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Original Article

Cancer of Unknown Primary Site: A Review of 28 Cases and the Efficacy of Cisplatin/Docetaxel Therapy at a Single Institute in Japan

Hisakazu Nishimori[a,b]*, Shunji Takahashi[a], Katsuyuki Kiura[b], Daisuke Ennishi[a,b], Takayuki Kobayashi[a], Koji Sano[a], Eiji Shinozaki[a], Masahiro Yokoyama[a], Yuko Mishima[a], Yasuhito Terui[a], Keisho Chin[a], Nobuyuki Mizunuma[a], Yoshinori Ito[a], Seiichiro Nishimura[c], Kengo Takeuchi[d], Yuichi Ishikawa[d], Masahiko Oguchi[e], Mitsune Tanimoto[b], and Kiyohiko Hatake[a]

[a]*Division of Medical Oncology and Hematology, Cancer Institute Hospital, Koto-ku, Tokyo 135–8550, Japan,*
[b]*Department of Hematology, Oncology, Allergy, and Respiratory Medicine, Okayama University Hospital, Okayama 700–8558, Japan,*
Divisions of [c]*Breast Surgery,* [e]*Radiology, Cancer Institute Hospital, and*
[d]*Division of Pathology, Cancer Institute of the Japanese Foundation for Cancer Research, Koto-ku, Tokyo 135–8550, Japan*

We evaluated the efficacy and toxicity of cisplatin/docetaxel (CDDP/TXT) chemotherapy and identified prognostic factors in Japanese patients with cancer of unknown primary site (CUP). Twenty-eight consecutive patients seen at a single institute were reviewed retrospectively. Sixteen patients were treated with TXT 80 mg/m^2, followed by CDDP 75 mg/m^2. The overall response rate to CDDP/TXT treatment was 62.5%, with a median survival time (MST) of 22.7 months. Common adverse reactions were myelosuppression and hyponatremia. The MST of all 28 patients with CUP was 8.3 months, and the 1-year overall survival rate was 45.6%. Univariate analysis identified 5 prognostic factors:performance status, liver involvement, bone involvement, pleural involvement, and lymph node involvement. In conclusion, CDDP/TXT chemotherapy is effective with tolerable toxicity in patients with CUP. Japanese patients with CUP might be chemosensitive and may survive longer.

Key words: cancer of unknown primary site (CUP), cisplatin, docetaxel, prognosis

Cancer of unknown primary site (CUP) is defined as the presence of metastatic cancer documented in the absence of an identifiable primary tumor site. These tumors are not rare; they represent 3–5% of all malignancies diagnosed in oncology practice [1, 2]. CUP occurs in a heterogeneous group of patients, and subgroups with treatment-responsive diseases exist that may achieve long-term, disease-free survival [1]. Generally, however, the prognosis of CUP is poor, with median survival times of 6–12 months, and the benefits of chemotherapy compared with best supportive care remain unclear [3].

Chemotherapy for patients with CUP is improving, but no chemotherapy regimen has been established as a standard first-line therapy for these patients [2]. Recent clinical reports have shown that cisplatin (CDDP)-containing regimens have good response rates of 32–55% in patients with CUP and are relatively well-tolerated [3, 4]. Docetaxel (TXT) has definite antitumor activity in various solid tumors and seems to

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*Corresponding author. Phone:+81-86-235-7227; Fax:+81-86-232-8226
E-mail:n-mori@md.okayama-u.ac.jp (H. Nishimori)

be a good candidate for inclusion in a chemotherapy regimen for patients with CUP [5]. A CDDP plus TXT phase II study revealed a 26% response rate with 42% 1-year survival [6].

This paper presents a retrospective analysis of 28 consecutive Japanese patients with CUP to clarify the disease course and prognostic factors. We also report an excellent response rate and survival of Japanese patients with CUP who were treated using a combination regimen of CDDP/TXT.

Patients and Methods

Patients. Twenty-eight consecutive patients referred to the Division of Medical Oncology and Hematology at the Cancer Institute Hospital between April 1, 2000 and September 30, 2004 were reviewed retrospectively. Patients referred with a presumed diagnosis of CUP were identified and registered in the database at the time of their initial clinical evaluation. All patients diagnosed with CUP during this period were registered; however, 2 female patients with adenocarcinoma involving only the axillary lymph nodes were treated for occult breast cancer and were excluded from this analysis. The medical records of the patients were reviewed for the results of diagnostic studies and pathologic and cytologic diagnosis before referral, the results of subsequent radiographic evaluations, pathology review, involved disease sites, treatment, and survival.

Clinical evaluation. All patients with CUP underwent a basic evaluation consisting of a complete medical history, a physical examination (including careful palpation of the thyroid, breasts, lymph nodes, and prostate), general laboratory studies, chest radiography, and computed tomography from the neck to pelvis. If possible, gastrointestinal endoscopy, nose and pharyngeal endoscopy, and bronchoscopy were conducted. Positron emission tomography (PET) was performed in some patients when all other tests were inconclusive. In some cases, an extensive immunohistochemical study was carried out with the biopsied specimen to minimize the possibility of a misdiagnosis of other malignancies such as non-Hodgkin's lymphoma, extragonadal germ cell tumor, malignant melanoma, or undifferentiated sarcoma [2]. The most commonly used markers were the leukocyte common antigen, cytokeratins, neuron-specific enolase or chromogranin, S-100 protein, vimentin, thyroid transcription factor-1 (TTF-1), estrogen receptors, HMB45, and prostate-specific antigen (PSA). The blood concentrations of CA19-9, CA15-3, CA125, and carcinoembryonic antigen (CEA) were assessed in most cases.

Decision-making in the 'cancer board meeting'. Determining whether the primary site is unknown or whether it will be possible to detect with further evaluation is difficult. In the present study, members of the cancer board, including medical oncologists, hematologists, surgeons, pathologists, and radiation oncologists, evaluated the diagnosis and treatment strategies for the patients with CUP.

Treatment schedule for CDDP/TXT therapy. Eligible patients with CUP were treated with CDDP/TXT combination chemotherapy. All patients gave written informed consent. TXT 80 mg/m^2 in 300 mL of normal saline was administered over 2 h, followed by CDDP 75 mg/m^2, which was administered via a 120-min intravenous infusion. Premedication included intravenous administration of 4 mg of dexamethasone 24 h before treatment, 30 min before starting the docetaxel infusion, and 24 h after the infusion. A single 3-mg intravenous dose of granisetron was given to all patients as an antiemetic. Concurrent radiotherapy for symptom control in the absence of disease progression was allowed, but the drugs were held for at least 2 weeks after irradiation. Chemotherapy cycles were repeated every 3 weeks. Doses were modified for some patients mainly due to hematological toxicity.

Assessment of response and toxicity. Responses were defined according to the World Health Organization criteria [7]. Briefly, complete response (CR) was defined as the entire disappearance of all assessable lesions and signs of disease for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the perpendicular dimensions of measurable lesions and the appearance of no new lesion for at least 4 weeks. No change (NC) was defined as a decrease of less than 50% or an increase of less than 25% in the 2 greatest dimensions of measurable lesions and the appearance of no new lesions. Progressive disease (PD) was defined as any evidence of disease progression of 25% or more, or the appearance of a new lesion. Chemotherapy-related adverse events were recorded according to the National Cancer Institute's Common

Terminology Criteria, version 3.0 [8].

Statistical methods. Survival was calculated from the first day of pathologically or cytologically diagnosed malignancy. Survival following CDDP/TXT therapy was calculated from the first day of treatment. Survival curves were estimated using the Kaplan-Meier method [9] and compared using the Cox-Mantel log-rank test [10]. StatView 5.0 (SAS Institute, Cary, NC, USA) was used for the statistical analyses.

Results

General patient characteristics. The characteristics of our 28 patients (19 men and 9 women) are listed in Tables 1 and 2. One female patient was excluded from the survival analysis because she was postoperatively diagnosed with ovarian cancer. The median age at diagnosis was 58.5 years (range 32–76 years). Performance status according to the Eastern Cooperative Oncology Group (ECOG) [11] was 0–1 in 17 patients (60.7%). The sites of metastasis documented pathologically, cytologically, or radiographically are listed in Table 3. Lymph nodes were involved most frequently (64.3%), and visceral metastases including bone, lung, or liver were also common. The lymph node involvement was further subclassified by anatomic site. Of the 18 patients with nodal metastases, 11 had retroperitoneal, 8 had supraclavicular or cervical, 7 had mediastinal, 4 had axillary, and 4 had inguinal lymph nodes.

Table 1 Characteristics of 28 CUP patients

Characteristic	No. of Patients
Sex	
Female	9
Male	19
Age, years	
0–40	1
41–50	6
51–60	8
61–70	10
71–80	3
Median	58.5
Range	32–76
Performance status	
0–1	17
2–3	11

The pathological diagnoses of the patients are also listed in Table 2. Thirteen patients (46.4%) were diagnosed with adenocarcinoma, 9 (32.1%) with poorly differentiated carcinoma, 2 (7.1%) with squamous cell carcinoma, and 4 with unknown or other diagnoses. One patient was diagnosed based only on the cytology of ascites. No patients with neuroendocrine carcinoma were included in this study. No patients appeared to belong to subgroups with a favorable prognosis [1].

Twelve patients (42.9%) had a single metastatic organ site, 4 (14.3%) had 2, 7 (25.0%) had 3, and 5 (17.9%) had 4 or more. Serum tumor markers at baseline were assessed in all 16 patients who underwent CDDP/TXT therapy.

Twenty-five patients (89.3%) were treated with chemotherapy with or without concurrent radiotherapy for symptom control. One patient was treated with radiotherapy only. Two patients were treated with supportive care alone.

CDDP/TXT treatment. Sixteen patients who received the CDDP/TXT combination according to the protocol were assessable for response. The patient

Table 2 Sites of tumor involvement and histologic diagnoses in 28 patients with CUP

Site of involvement	No. of patients
Lymph nodes	18
Bone	10
Lung	7
Liver	6
Pleura/pleural space	4
Peritoneum	4
Skin	3
Adrenal	2
Others	9
Histologic Diagnosis	**No. of patients**
Adenocarcinoma	13
Poorly differentiated	4
Papillary	1
No descriptor/other	8
Poorly differentiated carcinoma	9
Squamous cell carcinoma	2
Unknown/other	4
No. of involved organ sites	**No. of patients**
1	12
2	4
3	7
4 or more	5

Table 3 Characteristics of 16 patients treated with the CDDP/TXT regimen

Characteristic	No. of Patients
Sex	
Female	6
Male	10
Age, years	
Median	62.5
Range	41–76
PS	
0–1	12
2–3	4
Histology	
Adonocarcinoma	10
Poorly differentiated	2
Papillary	1
No descriptor/other	7
Poorly differentiated Carcinoma	4
Squamous cell carcinoma	0
Unknown/other	2
Metastatic sites at presentation	
Lymph nodes	10
Bone	6
Lung	2
Liver	1
Pleura/pleural space	1
Peritoneum	2
Skin	1
Adrenal	1
Others	4
No. of involved organ sites	
Single site	9
Multiple (≥2) sites	7
No. of courses given	
Median	3
Range	1–6

characteristics were similar to those of all 28 patients (Table 3): 10 men and 6 women, median age 62.5 years (range 41–76 years). However, performance status (PS) and the number of metastatic sites were lower, with PS 0–1 in 12 patients and single-site involvement in 9. In 8 patients (50%), more than 2 tumor markers had increased at diagnosis. The median duration from the day of the pathological diagnosis of metastatic carcinoma to the first day of CDDP/TXT therapy was 43 days (range 0–154 days). A total of 44 cycles of therapy was given, and the patients underwent a median of 3 treatment cycles (range 1–6 cycles). Doses were modified mainly because of hematological toxicity; 4 patients had a 20% dose reduction.

The overall response rate was 62.5% (95% CI 8.6–81.5%), with CR in one patient and PR in nine patients. Six of 10 patients with adenocarcinoma responded, and all 4 patients with poorly differentiated carcinoma responded. Tumor markers decreased in most responding patients. Fig. 1 shows the survival curve for these patients. The median follow-up was 20.4 months (range 1.7–60.2 months), the median disease-free survival (DFS) was 8.7 months, the 1-year overall survival (OS) rate was 68.8% (95% CI 40.6–91.5%), and the median OS was 22.7 months. The median hospitalization stay of the 16 patients treated with CDDP/TXT therapy was 65.5 days (range 26–162 days).

Toxicity data are listed in Table 4. Grade 3–4 neutropenia was frequent (14 patients, 87.5%). One patient who had multiple lung, liver, and bone metastases died of bacterial pneumonia due to neutropenia. Hyponatremia occurred in 14 patients (87.5%) and was grade 3–4 in 3 patients; however, all patients were able to continue the treatment. The hyponatremia was caused by a loss of sodium due to renal tubule damage caused by cisplatin or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Grade 3 allergic reactions due to docetaxel occurred in 2 patients during the first course. These 2 patients were given hydrocortisone and treated with cisplatin-only beginning with the next course. Other recorded toxicities were mild to moderate.

Prognostic factors for survival in the 28 patients with CUP. Fig. 2 shows the survival

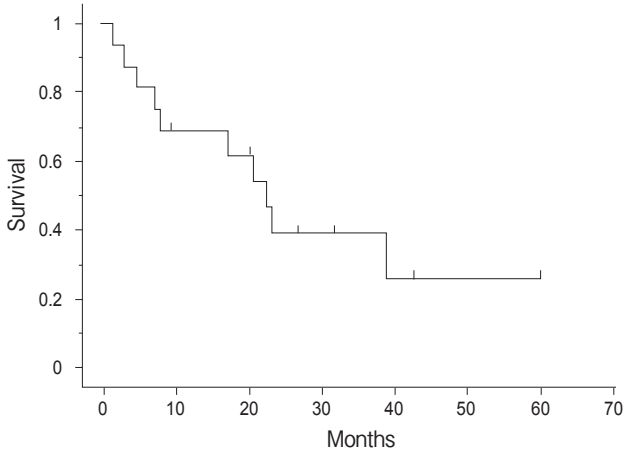

Fig. 1 Kaplan-Meier survival curve for the CUP patients treated with CDDP/TXT chemotherapy (n = 16).

curve for the 28 patients with CUP calculated from the day of diagnosis. The 1-year OS rate for all 28 patients was 45.6% (95% CI 26.8–64.4%), and the median survival was 8.3 months.

Table 5 lists the median survival of the CUP patient subgroups according to various factors. The univariate analysis revealed that 4 factors were deleterious: performance status 2–4, liver involvement, bone involvement, and pleural involvement. The advantageous clinical feature was lymph node involvement.

Discussion

In this study, we obtained an excellent response rate and survival with CDDP/TXT therapy for patients with CUP. An overall response rate of 62.5% was seen in patients with CUP who were given the CDDP/TXT combination once every 3 weeks. The median disease-free survival was 8.7 months. The 1-year OS was 68.8%, and the median OS was 22.7 months. The response rate and survival were superior to those obtained in the reported phase II trials of platinum plus taxane-based chemotherapy [2, 5, 6, 12]. Greco *et al.* reported a prospective phase II study of the CDDP/TXT regimen with a response rate of 22% and a 1-year survival of 40% [6]. The patient characteristics and dose intensity were similar to those in our study, although they had fewer patients with a single metastasis.

Yakushiji *et al.* have reported that 35 Japanese patients received a median of four cycles of CDDP and TXT, and had a response rate of 57.1%. The median survival time was 13.2 months [13]. These results in Japanese patients together with ours in the present study seem to be better than those reported from other countries. Although the prognostic factors in our reports are similar to those for other countries, Japanese patients with CUP might be chemosensitive and thus survive longer.

The treatment-related toxicity of the CDDP/TXT regimen mainly involved myelosuppression; in particular, grade 3–4 neutropenia was severe. Non-prophylactic G-CSF seemed to be the cause of this severity. One patient died of bacterial pneumonia due to neutropenia on day 12 of the first course. This patient was a 62-year-old man with PS 3. He had multiple metastases to lung, liver, and bone. He was therefore at high risk of pneumonia and had a very poor prognosis. Although hyponatremia occurred in 87.5% of our patients, it has not been reported in other studies that treated patients with CUP using platinum-containing regimens. Greco *et al.* have reported the toxicities of CDDP/TXT therapy to consist primarily of gastrointestinal events, with myelosuppression being moderate [6]. Based on urinalysis and the serum osmolarity, SIADH was the main cause of hyponatremia in the present study (data not shown). Since 1990, many Japanese researchers have reported SIADH following platinum administration for solid tumors [14, 15]. Collectively, Japanese patients seem to be more sensitive to platinum in terms of developing SIADH. Other recorded toxicities are mild to moderate. Overall, the regimen is generally tolerated in the majority of patients.

Table 4 Toxicity of CDDP/TXT therapy as worst grade per patient (n = 16)

Toxicity	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	6 (37.5)	6 (37.5)	1	0
Thrombocytopenia	4 (25.0)	1	0	1
Leukocytopenia	0	5 (31.3)	7 (43.8)	3 (18.8)
Granulocytopenia	0	1	3 (18.8)	11 (68.8)
Diarrhea	2 (12.5)	0	0	0
Nausea	3 (18.8)	5 (31.3)	4 (25.0)	0
Hyponatremia	11 (68.8)	0	3 (18.8)	0
High serum bilirubin	2 (12.5)	0	1	0
High serum creatinine	7 (43.8)	0	0	0
Allergic reaction	0	0	2 (12.5)	0

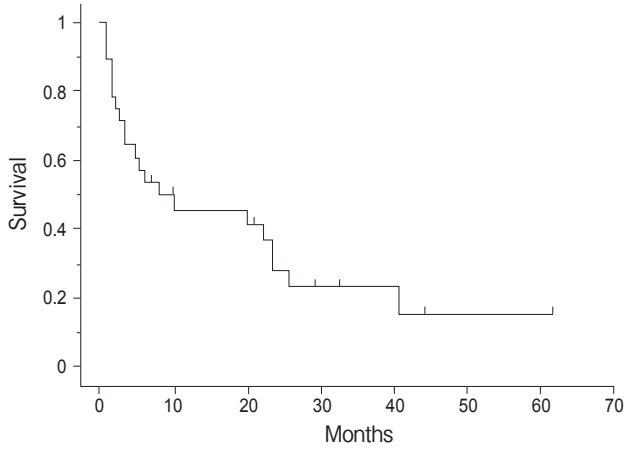

Fig. 2 Kaplan-Meier survival curve of all 28 CUP patients.

Table 5 Median survival duration of defined patient populations with CUP

Variable		No. of Patients	Median survival (days)	*p*-value
Sex				
Female		9	712	0.2599
Male		19	186	
No. of organ sites				
1		12	709	0.1180
2–6		16	108	
Performance status				
0–1		17	673	**0.0413**
2–3		11	79	
Involved organ sites				
Lymph nodes	+	18	673	**0.0310**
	−	10	148	
Liver	+	6	50	**0.0002**
	−	22	673	
Bone	+	10	108	**0.0380**
	−	18	673	
Lung	+	7	67	0.0642
	−	21	604	
Pleura/pleural space	+	4	31	**0.0040**
	−	24	604	
Brain	+	1	108	0.3704
	−	27	306	
Peritoneum	+	4	67	0.1458
	−	24	306	
Adrenal	+	2	33	0.6633
	−	26	249	
Skin	+	3	51	0.1820
	−	25	306	
Therapy				
CDDP/TXT		16	681	<0.0001
Other		12	73	
Histology				
Adenocarcinoma		13	673	
Poorly differentiated carcinoma		9	306	
Squamous cell carcinoma		2	33	
Unknown or others		4	67	

Clinical subsets of patients who are sensitive to platinum-containing treatment have been identified in the last 2 decades [2]. In this study, one patient almost fit into a favorable subset. She was a 73-year-old woman with peritoneal adenocarcinoma, but no papillary serous carcinoma, so she did not completely conform to a favorable subset. She was given three courses of CDDP/TXT, attained good PR, and was still alive at the 23.6-month follow-up. Therefore, although no patients completely matched the subgroups with a favorable prognosis, the CDDP/TXT regimen in this study was found to be very beneficial.

We also analyzed the course and prognostic factors of the patients with CUP. Univariate analysis identified 4 factors predicting a poor prognosis: performance status 2–4, liver involvement, bone involvement, and pleural involvement. The one favorable prognostic factor was lymph node involvement. Abbruzzese *et al.* examined prognostic factors in 657 consecutive patients and found that male sex, increased numbers of involved organ sites, adenocarcinoma histology, and hepatic involvement were negative prognostic factors in a multivariate analysis [16]. They also reported that lymph node involvement,

peritoneal involvement, and neuroendocrine histology are favorable prognostic factors [16]. Our results confirm the reported analyses; *i.e.*, visceral metastasis, multiple metastatic sites, and poor performance status may predict shorter survival.

Recently, a new combination of chemotherapy has been reported that includes gemcitabine, etoposide, or irinotecan combined with platinum plus taxane; these studies have shown similar response and survival rates [17, 18]. New agents such as vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors are being tested to improve the prognosis of CUP. Hainsworth *et al.* have reported that bevacizumab plus erlotinib therapy has a response rate of 10%, leading to stable disease in 61%, a median OS of 7.4 months, and a 1-year OS of 33% [19]. Therapeutic trials involving platinum and taxane plus VEGF or EGFR inhibitors should be conducted to improve the survival of patients with CUP.

In conclusion, although this was a retrospective study, we observed an excellent response rate and survival with CDDP/TXT chemotherapy in Japanese patients with CUP, despite their being in unfavorable subgroups. Our results show that bone, liver, and pleural metastasis, and poor performance status may predict a shorter survival.

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