

Carcinoma of Unknown Primary Site Treated with Carboplatin + Paclitaxel + Bevacizumab + Erlotinib and Its Maintenance Chemotherapy

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Key Words

Carcinoma of unknown primary site · Bronchoscopy · Immunohistochemistry · Carboplatin + paclitaxel + bevacizumab + erlotinib · Maintenance chemotherapy

Abstract

About 3% of all cancer patients suffer from carcinoma of unknown primary site (CUP). In spite of its rarity, we will encounter them. While CUPs manifest a wide variety of clinical presentations, they have often resulted in poor prognosis. Although platinum/taxane combination chemotherapy, e.g. carboplatin (CBDCA) + paclitaxel (PTX) is widely used for patients suffering from CUP, the response rate is only about 30–40% and the median overall survival (OS) is only 9 months, which means that improvement is needed. Among the new regimens, the combination of CBDCA, PTX, bevacizumab (BEV) and erlotinib is thought to be highly promising. Herein, we report a case with CUP treated with this regimen and his maintenance therapy. Our patient was a 75-year-old man who was admitted with a left neck lump. CT revealed systemic massive lymphadenopathy. In spite of various investigations for primary origin, he was diagnosed with CUP and treated with CBDCA + PTX + BEV + erlotinib (AUC 6 + 175 mg/m² + 15 mg/kg + 150 mg). Since the evaluation of the efficacy indicated partial response, maintenance chemotherapy (BEV and erlotinib) was performed. Chemotherapy was continued for 9 months until the patient was in a progressive disease state with meningeal dissemination. He died 12 months after the initiation of chemotherapy, which is a longer period than the previously reported OS. Of note, according to our case, CBDCA + PTX + BEV + erlotinib and its maintenance chemotherapy are feasible and well tolerated for CUP.

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Introduction

Carcinoma of unknown primary (CUP) currently accounts for approximately 3% of all cancer diagnoses. Although empiric chemotherapy with taxane/platinum regimens, e.g. carboplatin (CBDCA) + paclitaxel (PTX) is widely used for CUP patients, no clear evidence exists on the superiority to any other administered regimens. Taxane/platinum regimens yield response rates of 30–40%; the median overall survival (OS) and the median progression-free survival are 9.0 and 6.0 months with 1- and 2-year survival rates of approximately 40 and 20%, respectively [1].

During the last several years, new drugs targeting either the angiogenic pathway or the cancer cell proliferation pathway have been used for a variety of cancers, including lung, colon, breast, and pancreatic cancer. Because the lung, colon, and pancreas are often identified as the primary sites by autopsy in CUP patients, it seems that these new drugs are also pertinent in the empiric treatment for such patients. A phase II trial of PTX/CBDCA + bevacizumab (BEV)/erlotinib regimen for CUP patients was reported in 2009 [1]. This regimen produced a response rate of 53%, the median OS was 12.6 months, the median progression-free survival was 8 months, and the 1- and 2-year survival rates were 51 and 27%, respectively [1, 2]. Both the median progression-free survival and a 2-year survival rate are the best of the previously reported empiric chemotherapy regimens. Thus, this regimen seems to be promising for CUP patients. We herein report the case of a CUP patient treated with CBDCA, PTX, BEV and erlotinib and his maintenance therapy.

Case Presentation

A 60-year-old man presented to his primary care physician with cervical lymphadenopathy persisting for 1 month and was referred to an otolaryngologist at our hospital. The patient did not complain about any other symptoms (performance status: PS 0). He had suffered from a colon polyp, which was treated by endoscopic resection 7 years ago, and had a 40-year smoking history of 1.5 packs per day.

His whole-body contrast-enhanced CT showed lymphadenopathy of the right cervix, bilateral supraclavicle and mediastinum, emphysema and a small nonspecific node in the right upper lung (fig. 1a, b). His head MRI showed multiple ring and solid enhancing lesions, suggesting brain metastasis (fig. 1c, d). ¹⁸F-FDG PET/CT demonstrated FDG accumulation in the lymph nodes and a pulmonary node (fig. 1e–g). Serum levels of carcinoembryonic antigen (CEA) were elevated at 16.8 ng/ml (normal values <5 ng/ml), and no other abnormalities were found (table 1) when investigating for tumor markers.

In order to find a clue for the primary lesion pathologically, needle biopsy of the cervical lymph node was performed. Cytological examination revealed poorly differentiated adenocarcinoma, and immunohistochemistry (IHC) showed the following: cytokeratin (CK) 7 (+), CK20 (+), MUC1 (+), MUC2 (–), SP-A (–), TTF-1 (–), CD5 (–), CDX2 (–), human gastric mucin (–), ALK mutation (–), and EGFR mutation (–) (fig. 2). Bronchoscopy was performed but cytological examination was negative for bronchial lavage fluid, and upper and lower gastroscopy did not show any abnormality. In spite of these diagnostic approaches for detecting the primary site, it remained unclear, and the patient was diagnosed with CUP.

After approval by the Intramural Ethics Committee and written informed consent had been given, the patient was treated with CBDCA + PTX + BEV + erlotinib (AUC 6 + 175 mg/m² + 15 mg/kg + 150 mg). After the chemotherapy had started, the serum level of CEA decreased (fig. 3). Since his whole-body CT revealed a decrease in lymph node size after five

cycles of the regimen, the patient achieved partial response (fig. 1h–k). With this result, he was treated with maintenance chemotherapy of BEV + erlotinib (15 mg/kg + 150 mg). No clear side effect was detected in blood chemistry after five cycles (table 2). After six cycles of maintenance chemotherapy (i.e. 8 months after the initial chemotherapy), the patient complained of left facial paralysis. We diagnosed that meningeal dissemination caused this facial paralysis, based on the result of a CT/MRI scan which showed a new contrast-enhanced area in the left internal auditory canal (fig. 1l–o). This result was suggestive of progressive disease, and thus chemotherapy was stopped. Treatment-related toxicity was grade 3 peripheral neuropathy and grade 1 alanine aminotransferase (ALT) elevation as well as stomatitis, skin rash, and dysgeusia; he did not have any hematologic toxicity. Peripheral neuropathy was considered to be possibly related to PTX and indeed improved after CBDCA and PTX treatment was finished.

Further chemotherapy could not be performed due to the patient's worsening performance states (PS 3). In order to palliate his facial paralysis, neck pain and facial edema due to jugular venous distention by lymphadenopathy, cranial irradiation and radiation therapy for neck lymphadenopathy were performed. Our patient died of CUP 12 months after the initial chemotherapy (fig. 3).

Discussion

A primary tumor may not be detected because of its extremely small size or possible local regression due to antitumor immune defenses as well as its protracted clinical latency [3]. Since it is difficult to detect the organs where the primary tumor is located, investigation with imaging, tumor marker and IHC markers is performed to at least classify the type of carcinomas. CUP is classified into four major histopathological subtypes: well- or moderately differentiated adenocarcinomas (50%); undifferentiated or poorly differentiated adenocarcinomas or carcinomas (30%); squamous cell carcinomas (15%), and undifferentiated neoplasms (5%) [4]. In our case, neither CT, MRI and PET images nor endoscopy detected the primary site. IHC examinations showed adenocarcinoma, and positivity of CK7/CK20 suggested transient cell carcinoma, pancreatic ductal carcinoma, cholangiocellular carcinoma and gastric adenocarcinoma. MUC1 overexpresses in serous-type adenocarcinoma, such as breast or pancreatic cancer, MUC2 tends to overexpress in mucinous adenocarcinoma, such as colon, small intestine and bronchus carcinoma. CK7/CK20 results and MUC1 positivity and MUC2 negativity might indicate that our patient's primary tumor was pancreatic adenocarcinoma. Because other IHCs and examinations were not consistent in determining the primary tumor site, the patient was diagnosed with CUP.

Treatments for CUP patients have so far been empirical. Although data from phase III trials are lacking, regimens with new chemotherapeutic agents (e.g. taxanes, gemcitabine, irinotecan) show a modest improvement; most of these new regimens report response rates of 30–50% and a median OS of 8–10 months [5, 6]. CBDCA, PTX, BEV and erlotinib regimens attempt to incorporate molecular targeted agents with the existing empirical first treatment for CUP. BEV, a monoclonal antibody targeting vascular epithelial growth factor (VEGF), which inhibits neoangiogenesis, is used alone or in combination with other anticancer drugs in patients with advanced colon, lung, breast, renal, and ovarian cancer [7–10]. Erlotinib, an intracellular EGFR tyrosine kinase inhibitor, prolongs survival in lung and pancreatic cancer [11, 12]. Preclinical studies suggested that inhibition of EGFR also resulted in the suppression of VEGF levels and might allow the additional inhibition of the angiogenesis pathway. Moreover, blocking of VEGF receptor and EGFR signaling could lead to the primary tumor

overcoming its acquired resistance to EGFR inhibitors [2, 13]. Clinically, anti-EGFR and anti-VEGF combination therapy is well tolerated and effective in several malignancies [2, 13–15]. The combination regimen seemed to be tolerable and more effective than general CUP prognosis. However, the use of these four agents resulted in an expensive treatment. Further study is necessary regarding the cost-benefit of this treatment.

Conclusions

We reported the case of a CUP patient treated with CBDCA, PTX, BEV and erlotinib and its maintenance chemotherapy. According to our case, CBDCA + PTX + BEV + erlotinib and its maintenance chemotherapy are feasible and well tolerated for CUP.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Blood biochemistry and tumor markers before the therapy; CEA was elevated, and no other abnormalities were found

WBC	6,900/ μ l	TP	7.0 g/dl	CEA	16.8 ng/ml
Neutrophils	60.6%	AST	25 U/l	SCC	0.9 ng/ml
Lymphocytes	30.0%	ALT	36 U/l	SLX	36.1 U/ml
Monocytes	7.0%	LDH	267 U/l	NSE	9.8 ng/ml
Eosinophils	2.0%	ALP	233 U/l	AFP	3.2 ng/ml
Basophils	0.4%	γ GTP	32 U/l	CA19-9	12.9 U/ml
		T-Bil	0.6 mg/dl	PSA	0.853 ng/ml
RBC	486×10^4 / μ l	BUN	20 mg/dl	sIL2-R	443 U/ml
Hb	15.2 g/dl	Cre	0.82 mg/dl		
Ht	45.3%	Na	142 mEq/l		
Plt	23.2×10^4 / μ l	K	4.6 mEq/l		
		Cl	105 mEq/l		
		CRP	0.22 mg/dl		

TP = total protein; ALP = alkaline phosphatase; γ GTP = γ -glutamyl transpeptidase ; T-Bil = total bilirubin; SCC = squamous cell carcinoma antigen; SLX =sialyl lewis X-i antigen ; NSE = neuron-specific γ -enolase; AFP = α -fetoprotein.

Table 2. Blood biochemistry after five cycles of CBDCA + PTX + BEV + erlotinib; no side effects and abnormalities were detected

WBC	7,890/ μ l	TP	6.3 g/dl
Neutrophils	73.0%	AST	23 U/l
Lymphocytes	21.0%	ALT	38 U/l
		T-Bil	0.8 mg/dl
RBC	288×10^4 / μ l	BUN	24 mg/dl
Hb	10.7 g/dl	Cre	0.99 mg/dl
Ht	34.1%	Na	141 mEq/l
Plt	19.1×10^4 / μ l	K	4.5 mEq/l
		Cl	103 mEq/l
		CRP	0.03 mg/dl

For the abbreviations used, refer to table 1.

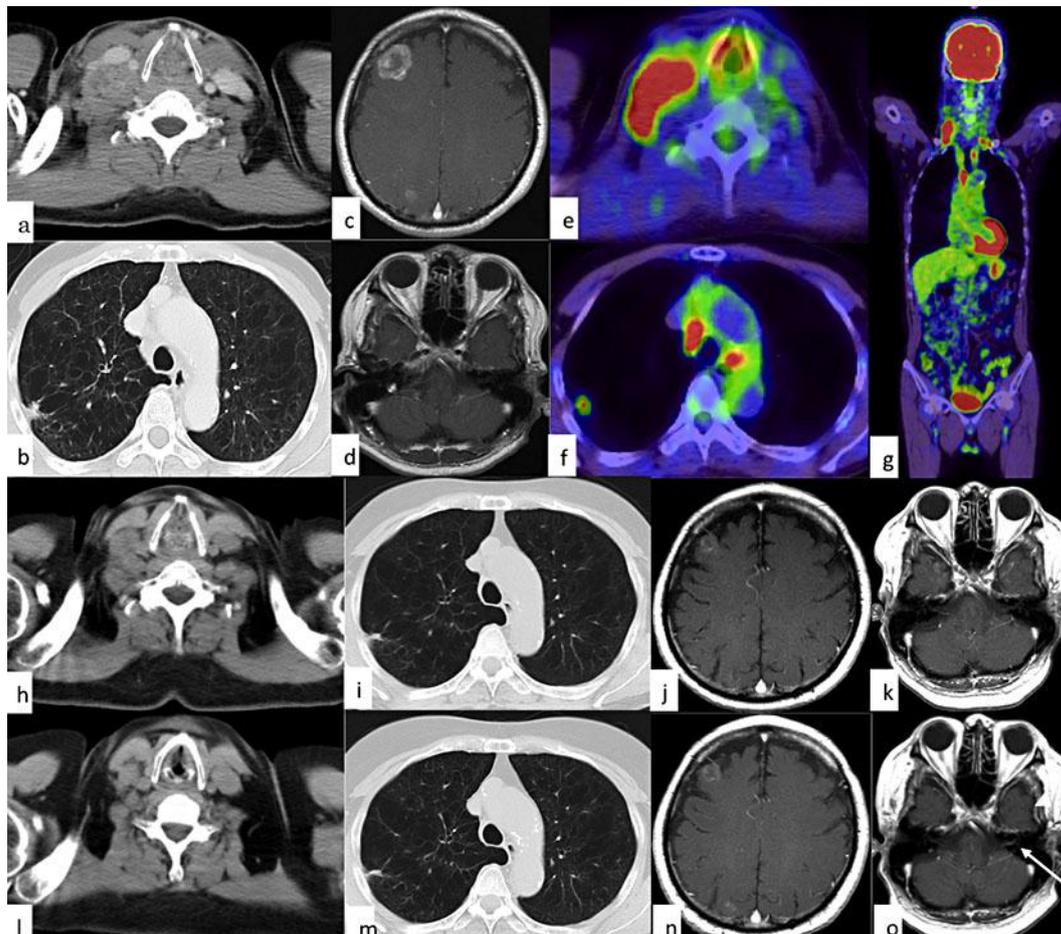


Fig. 1. **a, b** Lymphadenopathy of the right cervix and a small nonspecific node in the right upper lung on CT. **c, d** Metastasis in the right frontal and parietal lobe and no lesion in the internal auditory canals on head MRI. **e–g** Multiple metastatic lesions in the cervical lymph nodes, a pulmonary node, and accumulation in cervical and mediastinal lymph nodes on PET-CT. No other accumulation was observed except a pulmonary node. **h–k** Response on CT after five cycles of CBDCA, PTX, BEV, and erlotinib. Cervical lymph nodes decreased in size (**h**), but the pulmonary node did not change (**i**). Head metastasis was reduced (**j**) and no new lesion was observed (**k**). **l–o** Evaluation after six cycles of maintenance with BEV and erlotinib. CT and MRI (T1 weighted with gadolinium) showed no specific changes in each of the lesions except the appearance of a contrast-enhanced area in the left internal auditory canal (arrow).

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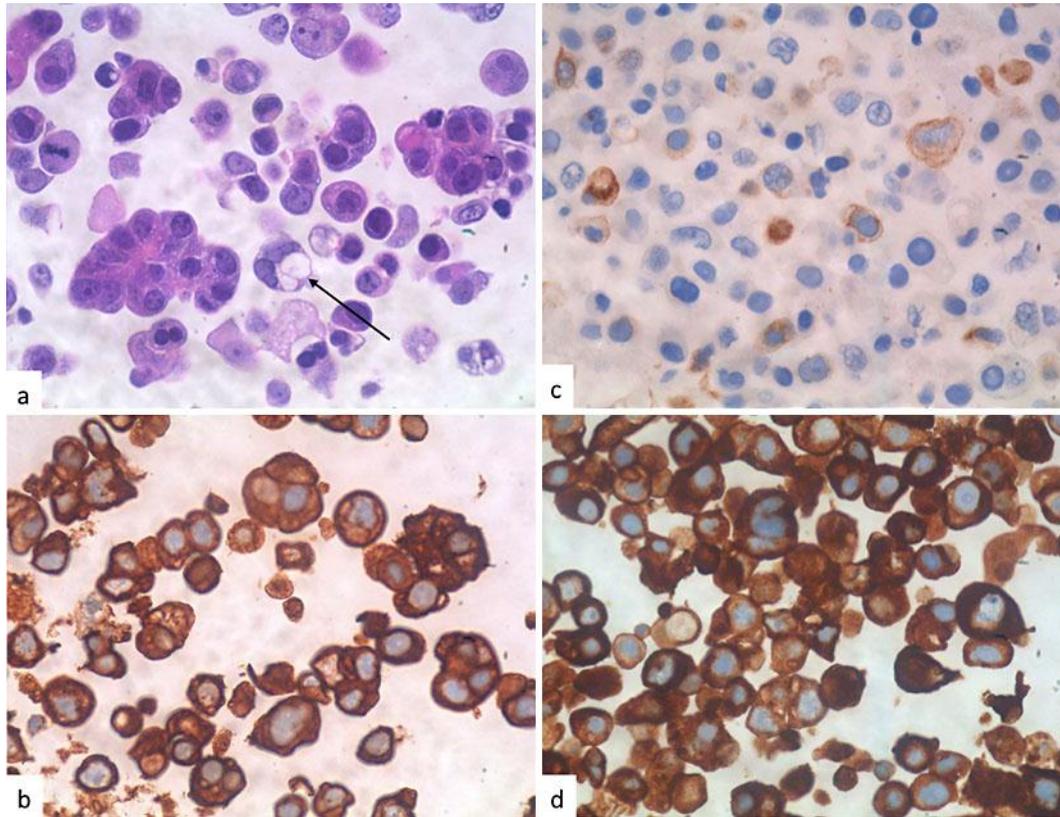


Fig. 2. Cytological examination of cervical lymph node needle biopsy. Original magnifications. $\times 400$. **a** HE stain; the arrow indicates the duct of the gland. IHC staining was positive for CK7 (**b**), CK20 (**c**), and MUC1 (**d**).

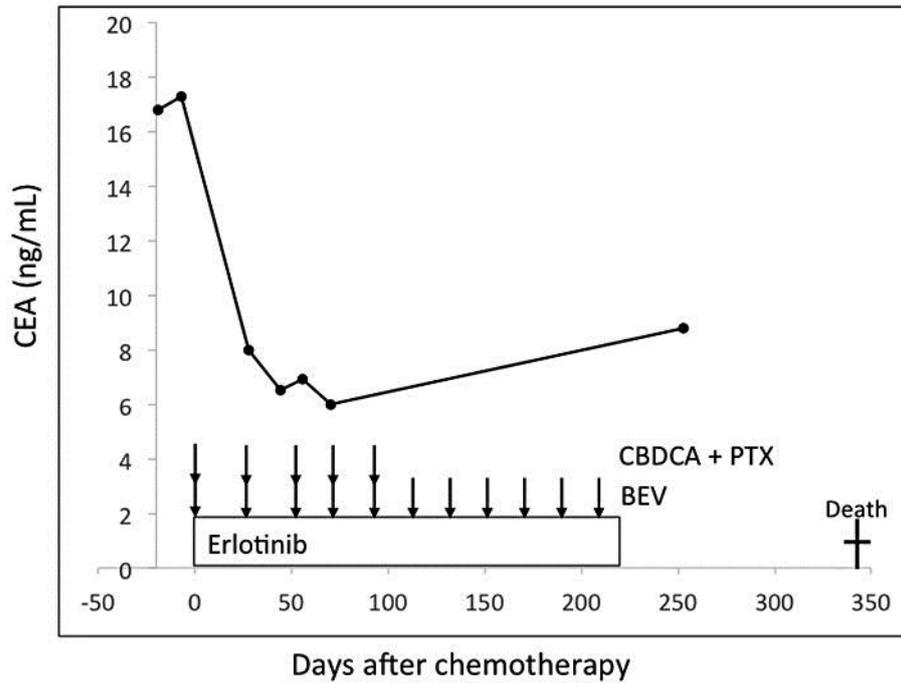


Fig. 3. Overview of the therapy and change of CEA. The arrows show chemotherapies (CBDCA, PTX, and BEV) and the bar shows erlotinib.