be decreased. Several reasons could be considered.

With regard to toxicity, the pretreatment characteristics of the patients in this study were highly variable. More than half of the patients in each arm had previously received platinum-based chemotherapy, and more than 30% had received radiotherapy. The laboratory parameters (ie, ALB, AAG, and ALP) were not balanced across the arms, although they were not included in the eligibility criteria (Table 1). These variable pretreatment characteristics and unbalanced laboratory parameters may have influenced the frequency and severity of the hematologic toxicity as well as the pharmacokinetic profiles. The antitumor effect may have been influenced by the intrinsic sensitivity of tumors, the variable pretreatment characteristics, and the imbalance in laboratory parameters. Non–small-cell lung cancer is a chemotherapy-resistant tumor. The response rate for docetaxel ranges from 18% to 38%,[5] and no significant positive correlation between docetaxel AUC and antitumor response has been found. We considered it quite difficult to control the interpatient PD variability by controlling the interpatient PK variability alone. Although we did not observe any outliers in either arm, such as the two outliers with severe toxicity observed in the study by Hirth et al,[28] our method may be more useful for identifying such outliers. If we had not excluded patients with more abnormal liver function or a history of liver disease by the strict eligibility criteria, the results with the two dosing regimens may have been more different, and the interpatient PD variability, such as the percentage decrease in ANC, may have been smaller in the individualized arm than in the BSA-based arm. Furthermore, the primary end point of this study was PK variability, evaluated by the SD of AUC in both arms, and the sample size was significantly underpowered to evaluate whether the application of our method to individualized dosing could decrease PD variability compared with BSA-based dosing.

For the genotypes of CYP3A4, several genetic polymorphisms have been reported (http://www.imm.ki.se/CYPalleles/); however, a clear relationship between genetic polymorphisms and the enzyme activity of CYP3A4 has not been reported. Our phenotype-based

individualized dosing using the total amount of urinary 6-β-OHF after cortisol administration produced good results. However, this method is somewhat complicated, and a simpler method would be of great use. We analyzed the expression of CYP3A4 mRNA in the peripheral-blood mononuclear cells of the 29 patients in the individualized arm. No correlation was observed between the expression level of CYP3A4 mRNA and docetaxel CL or the total amount of urinary 6-β-OHF after cortisol administration (data not shown).

In conclusion, the individualized dosing of docetaxel using the total amount of urinary 6-β-OHF after cortisol administration is useful for decreasing the interpatient PK variability compared with the conventional BSA-based method of dosing. This method may be useful for individualized chemotherapy.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Nonmyeloablative Allogeneic Stem Cell Transplantation for Patients With Unresectable Pancreatic Cancer

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Objectives: To clarify whether nonmyeloablative allogeneic stem cell transplantation (NST) can produce the graft versus tumor (GVT) effect in patients with pancreatic cancer.

Methods: A pilot trial of NST was conducted in 5 patients with unresectable pancreatic cancer. Preparative conditioning consisted of administration of 60 mg/kg cyclophosphamide on days 6 and 7 before transplantation, followed by 25 mg fludarabine per square meter of body surface on each of the last 5 days prior to transplantation. Cyclosporine was started 4 days before transplantation. Peripheral blood stem cells from the patients' HLA-identical siblings were transfused into the patients.

Results: Complete donor T-cell chimerism in peripheral blood was obtained in 4 patients on day 15 after transplantation. NST resulted in tumor reduction in 2 patients as determined by CT, decreasing levels of tumor markers in 2 patients, pain relief in 2 patients, and a decrease in pleural fluid in 1 patient. Two patients developed acute graft versus host disease (GVHD) of grade II or III and 2 had chronic GVHD involving skin and/or liver. Administration of immunosuppressive drugs for the treatment of GVHD resulted in the elevation of tumor marker levels.

Conclusion: These findings are the first to suggest that NST induces a GVT effect on pancreatic cancer.

Key Words: nonmyeloablative allogeneic stem cell transplantation, pancreatic cancer, graft versus tumor effect, graft versus host disease, tumor regression, chimerism

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The prognosis of patients with pancreatic cancer treated with conventional therapeutic modalities is extremely poor, and thus a novel modality is being actively sought for the treatment of this disease. Allogeneic stem cell transplantation has proved to have a potent antitumor effect not only in patients with hematological malignancies[1] but also in those with solid malignancies.[2,3] In a study of nonmyeloablative allogeneic peripheral blood stem cell transplantation (NST) for solid malignancies, Childs et al[4,5] reported the successful treatment of metastatic renal cell carcinoma and clinically demonstrated the presence of the graft versus tumor effect, known as the GVT effect. However, the GVT effect in patients with pancreatic cancer is unknown. Here, we describe the results of a pilot trial of NST in 5 patients with unresectable pancreatic cancer.

PATIENTS AND METHODS

All 5 patients were diagnosed with unresectable pancreatic cancer by abdominal CT scans and angiographies, which demonstrated major vascular invasion. Four patients had metastatic disease (patients 2, 3, 4, and 5), and 1 patient had locally advanced unresectable disease (patient 1) (Table 1). Two patients had multiple liver metastases (patients 2 and 3), 2 had subclavicular lymph node metastases (patients 4 and 5), 1 had bone metastasis (patient 5), and 1 had pleural metastasis (patient 4) on CT. All 5 tumors were confirmed histologically as adenocarcinoma by needle biopsy (patients 1, 2, and 3) or operative biopsy (patients 4 and 5). The CEA and CA19-9 levels were high in all but patient 1. Patients 2, 3, 4, and 5 were administered gemcitabine as chemotherapy. Patients 2 and 4 initially responded to the therapy with stable disease, but the tumor then began to progress again. Patients 3 and 4 underwent gastrojejunostomy for duodenal obstruction by the pancreatic cancer.

All patients accepted the protocol approved by the ethics committee of Tokyo Metropolitan Komagome Hospital, Japan, and full informed consent was obtained in writing.

Preparative conditioning consisted of intravenous infusion of 60 mg cyclophosphamide per kilogram of body weight on days 6 and 7 before transplantation, followed by an intravenous infusion of 25 mg fludarabine per square meter of body surface area on each of the last 5 days prior to transplantation. Cyclosporine was started 4 days before transplantation at a dose of 3 mg/kg daily.

Peripheral blood stem cell allografts were collected from HLA-identical siblings on day 5 of G-CSF administration.

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TABLE 1. Characteristics and Results of Pancreatic Cancer Patients Undergoing NST

Patient No.	Age/ Gender	Metastases	Prior Therapy	Histology	GVHD		GVT Effect	Response			Outcome
					Acute	Chronic		Clinical Effects	CA-19-9 (U/mL) Pre-NST	CA-19-9 (U/mL) Post-NST	
1	59 F	None	None	Adenocarcinoma	None	Extensive	+	80% Tumor reduction, pain relief	2.7	2.5	Dead (d 349)
2	40 M	Liver	Gemcitabine	Adenocarcinoma	Grade III, liver, gut	Extensive	+	40% Tumor reduction, pain relief	2744	228	Dead (d 156)
3	68 M	Liver	Gemcitabine	Adenocarcinoma	None	—	None	Progressive disease	21,396	26,060	Dead (d 52)
4	61 F	Pleura, lymphnodes	Bypass operation, gemcitabine	Adenocarcinoma	None	None	+	Decreased pleural fluid	39.4	23.2	Dead (d 172)
5	63 M	Bone, lymphnodes	Bypass operation, gemcitabine	Adenocarcinoma	Grade II, gut	—	None	Progressive disease	45,825	100,289	Dead (d 87)

On day 0, allografts from HLA-identical siblings were transfused into the patients.

Donor chimerism was examined by polymerase chain reaction assay of microsatellite regions (PCR assay).

RESULTS

The chimerism determined by PCR assay on days 15 and 30 is shown in Table 2. More than 90% T-cell donor chimerism in peripheral blood was obtained on day 15 in patients 1, 2, 4, and 5, and 100% was obtained in those patients on day 30 after transplantation. Complete donor myeloid chimerism was obtained in patients 1 and 4 who survived for >100 days after transplantation. Table 1 shows the characteristics, results, and course of the pancreatic cancer patients undergoing NST. Acute GVHD occurred in patient 2 (grade III with liver and gut) and patient 5 (grade II with gut). Patients 1 and 2 had chronic extensive GVDH in the skin >120 days after transplantation.

In patients 1 and 2, CT showed tumor reduction, and both experienced pain relief, as described in the following case report. Pleural fluid due to the pancreatic cancer decreased in patient 4 on day 150. Patients 3 and 5 showed progressive disease.

The levels of tumor markers (CEA and CA19-9) decreased in patient 2 on day 30 and patient 4 on day 150. No change in tumor marker levels was observed in patients 1, 3, and 5.

Patients 2, 3, 4, and 5 died of progression of pancreatic cancer on days 156, 52, 172, and 87, respectively, while patient 1 died of a syndrome suggestive of cerebral hemorrhage on day 349.

TABLE 2. Percentage of Donor Chimerism After NST

Patient No.	Day 15		Day 30		Day 100	
	T Cell	Myeloid Cell	T Cell	Myeloid Cell	T Cell	Myeloid Cell
1	92	40	100	43	100	100
2	95	23	100	23	*	*
3	42	1	73	28	*	*
4	94	93	100	84	100	100
5	98	83	100	72	*	*

*Not examined.

CASE REPORT

Two patients who responded to NST are described.

Patient 1

A 59-year-old woman was admitted to our hospital du to increasingly severe abdominal and back pain of 1-mont duration and body weight loss. Abdominal CT revealed a het erogeneously enhanced 10 × 8.0-cm mass, with an irregula low-density area (Fig. 1A), and angiography demonstrate major vascular invasion. Fine needle aspiration biopsy of th tumor confirmed adenocarcinoma (Fig. 2). Based on thes findings, the patient was diagnosed with pancreatic tumor, an although the tumor appeared not to be a typical pancreatic du cell cancer, it definitely arose from the pancreatic tissue itse as shown on CT and angiography. We deemed the tumor u resectable due to the major vascular invasion by the cancer.

Pretransplantation conditioning consisted of 60 mg/k cyclophosphamide intravenously on days −7 and −6 and 2 mg/m^2 fludarabine intravenously from days −5 to −1. Cycl sporine was started on day −2. Her HLA-identical sister (HL A24, B52, B55, DR15, DR9) was given 10 μg/kg granulocy colony-stimulating factor (G-CSF) subcutaneously daily fo days, and a mobilized peripheral blood stem cell allograft w collected by leukapheresis on the day 5 and day 6 of G-C

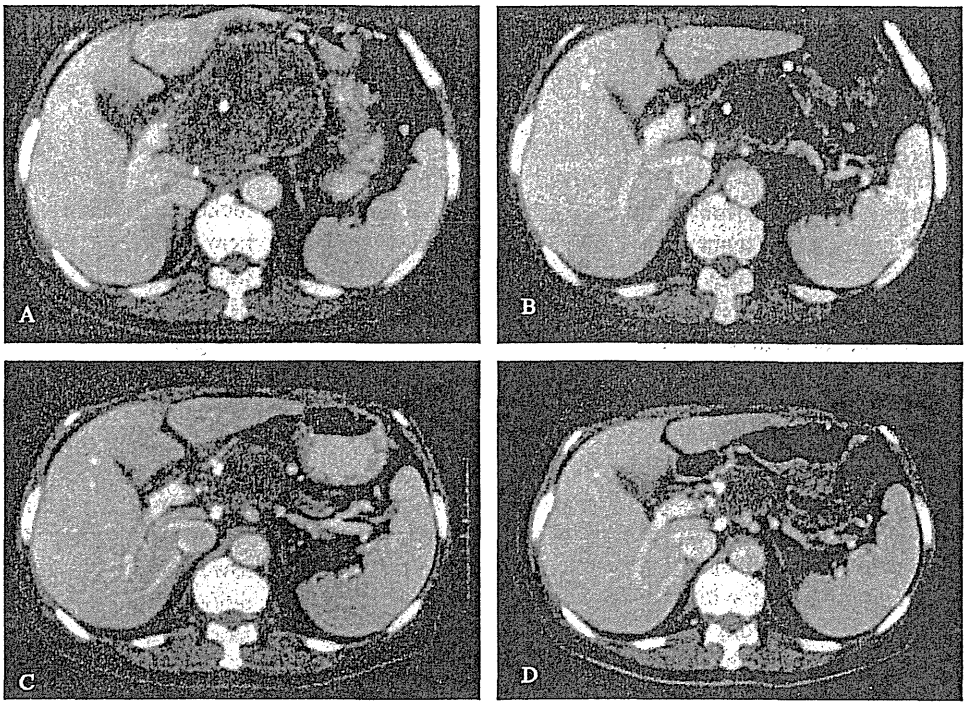

FIGURE 1. CT scan of the pancreatic tumor in patient 1. A: Heterogeneously enhanced 10.0 × 8.0-cm tumor located in the body and head of the pancreas before NST. B: The tumor was reduced 60% in size 30 days after NST; C: 75% reduced on day 100; D: 80% reduced on day 180 after NST.

administration. On day 0 and day +1, a total of 6.01×10^6 CD34+ cells/kg from her sister were transfused into the patient. Successful engraftment was achieved on day +6. Complete T-cell chimerism occurred by day +21, as determined by PCR assay.

Surprisingly, the patient's severe abdominal pain rapidly disappeared within 10 days, and consequently the morphine was stopped. In addition, the palpable upper abdominal tumor disappeared within 2 weeks. Abdominal CT revealed an impressive reduction in posttherapy pancreatic tumor diameter,

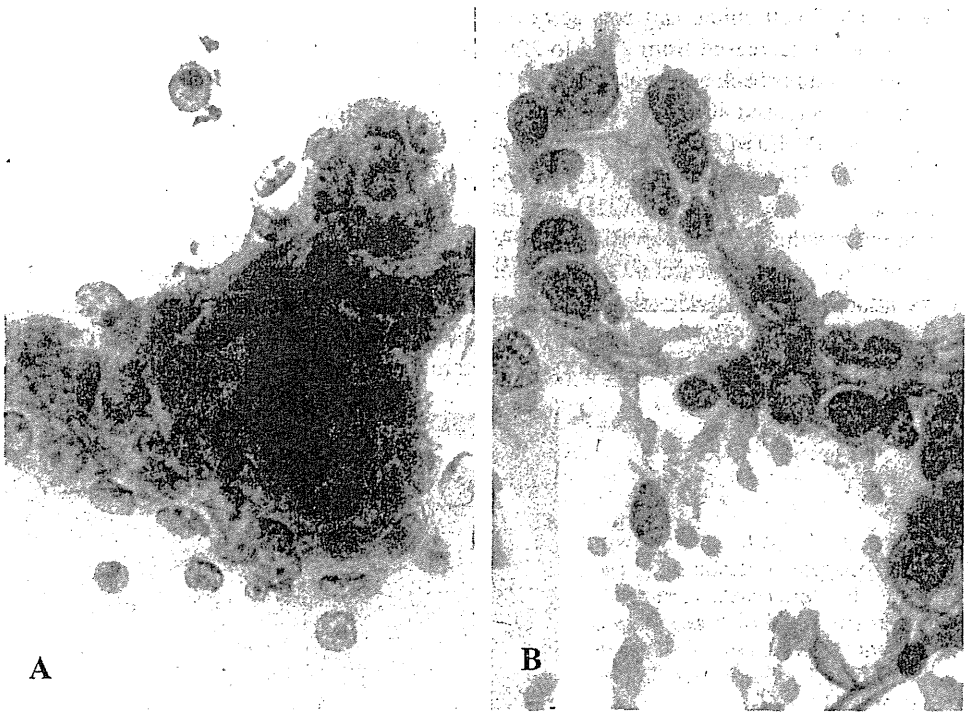

FIGURE 2. A: Epithelial malignant cells taken by needle biopsy from the pancreatic tumor in patient 1. B: The tumor cells forming adenomatous structures were considered adenocarcinoma.

which dropped from 10.0 to 6.5 cm (representative of a 60% reduction) on day +30 (Fig. 1B) to 5.0 cm (representative of a 75% reduction) on day +100 (Fig. 1C) and to 4.5 cm (representative of a 80% reduction) on day +180 (Fig. 1D).

Her posttransplantation course was uneventful, and no symptoms of acute GVHD were noted. The patient was discharged from our hospital on day 60 after NST. Cyclosporine was tapered and discontinued on day +100.

She subsequently developed extensive chronic GVHD of the skin on day +120 and was given corticosteroid ointment at the outpatient clinic. Complete myeloid chimerism was observed, almost at the same time. Cyclosporine treatment was started again on day +190 due to progression of the chronic GVHD of the liver. Although the GVHD had improved by this treatment, the pancreatic tumor had grown slightly by day +220. Thus, cyclosporine was stopped on day +230. Soon after the cyclosporine had been stopped, the tumor regressed again.

On day +348, she became unconscious and convulsed suddenly, showing symptoms suggestive of cerebral hemorrhage. She died on day +349 after NST. Unfortunately, an autopsy was unable to be performed.

Patient 2

A 40-year-old man was admitted to our hospital due to severe back pain and jaundice. MRI or CT revealed multiple liver metastases (Fig. 3A) and pancreas head cancer invading the duodenum (Fig. 3B). His CEA was 25 ng/mL and CA19-9 was 20,089 U/mL. The patient received 3 cycles of chemotherapy with gemcitabine. Transient regression was observed, but the tumor soon began progressing again.

NST was performed from his HLA-identical brother on day 0. Full T-cell chimerism was achieved on day +14. His CA19-9 level decreased from 2744 to 228 U/mL on day +30 (Fig. 4A), and his back pain was relieved. CT revealed that the tumor had decreased 40% in size on day +30 (Fig. 3C). However, acute GVHD of the liver and gut of grade III developed on day +25. The patient was given methylprednisolone and tacrolimus to treat the acute GVHD. The immunosuppressive treatment resulted in the elevation of CA19-9 from 228 to 20,509 U/mL. Steroid treatment was stopped on day +105, and consequently the CA19-9 level again decreased from 20,509 to 10,394 U/mL (Fig. 4B), suggesting the presence of the GVT effect. However, the pancreatic cancer and liver metastasis began to progress from day +130, and the patient died of progressive disease on day +156.

DISCUSSION

Allogeneic stem cell transplantation in the treatment of leukemia has proved to be a potent immune-mediated antileukemia effect [graft versus leukemia (GVL) effect].[1] Stem cells transplanted to the recipient from an HLA-identical donor proliferate and differentiate into T cells in the patient, and these recognize the patient's tissues as "not-self" and eliminate the "not-self" cells. These immunologic reactions produce a graft versus leukemia effect, which brings about leukemia regression and also sometimes produces GVHD. However, whether such an immune-mediated effect was induced in patients with solid tumors has been unclear. Eibl et al[2] and Ueno et al[3] reported a GVT effect in breast cancer patients treated with marrow ablative allogeneic transplantation. In 1999, Childs et al[4,5] reported that nonmyeloablative allogeneic stem cell transplantation induced sustained regression of metastatic renal cell carcinoma in patients who had no response to conventional treatment. However, the existence of the GVT effect of allogeneic stem cell transplantation in patients with pancreatic cancer is as yet unknown.

Myeloablation and immunosuppression have been considered to be the 2 major requirements of preparative conditioning for successful engraftment of stem cells into bone marrow. However, recent studies have established that immunosuppression is the more important of the 2 and that myeloablation, including strong anticancer agents or total body irradiation, is unnecessary for engraftment.[6,7] Thus, nonmyeloablative stem cell transplantation is developing into a method free from severe adverse effects for transplantation.

We performed a pilot trial of nonmyeloablative allogeneic stem cell transplantation in patients with unresectable pancreatic cancer refractory to conventional treatment options.

In our trial, patient 1 showed remarkable regression of the tumor and pain relief. There have been no reports that the small amount of chemotherapeutic agents used in our conditioning regimen (60 mg/kg cyclophosphamide × 2, 25 mg/m^2 fludarabine × 5) are efficacious for pancreatic tumor. Moreover, the tumor consistently decreased in size until day +190,

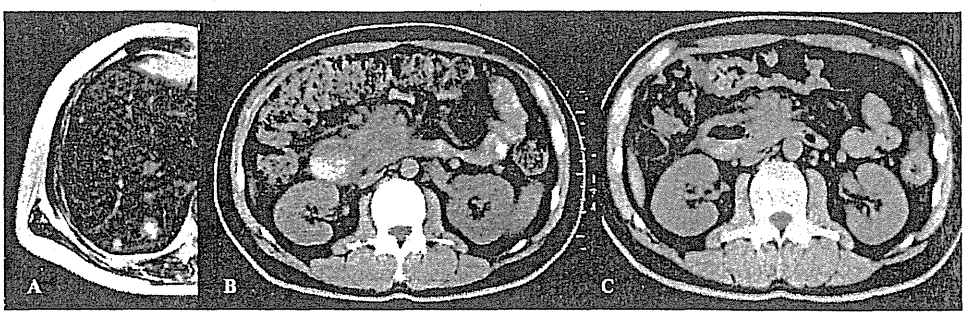

FIGURE 3. A: MRI of the liver shows multiple metastases in patient 2. B: Pancreatic tumor located in the head of the pancreas in patient 2 before NST. C: The tumor decreased 40% in size on day 30 after NST.

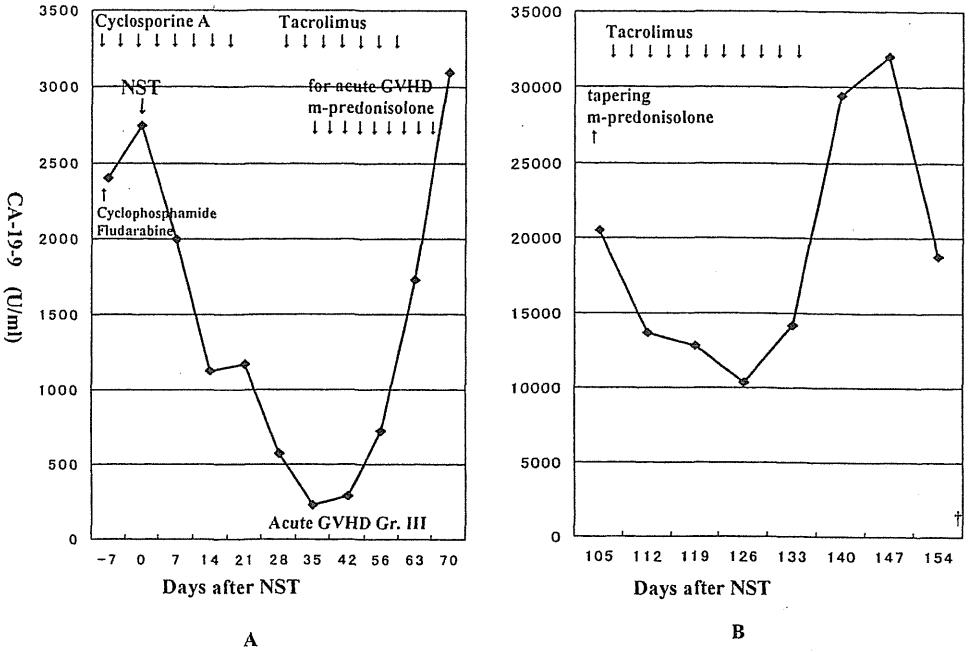

FIGURE 4. CA19-9 levels relative to posttransplantation days and interventions in patient 2. A: NST resulted in decreased levels of CA19-9. B: After tapering methylprednisolone, elevated CA19-9 level decreased.

when cyclosporine treatment was started again due to progression of the chronic GVHD. Subsequently, the pancreatic tumor grew slightly after administration of the cyclosporine, and soon after the drug was stopped, the tumor regressed again. Thus, the continuous regression of the tumor following NST and the changes in tumor size produced by immunosuppressive cyclosporine suggest that the GVT effect was produced by NST in this patient with unresectable pancreatic cancer. Unfortunately, the patient died, probably of a cerebral hemorrhage, but it was not possible to perform an autopsy. We, however, presume that the cerebral hemorrhage was caused by the chronic GVHD. Nonetheless, this may be the first case of the GVT effect on pancreatic cancer.

Patient 2 experienced pain relief, tumor reduction, and changes in the levels of tumor markers. These findings also suggest the presence of the GVT effect on pancreatic cancer.

Patient 4 survived under stable disease conditions until day +250, exhibiting decreased cancerous pleural fluid due to pancreatic cancer and a decreased level of CA19-9. We also believe this to represent the GVT effect.

T-cell chimerism persisted in all patients from the beginning of tumor regression. Notably, the GVT effect occurred only after T-cell chimerism had become complete.

Two of the 5 patients undergoing NST developed acute grade II or III GVHD. GVHD did not always occur in all patients who developed the GVT effect in our trial; patients 1 and 4 did not have acute GVHD when their disease regressed. The antigens of the donor cells that mediated the GVT effects and acute GVHD are the focus of future investigation.

In conclusion, the results of our pilot clinical trial suggest that NST induces the GVT effect in pancreatic cancer, just as in renal cell carcinoma, as demonstrated by Childs.[4,5] NST might represent a new treatment modality for intractable pancreatic cancer. However, we should emphasize that our study was very small and allogeneic stem cell transplantation can cause the substantial and sometimes fatal adverse effects of GVHD. Moreover, since GVT effects are usually delayed after NST, careful selection of pancreatic cancer patients for similar trials is warranted because death from early disease progression has previously been shown to limit this approach in metastatic renal cell carcinoma patients.[5]

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A Multicenter and Open Label Clinical Trial of Zoledronic Acid 4 mg in Patients with Hypercalcemia of Malignancy

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Background: Hypercalcemia of malignancy is a serious complication of cancer. The objective of this study was to investigate the efficacy and safety of zoledronic acid, a new-generation bisphosphonate and the most potent inhibitor of bone resorption identified to date, for hypercalcemia of malignancy in Japanese patients.

Methods: Patients with hypercalcemia of malignancy, defined as an albumin-corrected serum calcium level ≥12.0 mg/dl, were treated with a single dose of zoledronic acid, 4 mg, by 15 min infusion. Clinical end-points included the proportion of patients with complete response, which was defined as a decrease of corrected serum calcium ≤10.8 mg/dl by day 10, and time to relapse, which is defined as the duration in days between the date of infusion and last available corrected serum calcium <11.6 mg/dl.

Results: Twenty-seven patients were enrolled in this study and 25 patients were evaluable for the efficacy of zoledronic acid. The mean corrected serum calcium level decreased from 14.5 to 9.6 mg/dl by day 10. The complete response rate was 84%. The median time to relapse was 23 days, ranging from 0 to 56 days. The most frequently observed adverse event was fever (≤38°C). Electrolyte abnormalities suspected to be drug related including grade 3 or 4 hypocalcemia, hypophosphatemia and hypokalemia were observed in 11 patients; however, all patients were asymptomatic. No serious adverse events associated with renal toxicity were reported.

Conclusions: Zoledronic acid is well tolerated and is effective for hypercalcemia of malignancy in Japanese patients.

Key words: bisphosphonate – hypercalcemia – zoledronic acid

INTRODUCTION

Hypercalcemia of malignancy (HCM) is among the most common and most serious complications of malignancy in the late stage. It occurs in 5–10% of all cancer patients at some point during the course of their disease, frequently in patients with cancer of the lung, breast, kidney, or head and neck, and adult T-cell leukemia. The early symptoms of HCM are mild and can be difficult to distinguish from symptoms of the underlying disease or the side effects of cancer therapy. If left untreated, it can progress rapidly and may become life-threatening. Patients who develop HCM generally have a short life expectancy, ranging from weeks to months (1). Treatment of HCM is important considering its life-threatening nature and symptoms such as anorexia, nausea, polyuria, confusion and coma.

Bisphosphonates are potent inhibitors of bone resorption and are the most effective therapy for HCM. Bisphosphonate compounds can be divided into two distinct pharmacological classes with different mechanisms of action depending on

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whether they contain a nitrogen atom in their side chains (2). Non-nitrogen-containing bisphosphonates, which are first-generation bisphosphonates, including etidronate and clodronate, are metabolized intracellularly to cytotoxic, non-hydrolyzable analogs of ATP that may inhibit ATP-dependent intracellular enzymes in osteoclasts (2). Nitrogen-containing bisphosphonates, which are second- or third-generation bisphosphonates including pamidronate, alendronate and ibandronate, inhibit protein prenylation, which leads to loss of membrane localization of small G proteins such as Ras, Rho and Rac. Consequently, osteoclasts may undergo apoptosis (2). They are more potent than the first-generation bisphosphonates and have been used for the treatment of HCM.

Zoledronic acid (ZOMETA; Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a newer nitrogen-containing bisphosphonate that has been shown in preclinical studies to be more potent than currently available bisphosphonates including pamidronate. Zoledronic acid was 850-fold more effective than pamidronate in inhibiting the induction of hypercalcemia in rats, and 100-fold more potent than pamidronate in inhibiting calcium release in an *in vitro* calvaria assay (3).

Zoledronic acid at doses of 2, 4 and 8 mg/body was well tolerated in a phase 1 study for Japanese cancer patients with bone metastases (4). This phase 1 study also demonstrated that 4–8 mg of zoledronic acid was more effective with respect to suppressing markers of bone resorption than the lower dose, suggesting that these dose levels might be more potent to inhibit osteoclast activity.

For treating HCM, randomized, controlled clinical studies were conducted in the USA, Canada, Australia and European countries to compare the efficacy and safety of zoledronic acid and pamidronate (5). The complete response rate and time to relapse among patients treated with zoledronic acid 4 or 8 mg were superior to those among patients treated with pamidronate 90 mg, while maintaining a similar safety profile. Zoledronic acid at a single dose of 4 mg was nearly as effective as 8 mg, and the differences between the two doses were not statistically significant. Therefore, zoledronic acid at a single dose of 4 mg was recommended and has been approved for treatment of HCM in many countries since 2000.

A multicenter study was conducted to investigate the efficacy and safety of zoledronic acid in Japanese patients with HCM.

PATIENTS AND METHODS

This clinical study was conducted at seven hospitals in Japan between July 2001 and May 2002. The institutional review boards of the study hospitals approved the protocol. Written informed consent was obtained from each patient before participation in the study; however, if the patient was in a severe diminished state of consciousness due to HCM, written consent could be obtained from a relative such as the patient's spouse. In that case, the patient's informed consent to continue in the study was obtained after his/her level of consciousness was improved.

PATIENTS

Patients aged 20 years and older with histological or cytological confirmation of cancer and hypercalcemia, defined as an albumin-corrected serum calcium (CSC) $\geq$12.0 mg/dl, were eligible. The CSC was calculated by the following formula: CSC (mg/dl) = patient's measured serum calcium (mg/dl) + 0.8 $\times$ [mid-range serum albumin of each institutional laboratory standard (g/dl) – patient's measured albumin (g/dl)]. Patients who had a history of allergic reaction to bisphosphonates or who had been treated with bisphosphonates for HCM within 3 months of study entry were excluded, as were patients who exhibited serum creatinine >4.5 mg/dl or who were treated with calcitonin within 72 h of study entry. Patients who were treated with newly initiated antineoplastic cytotoxic chemotherapy or hormonal therapy 6 days before or 10 days after the initial administration of this study drug, or with any investigational drugs within 1 month of study entry were also excluded. Additional exclusion criteria were for patients who were severely dehydrated, could not tolerate intravenous hydration, or suffered from hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes.

TREATMENT

Patients were treated with a single dose of 4 mg of zoledronic acid via a 15 min intravenous infusion followed by hydration with 500 ml of saline over 2 h. Then patients were followed-up for 56 days or until relapse defined as CSC $\geq$11.6 mg/dl. Patients who were refractory to the initial therapy or who relapsed within 56 days after the initial treatment could be re-treated with a single dose of 4 mg of zoledronic acid and followed-up for 28 days or until relapse.

ASSESSMENT OF SAFETY AND EFFICACY

Efficacy was assessed by the CSC level, which was measured on days 4, 7, 10, 14, 17, 21, 24 and 28, and weekly thereafter up to day 56. Efficacy was also assessed by improvement of the symptoms of HCM on days 4, 7, 10 and 56. The improvement of symptoms, i.e. depressed level of consciousness, anorexia, nausea, vomiting, fatigue and mouth dryness, was defined as an improvement in the grade as evaluated according to the National Cancer Institute's Common Toxicities Criteria version 2 in comparison with those before treatment.

Safety was evaluated by clinical findings, adverse events, vital signs, routine blood chemistries, hematological values and urinalysis. The severity of adverse events was graded according to the National Cancer Institute's Common Toxicities Criteria version 2.

STATISTICAL METHODS

The determination of the sample size was based on the proportion of patients achieving a complete response (CR), which

was defined as a decrease of CSC below 10.8 mg/dl by day 10, using Fleming's single-stage procedure. The CR rate representing a level of activity of definitive interest was considered to be 85% as expected from the efficacy of zoledronic acid 4 mg reported by Major et al. (5). A minimal threshold response rate was considered to be 60%, based on the CR rate of pamidronate 45 mg in three previous Japanese clinical trials for treatment of HCM (in-house data of Novartis). Thus, the required sample size was calculated to be 25, based on a hypothesis of an anticipated efficacy rate of 85%, threshold efficacy rate of 60%, alpha = 0.05 (two-sided) and beta = 0.2.

Primary analysis was based on the CR rate by day 10. The proportions of patients who achieved a CR by day 4 and/or day 7 were also evaluated. The change from baseline in CSC was also assessed at days 4, 7 and 10. For patients with missing CSC values, the last CSC observation available was carried forward. The time to relapse was defined as the number of days from the date of study drug infusion to the date of the last CSC <11.6 mg/dl. All patients who did not achieve a CR had their time to relapse set to zero and were not censored. Patients who died after a CR was achieved but before documentation of relapse were assumed to have relapsed on the day the last CSC was obtained. All other complete responders who discontinued or completed the study without documented relapse were censored on the last day on which CSC was obtained. Duration of CR was calculated using rules similar to time to relapse, except that the duration was based on the day of onset of the CR rather than the start date of the infusion. Duration of CR was calculated only for the subset of patients who had a CR. Time to relapse and duration of CR were estimated by the Kaplan–Meier method.

The impact of the baseline CSC ($\geq$13.6 or <13.6 mg/dl), with or without bone metastases, cancer type (breast/myeloma or other) and the parathyroid hormone-related protein (PTHrP, $\leq$2.0 or >2.0 pmol/l) on whether the patient achieved a CR was analyzed by Fisher's exact test. Log rank test was also used to analyze the impact of the above-mentioned demographic factors on the time to relapse.

RESULTS

Characteristics of the Patients

Twenty-seven patients were enrolled in the study and 26 patients were treated with zoledronic acid. One patient withdrew his consent before study drug infusion. Table 1 lists the characteristics of the treated patients. Half of the patients (13 out of 26) had a poor performance status of 3 or 4, and 24 patients had symptoms associated with HCM. Twenty-one out of 26 patients had an elevated (>2 pmol/l) PTHrP at baseline. As one patient died due to progressive disease without any CSC values after administration of the study drug, this subject could not be included in the efficacy analysis.

Table 1. Patient characteristics

No. of patients	26 (100%)
Gender	
Male	12 (46%)
Female	14 (54%)
Age (years)	
Mean ± SD	59.0 ± 9.8
Median	58.5
Range	37–75
Weight (kg)	
Mean ± SD	53.9 ± 12.2
Median	50.2
Range	37.6–85.7
ECOG PS	
0	0
1	9 (35%)
2	4 (15%)
3	8 (31%)
4	5 (19%)
Primary cancer site	
Lung	5 (19%)
Breast	8 (31%)
Multiple myeloma	3 (12%)
Head and neck	5 (19%)
Other	5 (15%)
Bone metastases (*n*, %)	
No	11 (42%)
Yes	15 (58%)
Symptom of hypercalcemia (*n*, %)	
No	2 (8%)
Yes	24 (92%)
PTHrP (pmol/l)	
Mean ± SD	10.2 ± 11.8
Median	4.4
Range	0.6–48.8
$\leq$2.0 pmol/l	5 (19%)
>2.0 pmol/l	21 (81%)
Baseline serum creatinine (mg/dl)	
Mean ± SD	0.9 ± 0.3
Median	0.9
Range	0.5–1.6
Baseline CSC (mg/dl)	
Mean ± SD	14.4 ± 1.8
Median	14.1
Range	12.4–18.4

ECOG PS, Eastern Cooperative Oncology Group performance status; PTHrP, parathyroid hormone-related protein; CSC, corrected serum calcium.

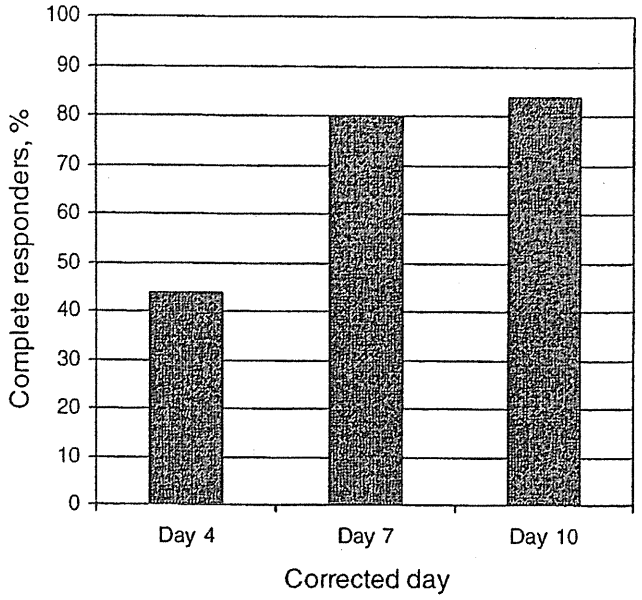

Figure 1. Percentage of patients achieving a CR (CSC ≤10.8 mg/dl). Days 4, 7 and 10 have a time window of days 2–5, 6–8 and 9–11, respectively.

CR Rate and Time to Relapse

The primary efficacy variable, CR rate by day 10, was 84% [95% confidence interval (CI), 63.9–95.5%] (Fig. 1). Approximately half of patients treated with zoledronic acid reached CR by day 4.

The CSC level decreased in all patients after zoledronic acid treatment (Fig. 2). Finally, four out of 25 patients did not achieve CR; however, their CSC levels decreased to ~11 mg/dl including a patient whose CSC was lowered by >5 mg/dl from baseline. The mean CSC level decreased from 14.5 mg/dl before treatment to 9.6 mg/dl on day 10. The mean (±SD) change in CSC level from day 1 (baseline) to days 4, 7 and 10 was −3.30 (±1.63), −4.67 (±1.84) and −4.89 mg/dl (±1.97), respectively.

The median time to relapse was 23 days, ranging from 0 (not CR) to 56 days (95% CI, 16–29 days). In patients who achieved CR, the median duration of CR was 22 days (95% CI, 11 to >56 days).

Efficacy According to Selected Subgroup

The CR rate and time to relapse were compared between patients with a baseline CSC of ≥13.6 or <13.6 mg/dl, with or without bone metastases, with breast/myeloma or other cancer types and with PTHrP ≤2.0 or >2.0 pmol/l (Table 2). Although there were only five patients with the lower value, there was a significant difference in time to relapse according to the baseline PTHrP ($P = 0.004$).

Clinical Symptoms Associated with HCM

Clinical symptoms associated with HCM, including depressed level of consciousness, anorexia, nausea, vomiting, fatigue

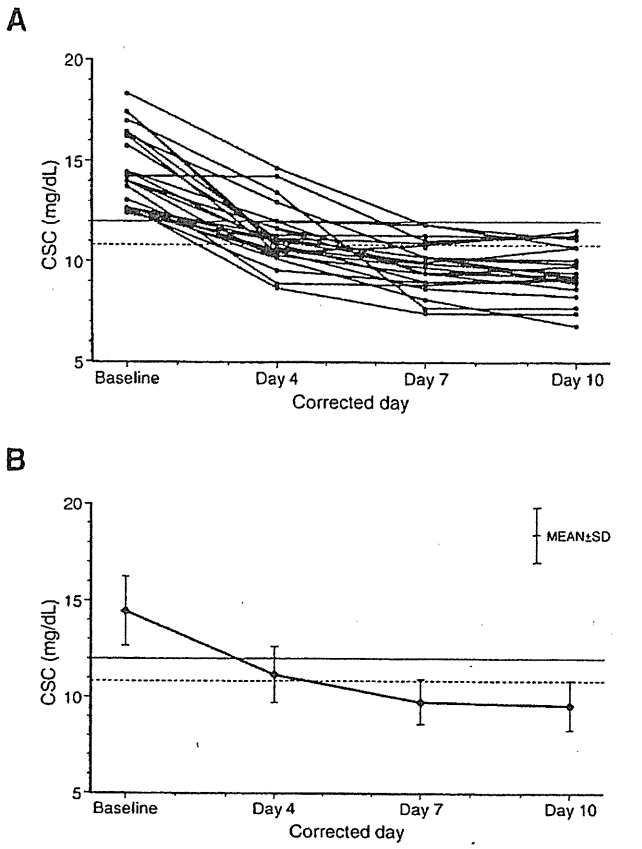

Figure 2. Course of the CSC in individual patients (A) and mean CSC (B) at baseline and days 4, 7 and 10 after treatment with zoledronic acid. Days 4, 7 and 10 have a time window of days 2–5, 6–8 and 9–11, respectively.

Table 2. CR rate and time to relapse of initial treatment for selected subgroup

	CR patients/ all patients	Median time to relapse in days (range)
All	21/25 (84%)	23 (0–56)
Baseline CSC		
≥13.6 mg/dl	13/16 (81%)	18 (0–56)
<13.6 mg/dl	8/9 (89%)	29 (0–56)
	$P = 1.00$	$P = 0.56$
Bone metastasis		
Present	14/15 (93%)	23 (0–56)
Absent	7/10 (70%)	22.5 (0–56)
	$P = 0.27$	$P = 0.90$
Cancer type		
Breast/myeloma	9/11 (82%)	28 (0–56)
Other	12/14 (86%)	17 (0–52)
	$P = 1.00$	$P = 0.33$
PTHrP level		
≤2.0 pmol/l	5/5 (100%)	>56 (10–56)
>2.0 pmol/l	16/20 (80%)	17 (0–52)
	$P = 0.55$	$P = 0.004$

Statistical data of CR rate and time to relapse were analyzed by Fisher's exact test and log rank test, respectively.

Table 3. Adverse events

	Grade 0, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Total (*n* = 26), *n* (%)
Fever	2 (8)	10 (39)	1 (4)	1 (4)	0	14 (54)
Hypophosphatemia (decreased blood phosphate)	0	0	0	8 (31)	2 (8)	10 (38)
Hypokalemia (decreased blood potassium)	0	0	0	4 (15)	0	4 (15)
Increased urinary β_2 microglobulin	0	4 (15)	0	0	0	4 (15)
Hematuria (occult blood in urine)	0	2 (8)	0	0	0	2 (8)
Increased AST	0	0	2 (8)	0	0	2 (8)
Increased ALT	0	0	1 (4)	1 (4)	0	2 (8)
Increased γ-GTP	0	0	0	1 (4)	0	1 (4)
Increased serum creatinine	0	0	1 (4)	0	0	1 (4)
Anemia (decreased hemoglobin)	0	0	0	0	1 (4)	1 (4)
Hypocalcemia (decreased blood calcium)	0	0	0	0	1 (4)	1 (4)
Nausea	0	1 (4)	0	0	0	1 (4)
Vomiting	0	0	1 (4)	0	0	1 (4)
Blister	0	1 (4)	0	0	0	1 (4)
Pulmonary edema	0	0	0	0	1 (4)	1 (4)
Disturbance of consciousness	0	0	1 (4)	0	0	1 (4)
Hypoesthesia	0	1 (4)	0	0	0	1 (4)
Headache	0	1 (4)	0	0	0	1 (4)
Polyuria	0	0	1 (4)	0	0	1 (4)
Eczema	0	1 (4)	0	0	0	1 (4)

Adverse events where a causal relationship with the study drug could not be ruled out are shown.

and mouth dryness, improved in accordance with decreasing CSC level. The proportions of patients in whom each symptom was improved at day 10 were 88.9% (eight out of nine), 68.2% (15 out of 22), 64.7% (11 out of 17), 75.0% (three out of four), 66.7% (14 out of 21) and 64.7% (11 out of 17), respectively.

Re-treatment with Zoledronic Acid

Seven patients who relapsed within 56 days after having achieved a CR and one patient who did not achieve a CR to the initial treatment were re-treated with a 4 mg dose. The mean baseline CSC before the re-treatment was 12.8 mg/dl (range, 11.7–15.2), while it was 15.3 mg/dl (range, 12.4–18.4) before the initial treatment in these eight patients. After re-treatment with a 4 mg dose, four patients achieved a CR by day 10, including the patient who did not achieve a CR to the initial treatment. These patients were not documented as relapsed until death or the end of study except for the patient with non-CR to the initial treatment, who had increased CSC at day 8 after re-treatment.

Safety

Safety was evaluated in all 26 treated patients. Zoledronic acid 4 mg was well tolerated. Adverse events with which a causal relationship with the study drug could not be ruled out are listed in Table 3. The most frequently observed adverse event was fever (≤38°C). Electrolyte abnormalities suspected to be drug related including grade 3 or 4 hypocalcemia, hypophosphatemia and hypokalemia were observed in 11 patients; however, all patients were asymptomatic. Grade 4 pulmonary edema, as a serious adverse event, was observed 2 days after the first administration of zoledronic acid in a patient with lung cancer who had lymphangitis, pleural effusion and pericardial effusion before the therapy. The pulmonary edema might have been related to the primary cancer and/or hydration, but a causal relationship to infusion of zoledronic acid could not be ruled out completely. No serious adverse events associated with renal toxicity were reported.

DISCUSSION

This study demonstrated the calcium-lowering effect and safety of zoledronic acid in the treatment of HCM in Japanese patients. The CSC level decreased in all patients after zoledronic acid treatment, and 84% of the patients became normocalcemic by day 10. The CR rate of our study was similar to that of large randomized studies of zoledronic acid in patients with HCM reported by Major et al. (84 versus 88%) (5) on the same eligibility and response criteria.

In the above studies by Major et al., subgroup analysis indicated zoledronic acid 4 mg to be equally effective with regard to the CR rate independent of a patient's demographics, such as baseline CSC, PTHrP, presence of bone metastases and cancer type. Although the subgroup analysis of CR rate in this Japanese trial showed some variation, our observation seemed to be comparable considering that the number of patients in each subgroup was small.

Our study demonstrated shorter time to relapse than reported by Major et al. (median, 23 versus 30 days). Duration of CR demonstrated the same tendency (median, 22 versus 32 days). The reason for the difference in duration of response might be due to a difference in patient demographics between these studies. Although the background of the patients including tumor type, sex, age and CSC at baseline were similar, the frequency of elevated (>2 pmol/l) PTHrP in our study was higher than that in the studies by Major et al. (80 versus 23%). Time to relapse was shorter in patients with high PTHrP levels than in patients with low levels. Considering PTHrP is accompanied by enhancement of kidney re-absorption of calcium and activation of osteoclasts, the higher proportion of patients with high PTHrP levels in our study may explain the shorter time to relapse and CR duration compared with the study by Major et al.

It is also noteworthy that the calcium-lowering effect of zoledronic acid 4 mg was retained even if patients had an elevated PTHrP level; nevertheless, it was reported that bisphosphonates such as pamidronate and ibandronate were less effective in reducing the serum calcium level in patients who had a higher PTHrP level (6–10). This important property is presumably due to the more potent pharmacological activity of zoledronic acid.

Currently, pamidronate, incadronate and alendronate are available for treatment of HCM in Japan. Although incadronate and alendronate have not been compared directly in clinical studies, available data indicate that zoledronic acid is more effective. For instance, a single recommended dose of incadronate 10 mg yielded normalization of calcium in 58% of patients with mean initial CSC of 14.2 mg/dl in a Japanese dose response study with HCM (11); and single doses of 5, 10 or 15 mg of alendronate resulted in an overall normalization rate of 74% and a time to relapse of 15 days with an initial CSC of 11.5 mg/dl (12).

The safety profile of zoledronic acid was similar to that of other bisphosphonates. The most frequent adverse events occurring in this study, i.e. transient fever and abnormality of electrolytes, were typical of bisphosphonates as a class. The incidence of these adverse events was generally within the expected range from the previous pamidronate trials (13). Although urinary laboratory abnormalities, such as urinary β_2 microglobulin and hematuria, were reported, no clinically relevant symptoms were observed. No patient developed grade 3 or 4 serum creatinine changes. Bisphosphonates, however, have been associated with impairment of renal function. The risk of renal dysfunction with zoledronic acid was also reported in cancer indications necessitating repeated dosing, but was similar to pamidronate (14). Monitoring of renal function therefore should be routine practice, particularly when patients have underlying or concomitant illnesses associated with renal function impairment. HCM constitutes a potentially life-threatening condition, thus serum creatinine levels of up to 4.5 mg/dl were accepted as baseline level at study entry.

In conclusion, zoledronic acid at a dose of 4 mg is well tolerated, and it effectively induces durable reduction in the corrected serum calcium level and improves the symptoms of HCM in Japanese patients.

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Original Paper

Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

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ABSTRACT

Background/Aims: Many gallbladder carcinomas are detected at an advanced stage, and the outcome of the patients with these tumors is dismal despite aggressive tumor removal. We have treated advanced gallbladder carcinoma with chemoradiotherapy combined with hyperthermia. In this study, clinical effectiveness of thermo-chemo-radiotherapy (TCRT) for advanced gallbladder carcinoma was evaluated in comparison with other treatment modalities.

Methodology: Two hundred and seventy patients with advanced gallbladder carcinoma (Stage VI) were treated. According to treatments received, they were divided into five groups as follows: group 1; 30 patients treated with TCRT, group 2; 19 patients underwent R0-resection, group 3; 39 patients underwent R1,2-resection, group 4; 57 patients treated with chemo- and/or radiotherapy, group 5; 125 patients with only supportive therapy.

Results: In group 1, there were 19 objective responses (5 complete response and 14 partial response) in respect to tumor regression, and 15 (6 complete response and 9 partial response) of 20 patients with obstructed bile duct showed resolution of the bile duct. The survival rate was best in group 2. A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5, and there was no significant difference between group 1 and 3 ($p<0.01$).

Conclusions: TCRT can produce significant response and improvement of survival time in patients with advanced gallbladder carcinoma, and may be a favorable alternative to aggressive surgical approaches.

KEY WORDS:
Hyperthermia; Gallbladder carcinoma; Thermo-chemo-radiotherapy

ABBREVIATIONS:
Thermo-chemo-radiotherapy (TCRT); American Joint Committee on Cancer (AJCC); Cis-platinum (CDDP); 5-Fluorouracil (5-Fu); Methotolexate (MTX); Intraoperative Radiation Therapy (IORT); External Beam Radiation Therapy (EBRT); Complete Regression (CR); Partial Regression (PR); No Change (NC); National Cancer Institute Common Toxicity Criteria (NCI-CTC); Percutaneous Transhepatic Cholangiodrainage (PTCD); Radiotherapy (RT)

INTRODUCTION

Despite recent tremendous advances in diagnostic technologies, many gallbladder carcinomas are detected at an advanced stage when the tumor has already invaded adjacent organs or major vessels. Then, various kinds of combined resection are required to obtain higher resectability and curability. Recently, aggressive surgical approaches, including resection of the liver, pancreas, and major vessels have been challenged, but their results have been discouraging and long-term survivors are the exceptions (1,2).

Hyperthermia has been used in combination with radiation therapy and/or chemotherapy and is considered to be effective for certain type of tumors (3). Since 1985, we have performed triodality treatment with hyperthermia, chemotherapy and radiotherapy (thermo-chemo-radiotherapy: TCRT) for advanced gallbladder carcinoma (4). The aim of this report is to assess the value of TCRT for advanced gallbladder carcinoma in comparison with other treatment modalities.

METHODOLOGY

Patients

We experienced 357 patients with gallbladder carcinoma in Tokyo Metropolitan Komagome Hospital between 1976 and 2001. According to the pTNM system proposed by the American Joint Committee on Cancer (AJCC) (5), 270 cases were advanced gallbladder carcinomas histologically or roentographically confirmed as Stage IV tumors. Stage IV gallbladder carcinoma is defined as tumor extending more than 2cm into liver and/or into two or more adjacent organs (T4), or with metastasis in peripancreatic, periduodenal, periportal, celiac and/or superior mesenteric lymph nodes (N2), or with distant metastasis (M1). Roentographic diagnosis was based on the results of more than three imaging diagnostic techniques: computed tomography, ultrasonography, magnetic resonance cholangiopancreatography, angiography, percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography. Thus, 270 patients were analyzed in this study.

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