

Minireview

Carcinoma of Unknown Primary Site: A Mini-Review on Chemotherapy and the Expectation for Treatment with Nab-Paclitaxel Plus Carboplatin

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Abstract

Cancer of unknown primary site (CUP) is a heterogeneous group of cancers with widely varying natural histories and biological characteristics for which the anatomical site of origin remains occult after detailed investigations. Several clinicopathological subsets with favorable prognosis have been identified. CUP presents a clinical situation quite difficult to manage due to the absence of a standard of care for the initial therapeutic approach, as well as an impossibility to include these cases in randomized clinical trials. Historically, a “favorable subset” designation was made based on a presentation that overwhelmingly suggested a specific primary origin. Although several clinicopathologic subsets with favorable prognosis have been identified, most patients do not fit into any of these subsets. CUP is often associated with a poor prognosis, as patients are usually treated with a non-selective empirical therapy. During the past 3 decades, some phase II trials of platinum-based combination regimens containing newer cytotoxic agents (taxanes, gemcitabine, irinotecan, etc.) resulted in response rates of 20%–60% and median survivals of 6–11 months. In these trials, taxane-based regimens showed better responses and longer survivals. Therefore, taxane–platinum regimens as empiric chemotherapy are widely used for these patients. In the current paper, we summarize both the therapeutic challenges for patients with CUP as well as the current available therapeutic options, and introduce our trial currently in progress for this population.

Keywords: cancer of unknown primary site, taxane, carboplatin, nab-paclitaxel

Introduction**Definition and characteristics of cancer of unknown primary site**

Cancer of unknown primary site (CUP) is a collective term for cancers for which metastatic sites have been identified, but the primary site has not, despite detailed investigations. CUP, which has various origins, is a heterogeneous group of various cancers [1,2]. While CUP is estimated to account for 1% to 5% of all cancer cases, the reported incidence may change due to advances in diagnostic technology [3,4]. Anatomically identified common origins are pancreas, biliary tract, and lung, but

even autopsy fails to reveal the site of origin in 20% to 50% of patients [5,9]. CUP generally has a poor prognosis, partly due to metastases to multiple organs at the time of diagnosis in more than half of patients, with an estimated median survival time (MST) of 6 to 9 months [10,11]. CUPs, which have common biological characteristics such as latent rapid progression and dissemination regardless of origin, were initially distinguished from conventional cancers. However, chromosomal abnormality, microvascularization, aneuploidy, and genetic abnormality are not specific to CUP [12-19]. In addition, it is said

that genetic mutation is detected in as low as 18% of patients with CUP [20]. Accordingly, CUP retains the characteristics of cancer involving the putative organ of origin, and may therefore be optimally treated if managed like cancer involving the putative organ of origin.

Among CUPs, seven subsets of cases with favorable prognosis for which appropriate treatment is available to some extent have been identified, as listed below [2]. These CUPs, as well as sarcoma, malignant lymphoma, and malignant melanoma, have been excluded from recent clinical studies on CUP.

- i. Females who have adenocarcinoma with evidence of only enlarged axillary lymph nodes (treated as axillary lymph node-positive breast cancer)
- ii. Females who have adenocarcinoma with evidence of only peritoneal dissemination (ascites) and increased CA125 (treated as ovary cancer)
- iii. Patients with squamous cell carcinoma with evidence of only enlarged neck lymph nodes (treated as head and neck cancer)
- iv. Patients with squamous cell carcinoma with evidence of only enlarged groin lymph nodes (resection, radical radiation therapy, and/or radical chemoradiotherapy)
- v. Males aged 50 years or less who have lesion(s) in the midline (treated with cisplatin-based chemotherapy as germ cell tumor)
- vi. Patients who have histological characteristics of neuroendocrine tumor of unknown primary site (advanced well-differentiated neuroendocrine tumor of midgut origin is treated with somatostatin analogues, advanced well-differentiated neuroendocrine tumor of pulmonary or gastrointestinal origin is treated with everolimus, and poorly-differentiated neuroendocrine carcinoma is treated as small cell lung cancer)
- vii. Males who have adenocarcinoma with evidence of only osteoblastic bone metastasis and increased PSA (treated as prostate cancer)

Approaches to cancer of unknown primary site

While approaches to CUP have changed due to advances in diagnostic imaging as well as developments in immunostaining and molecular profiling, much remains unknown and continuous attempts are being made to develop treatments even in the era of individualized medicine.

Changes in our understanding of CUP have come about over the past three decades [21]. Initially, the category of CUP was established due to advances in diagnostic imaging. Subsequently, among CUPs, seven subsets with favorable prognosis were identified based on histopathological findings, patterns of involved organs, and serum marker findings [2]. More recently, new immunohistochemical markers and advances in pathological diagnostic tools, as well as their combinations, have helped in identifying the primary site more accurately, and

proteomics and genetic tools are currently studied [13,14, 22-34].

Changes in chemotherapy for cancer of unknown primary site

Chemotherapy, a systemic therapy, is generally indicated for CUP, for which only metastatic sites are detected. In general, therefore, surgery or radiation therapy, which is locally applied, is used in combination with chemotherapy as part of multidisciplinary treatment or is not indicated at all. To date, many clinical studies of chemotherapy in CUP have been reported (Table 1). However, no large phase III studies, including comparative studies of chemotherapy versus best supportive care, have been reported. In addition, the previous clinical studies were mostly conducted in narrowly defined CUP, that is, adenocarcinoma, undifferentiated carcinoma, and epithelial tumor such as squamous cell carcinoma, while excluding sarcoma, malignant lymphoma, and malignant melanoma.

Chemotherapy for CUP was attempted with 5-fluorouracil (5-FU), cyclophosphamide, and doxorubicin in the 1980s, but failed to achieve great success, with a response rate of less than 40%, an MST of less than 9 months, and a 1-year survival rate of less than 25% [35-38]. Later, cisplatin was introduced, but a very small comparative study failed to verify the superiority of cisplatin, leading to no conclusion on whether or not to include cisplatin in the treatment regimen [37,38,40]. In the 1990s, new drugs, including taxanes, gemcitabine, irinotecan hydrochloride, and vinorelbine, were introduced for many cancers, and many phase II studies of these drugs primarily in combination with platinum were conducted in CUP [39,41-63]. The results, although from phase II studies, were much more favorable than those of the previous drugs, as shown by response rates of 20% to 60%, MST of more than 12 months in some studies, and 1-year survival rates of 25% to 50%. Since taxanes combined with platinum consistently produced favorable results, combination therapy with carboplatin and paclitaxel is widely used in current clinical settings.

Other phase II studies had been conducted using various regimens, including non-platinum combination regimens and at least triple therapy, but mostly did not produce satisfactory results [40-68]. Since at least triple therapy is especially associated with more intense adverse events than dual therapy, platinum-based dual therapy may be appropriate chemotherapy for CUP in clinical settings.

Clinical studies in cancer of unknown primary site

In a search of ClinicalTrials.gov for “cancer of unknown primary site” or “cancer of unknown origin,” more than 100 clinical studies were identified as of March 2019 [69]. Among all, the study with identifier NCT03278600 is an ongoing randomized study identifying the primary site through 90 genetic analyses and

Table 1. Main previous clinical studies in cancer of unknown primary site.

Authors	Publication	Regimen	n	Phase	RR (%)	MST (months)	1-year survival rate (%)
Woods RL et al. [35]	1980	CFM+MTX+5-FU DXR+MMC	22	r	5	1.8	18*
			25		36	4.5	42*
Goldberg RM et al.[36]	1986	DXR+MMC+5-FU	45	P2	30	9.4	44
Eagan RT et al. [37]	1987	DXR+MMC CDDP+DXR+MMC	28	r	14	4.6	19
			27		27	5.5	12
Milliken ST et al. [38]	1987	DXR+MMC CDDP+VCR+Bleo	48	r	42	4.5	20*
			47		32	6.3	18*
Hainsworth JD et al. [39]	1997	CBDCa+PTX+VP-16	71	P2	48	13.4	50
Falkson CI et al. [40]	1998	CDDP+Epi+MMC MMC	41	r	50	9.4	38*
			39		17	5.4	26*
Greco FA et al.[41]	2000	CDDP+DTX CBDCa+DTX	26	P2	26	8	42
			47	P2	22	8	29
Voog E et al.[42]	2000	CDDP+VP-16	25	P2	32	8	
Parnis FX et al.[43]	2000	CDDP+FU+EPI	43	P2	23	5.8	
Briasoulis E et al.[44]	2000	CBDCa+PTX	77	P2	39	13	50*
Dowell JE et al.[45]	2001	CBDCa+VP-16 PTX+5-FU+lv	17	rP2	19	6.5	30*
			17		19	8.4	30*
Guardiola E et al.[46]	2001	CDDP+DXR+CFM	22	P2	50	10.7	25
Culine S et al.[47]	2002	DXR+CFM/CDDP+VP-16	82	P2	39	10	
Greco FA et al.[48]	2002	CBDCa+PTX+GEM	113	P2	25	9	42
Culine S et al. [49]	2003	CDDP+GEM CDDP+CPT-11	39	rP2	55	8	
			40		38	6	
Balaña C et al.[50]	2003	CDDP+GEM+VP-16	30	P2	37	7.2	27
Park YH et al. [51]	2004	CDDP+PTX	37	P2	42	11	38
Piga A et al. [52]	2004	CBDCa+DXR+VP-16	102	P2	27	9	35
El-Rayes BF et al.[53]	2005	CBDCa+PTX	22	P2	23	6.5	27
Palmeri S et al.[54]	2006	CDDP+GEM+PTX CDDP+GEM+VNR	33	rP2	49	9.6	30*
			33		42	13.6	55*
Pittman KB et al.[55]	2006	CBDCa+GEM	51	P2	31	7.8	26
Hainsworth JD et al. [56]	2007	Erl+Bev	51	P2	10	7.4	33
Schneider BJ et al.[57]	2007	CBDCa+GEM+Cape	33	P2	39	7.6	36
Pentheroudakis G et al.[58]	2008	CBDCa+DTX	23	P2	32	16	
Briasoulis E et al.[59]	2008	OX+CPT-11	47	P2	13	9.5	40
Huebner G et al. [60]	2009	CBDCa+PTX GEM+VNR	46	rP2	24	11	38
			46		20	7	29
Yonemori K et al.v[61]	2009	CBDCa+CPT-11	45	P2	42	12.2	44
Hainsworth JD et al. [62]	2009	CBDCa+PTX+Bev+Erl	49	P2	53	12.6	2y-SR 27
Mukai H et al. [63]	2010	CDDP+DTX	45	P2	65	11.8	50*
Hainsworth JD et al. [64]	2010	CBDCa+PTX+VP-16 GEM+CPT-11	93	P3	18	7.4	2y-SR 15
			105		18	8.5	2y-SR 18
Holtan SG et al. [65]	2012	GEM+CPT-11	31	P2	12	7.2	
Gross-Goupil M et al. [66]	2012	CDDP+GEM CDDP	27	rP2	19	11	46
			25		16	8	35
Tsuya A et al. [67]	2013	CDDP+S-1	46	P2	41	17.4	67
Shin DY et al. [68]	2016	FOLFOX6	23	P2	35	9.5	50*

r: Randomized study with unspecified development phase

P2: Phase 2; rP2: Randomized phase 2; RR:

Response rate; MST: Median survival time; 2y-SR: 2-year survival rate

*Estimated based on survival curve in original article

Blank: Not specified in original article

CFM: Cyclophosphamide; MTX: Methotrexate; 5-FU: 5-fluorouracil; DXR: Doxorubicin; MMC: Mitomycin C; CDDP: Cisplatin; VCR: Vincristine; Bleo: Bleomycin; CBDCA: Carboplatin; PTX: Paclitaxel; VP-16: Etoposide; Epi: Epirubicin; Iv: leukovorin; DTX: Docetaxel; Cape: Capecitabine; CPT-11: Irinotecan; GEM: Gemcitabine; Erl: Erlotinib; OX: Oxaliplatin; VNR: Vinorelbine; Bev: Bevacizumab; S-1: Tegafur/Gimeracil/Oteracil

molecular profiling to compare standard chemotherapy for the putative organ of origin and general chemotherapy for CUP [70]. Currently, stereotypical chemotherapy is administered for CUPs regardless of characteristics of individual cancers. This study is designed to identify the organ of origin for each cancer not through morphological analysis, but through genetic analysis, and to treat the cancer accordingly. It is a very interesting clinical study in that a so-called precision medicine is introduced to treat the putative organ of origin.

On the other hand, combination therapy with carboplatin and paclitaxel, which is widely used in current clinical settings, has the following problems: need of premedication with steroid or antihistaminic to prevent hypersensitivity to paclitaxel; long duration of intravenous infusion; contraindicated in patients with hypersensitivity to ethanol, which is contained in a vehicle for paclitaxel; and intense and frequent peripheral nerve disorder. In recent years, nab-paclitaxel has been developed to resolve these problems. Consequently, high expectations are placed on combination therapy with carboplatin and nab-paclitaxel in clinical settings.

Outcome of treatment of cancers with nab-paclitaxel

Nab-paclitaxel, which is nanoparticle paclitaxel bound to human serum albumin, is a taxane, and paclitaxel, the active ingredient, exhibits antitumor activity by promoting microtubule protein polymerization and inhibiting microtubule protein depolymerization [71,72]. Nab-paclitaxel, which is manufactured by binding highly water-insoluble paclitaxel to human serum albumin and then lyophilizing albumin-bound paclitaxel, can be administered as a suspension in normal saline without using conventional vehicles for paclitaxel (polyoxyethylene castor oil and ethanol).

Four clinical studies described below showed higher efficacy of nab-paclitaxel than that of conventional paclitaxel. In a non-Japanese phase III comparative study in patients with metastatic breast cancer (Study CA012-0), [73] the response rate was 24% (55/229 subjects) in the nab-paclitaxel group and 11% (25/225 subjects) in the paclitaxel group ($p < 0.001$). In a Japanese single-arm phase II study in patients with advanced/recurrent gastric cancer who received second-line treatment (Study J-0200), the response rate in the nab-paclitaxel group was 28% (15/54 subjects), which exceeded an expected response rate of 25% [74]. In a global phase III study in patients with advanced non-small cell lung cancer (Study CA031), the response rate was 33% (170/521 subjects) in the nab-paclitaxel group and 25% (132/531 subjects) in the paclitaxel group (combined with carboplatin in both groups) ($p = 0.005$). In a global phase III study in patients with metastatic pancreatic cancer, gemcitabine used in combination with nab-paclitaxel

significantly improved overall survival time, compared with gemcitabine alone (8.5 months vs. 6.7 months, HR 0.72, $p < 0.001$) [75,76].

Nab-paclitaxel has thus been demonstrated to be effective for various cancers, but has not been studied in CUP. Nonetheless, nab-paclitaxel, which is effective for various solid tumors of different origins, may likely be effective for CUP of unknown origin.

We are therefore conducting a single-arm phase II study to determine the efficacy of combination therapy with nab-paclitaxel and carboplatin for untreated CUP. The protocol of this study is summarized below. If the study demonstrates high efficacy and tolerability of nab-paclitaxel plus carboplatin, this combination is highly expected to be more widely used than combination therapy with carboplatin and paclitaxel, which is currently used in clinical settings.

Protocol digest

“Efficacy and safety of nab-paclitaxel plus carboplatin in patients with carcinoma of unknown primary site”

Study objective

To determine the efficacy and tolerability of combination therapy with nab-paclitaxel and carboplatin in untreated cancer of unknown primary site

Study design

Single-arm phase II study

Endpoints

Primary endpoint: 1-year survival rate

Secondary endpoints: overall survival time, progression-free survival time, response rate, safety, quality of life (QOL)

Inclusion criteria

Patients who meet all of the following criteria are eligible to participate in the study:

- i. Histological or cytological evidence of metastatic tumor and unknown primary site
- ii. Chemotherapy-naive
- iii. Aged 20 years or more at the time of informed consent
- iv. PS: 0-2
- v. Preserved organ functions as evidenced by neutrophil count $\geq 1500/\text{mm}^3$, hemoglobin $\geq 9.0 \text{ g/dL}$, platelet count $\geq 100,000/\text{mm}^3$, total bilirubin $\leq 1.5 \text{ mg/dL}$, AST/ALT $\leq 2.5 \times$ upper limit of normal (ULN), and serum creatinine $\leq 1.5 \times$ ULN (based on data collected within 14 days before enrollment)
- vi. Written informed consent directly provided by the patient

Exclusion criteria

Patients who meet any of the following criteria are not eligible to participate in the study:

(1) Among patients with CUP, there may be a population of those with favorable prognosis for whom standard therapy is available. Therefore, the following patient groups are excluded from the study:

- i. Females who have adenocarcinoma of unknown primary site with evidence of only enlarged axillary lymph nodes
- ii. Females who have adenocarcinoma with evidence of only peritoneal dissemination (ascites)
- iii. Patients who have squamous cell carcinoma with evidence of only enlarged neck lymph nodes
- iv. Patients who have squamous cell carcinoma with evidence of only enlarged groin lymph nodes
- v. Patients who have characteristics of germ cell tumor or neuroendocrine tumor
- vi. Males who have only osteosclerotic bone metastasis and increased PSA, a tumor marker in serum or tumor

(2) Patients for whom radical surgery or radical radiation is indicated

Palliative radiation therapy is acceptable, including radiation therapy for bone metastasis applied to 30% or less of hematopoietic bone marrow.

(3) Patients with serious infection or serious other concurrent disease (e.g., gastrointestinal hemorrhage, heart disease)

These diseases are acceptable if treated appropriately and considered to be inactive.

(4) Patients with central nervous symptom due to brain metastasis at enrollment

(5) Patients with evidence of interstitial pneumonia or pulmonary fibrosis

(6) Patients who have undergone bone marrow transplantation

(7) Patients who have undergone peripheral blood stem cell transplantation

(8) Patients with a history of clinically significant serious drug allergy

(9) HBsAg-positive patients

(10) Pregnant women, lactating women, women who may be pregnant, and patients who wish to become pregnant

(11) Fertile males who do not agree to use contraceptives during the study

(12) Patients with inadequately controlled diabetes mellitus

(13) Patients who, in the opinion of the investigator or subinvestigator, are not appropriate for the study

Treatment

Nab-paclitaxel will be administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m² once

daily, followed by at least 6 days of washout. Treatment will be repeated, with one course consisting of once-weekly administration for three consecutive weeks. Carboplatin, dissolved in 250 mL of 5% glucose solution or normal saline, will be administered as an intravenous infusion over 60 minutes once daily after intravenous infusion of nab-paclitaxel, followed by at least 20 days of washout. Treatment will be repeated, with one course consisting of single administration in three weeks.

Day 1 of each course will be started according to the following criteria:

- i. PS: 0-2
- ii. Neutrophil count $\geq 1,000/\text{mm}^3$
- iii. Platelet count $\geq 50,000/\text{mm}^3$
- iv. Peripheral nerve disorder \leq CTCAE Grade 2

Treatment with nab-paclitaxel on day 8 or 15 will be started according to the same criteria. Treatment on day 1, 8, or 15 will be skipped if the treatment criteria are not met. Protocol treatment will be discontinued according to the following criteria:

- i. Obvious tumor growth or a new lesion is detected.
- ii. The next course cannot be resumed within 21 days after the original scheduled date due to unfavorable test value or subject condition
- iii. Treatment cannot be continued due to a serious adverse event.
- iv. The patient requests withdrawal from the study.

Rationale for sample size selection

Given 1-year survival rates of 25% to 50% reported with conventional combination chemotherapy with platinum and taxane, the expected and threshold 1-year survival rates are assumed to be 50% and 25%, respectively, in this study. Based on this assumption, 25 subjects are needed at a one-sided significance level of 5% with a statistical power of 80%. Allowing for enrollment of dropouts and ineligible patients, a total target sample size of 30 patients is determined.

Abbreviations

CUP: cancer of unknown primary site; MST: median survival time; PSA: Prostate Specific Antigen; "QOL: quality of life; "PS: Performance status; AST: Aspartate transaminase; ALT: alanine aminotransferase; ULN: upper limit of normal; CTCAE: Common Terminology Criteria for Adverse Events

Conflicts of Interest

Dr. Seki reports personal fees from Taiho Pharmaceutical during the conduct of the study; personal fees from Chugai Pharma, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Lilly Japan, personal fees from Daiichi Sankyo, personal fees from Ono Pharmaceutical, personal fees from

Daichi Sankyo, personal fees from Ono Pharmaceutical, personal fees from Bristol-Myers Squibb, personal fees from MSD Oncology, personal fees from Nihon Medi-Physics outside the submitted work.

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