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Original Article

Site-specific Chemotherapy Based on Predicted Primary Site by Pathological Profile for Carcinoma of Unknown Primary Site

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Abstract

Aims: Although platinum-based combination chemotherapies are commonly used for unfavourable subsets of cancer of unknown primary (CUP), the prognosis remains poor. Several studies have suggested that gene expression profiling or immunohistochemistry was useful for the prediction of primary sites in CUP, and site-specific therapy based on predicted primary sites might improve overall outcomes. In Japan, to identify primary sites, immunohistochemical tests were commonly used for CUP in clinical practice. However, it is unclear whether site-specific therapy based on predicted primary sites by pathological examination contributes survival benefit for unfavourable CUP subsets.

Patients and methods: In this study, 122 patients with unfavourable subsets of CUP were retrospectively reviewed. Ninety patients assigned to cohort A after July 2012 had received chemotherapy according to predicted primary sites; 32 patients assigned to cohort B before June 2012 had received platinum-based empiric chemotherapy.

Results: In cohort A, 56 patients (62.2%) with predicted primary sites by pathological examination received site-specific therapy; 34 patients (37.8%) with unpredictable primary sites received platinum-based empiric chemotherapy, the same as cohort B. The median overall survival was 20.3 months in patients with predictable primary sites in cohort A and 10.7 months in those of cohort B, with a significant difference between these cohorts ($P = 0.03$, adjusted hazard ratio = 0.57, 95% confidence interval 0.34–0.94).

Conclusion: Site-specific therapy based on predicted primary sites by pathological examination could improve prognosis in patients with an unfavourable subset of CUP.

Key words: Carcinoma of unknown primary site; immunohistochemistry; site-specific therapy

Introduction

Carcinoma of unknown primary site (CUP) accounts for about 3–5% of all adult malignancies [1]. CUP is a heterogeneous group with metastatic disease for which the site of origin cannot be identified at the time of diagnosis despite careful clinical and laboratory examinations [2]. About 20% of patients with CUP are categorised as favourable subsets with specific therapies based on clinical characteristics, disease distribution and histology. However, the remaining 80% of patients belong to unfavourable subsets, which are empirically treated with platinum-based chemotherapy [3]. For these unfavourable subsets, immunohistochemistry (IHC) to predict primary sites and several combination therapies have been evaluated and investigated over the past two decades, but prognosis remains poor [4–7].

Recently, gene expression profiling (GEP) has been reported to be a promising diagnostic method for predicting primary sites and subsequent site-specific therapy may improve overall outcomes [8–12]. Regardless of primary sites, CUP have biological properties with rapid progression and dissemination. Current research involves the application of GEP to CUP and individualised therapies for

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predicted site-of-origin by GEP have become reasonable. Moreover, in Japan, traditional IHC is mainly used for diagnosing CUP with GEP, being rarely used in clinical practice because of cost containment and cost-effectiveness.

Therefore, this retrospective study aimed to evaluate the clinical significance of site-specific therapy based on pathological diagnosis and clinical features by comparing with platinum-based empiric therapy without consideration of primary sites.

Patients and Methods

Study Population

Between January 2010 and January 2016, we retrospectively reviewed 160 consecutive patients diagnosed as CUP at Aichi Cancer Center Hospital after standard examinations: medical history, physical examination, laboratory studies including tumour markers consisting of cancer antigen (CA) 125 and 15-3 in women, prostate-specific antigen (PSA) in men, beta-human chronic gonadotropin and α-fetoprotein, computed tomographic scan or positron emission tomography of thorax, abdomen and pelvis, mammography in women, gastrointestinal endoscopy and urinary cytology. Additional diagnostic examinations were carried out if clinically indicated. A core needle biopsy or an open biopsy before chemotherapy was carried out for all patients for diagnosis. Patients enrolled in this study fulfilled the following eligibility criteria: histologically proven metastatic carcinoma; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate organ function; received chemotherapy as first-line treatment. Patients classified in the favourable subsets were excluded from this study; women with axillary lymph node metastasis; women with elevation of serum CA 125 levels with peritoneal metastasis; men with elevation of serum PSA levels, suspected of extra gonadal germ cell tumours with elevation of serum α-fetoprotein, human chronic gonadotropin; and squamous carcinoma limited to cervical, supraclavicular, inguinal lymph node [13]. Eligible patients were divided into two cohorts according to different treatment strategies at July 2012 to evaluate the impact of site-specific therapy: patients who received first-line chemotherapy based on pathological examination, including IHC tests and gene analysis, after July 2012 were assigned to cohort A, whereas patients before June 2012 who received platinum-based empiric chemotherapy without consideration of pathological examination were assigned to cohort B (Figure 1). This study was approved by the institutional review board of Aichi Cancer Center Hospital.

Pathological Evaluation

The diagnostic evaluation was pathological review of biopsy specimens by haematoxylin–eosin and IHC. Pathologists examined the appearance, shape, morphological and histological features of tumour cells. They were classified as adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma and carcinoma based on the microscopic appearance of the tumour biopsy.

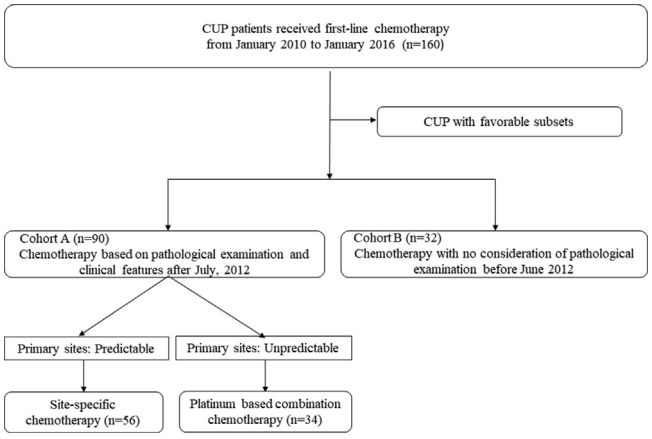

Fig 1. Study population. CUP, carcinoma of unknown primary.

Formalin-fixed paraffin-embedded tissue samples were used for IHC. Several organ-specific IHC markers, such as thyroid transcription factor-1 (TTF-1), calretinin, D2-40, Wilms tumour-1, mammaglobin, GATA-3, oestrogen receptor (ER), progesterone receptor, hepatocyte nuclear factor 4 alfa, CDX2, paired box gene 8, renal cell carcinoma, CD10, PSA, prostate-specific membrane antigen, Nkx3-1, p16, p40, chromogranin, synaptophysin and CD56 in addition to conventional antibodies (CK7 or CK20) were used after histopathological examination to predict primary sites, as shown in Figure 2 [14–18], which was mainly used after July 2012. In addition to IHC tests, gene analysis, such as HER2 gene amplification [19], KRAS gene mutation [20] and oncogenic point mutation in EGFR [21], was used for differential diagnosis in the patients of cohort A.

Evaluation of Metastatic Lymph Nodes on Computed Tomography

Computed tomography was carried out from pelvic to neck for all patients. Especially for patients with predicted primary sites in cohort A, we mainly assessed the dominant lymph nodes, which were considered metastatic if they were larger than 10 mm in short-axis diameter on computed tomography scan, to confirm whether the location of metastatic lymph nodes was compatible with the predicted primary sites based on pathological examination including IHC tests.

Statistical Analysis

Overall survival was defined as the time from the start of first-line chemotherapy to death from any cause or last follow-up. Overall survival was calculated using the Kaplan–Meier method and compared with the Log-rank test. Multivariate analyses were carried out using the Cox proportional hazards model to adjust for baseline covariates, including four prognostic significant factors evident

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