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A phase II trial of irinotecan in patients with advanced or recurrent endometrial cancer and correlation with biomarker analysis

Shin Nishio [a,*], Mototsugu Shimokawa [b], Kazuto Tasaki [a], Hiroki Nasu [a], Teruyuki Yoshimitsu [a], Ken Matsukuma [a], Atsumu Terada [a], Naotake Tsuda [a], Kouichiro Kawano [a], Kimio Ushijima [a]

[a] Department of Obstetrics and Gynecology, Kurume University School of Medicine, Japan
[b] Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan

HIGHLIGHTS

- CPT-11 has a clinically significant response rate for endometrial cancer.
- Clinical benefits and overall survival make it a promising treatment.
- Adverse events are manageable and do not compromise treatment administration.

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ABSTRACT

Objective. Chemotherapy for advanced or recurrent endometrial cancer requires further development. Irinotecan hydrochloride (CPT-11) suppresses tumor growth in several endometrial cancer strains. The present study evaluated the anti-tumor activity and toxicity of CPT-11 in patients with advanced or recurrent endometrial cancer.

Methods. Enrolled patients had advanced endometrial cancer with measurable lesions and received 2 pretreatment regimens. A 90-minute intravenous infusion of CPT-11 (100 mg/m^2) was given on days 1, 8, and 15 of a 4-week cycle, aiming for an effect with ≤2 cycles. Treatment was continued until the primary disease worsened or severe toxicity occurred. The primary endpoint was response rate, and the secondary endpoints were progression-free survival, overall survival, and adverse events. Antitumor effect and adverse events were evaluated according to RECIST version 1.1 and NCI-CTC AE version 3.0, respectively.

Results. Twenty-two patients were registered (11 endometrioid carcinomas and 11 serous carcinomas). The median duration of the treatment-free interval (TFI) was 7.5 months, and the median number of administered cycles per patient was 4. Response rate was 36.4% (complete response: 1 patient, partial response: 7 patients). Clinical benefit rate, including stable disease, was 77.3%. Median progression-free and overall survival was 4.4 and 18.4 months, respectively. Observed adverse events included grade 4 hematotoxicity (neutropenia and thrombocytopenia), and grade 2 or 3 non-hematotoxicity (diarrhea). All adverse events were manageable. Biomarker predictors of therapeutic effectiveness were not observed.

Conclusion. As a single agent, CPT-11 has anti-tumor activity for advanced or recurrent endometrial cancer and has manageable adverse events.

1. Introduction

Endometrial cancer occurs mainly in post-menopausal women between 50 and 60 years of age [1], and its most common form is the most prevalent gynecological cancer, ranking 4th among cancers in women and 8th in terms of age-adjusted mortality [2]. According to the GLOBOCAN 2012 database, the worldwide annual incidence of new cases of uterine corpus cancer was 319,600, with 167,900 cases occurring in developed countries and 151,700 cases in developing countries [3].

The treatment of endometrial cancer depends on the histologic characteristics, disease grade, and stage. While most cases of endometrial cancer present at an early stage and can usually be cured by surgery with or without adjuvant radiotherapy [4] in patients who present with advanced or recurrent endometrial cancer, the long-term prognosis is poor, as most available treatments produce only modest, short-

* Corresponding author at: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan.
E-mail address: shinshin@med.kurume-u.ac.jp (S. Nishio).

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lived responses [5]. In previous prospective randomized trials, chemotherapy was found to be the only adjuvant treatment that improved survival [6–8]. It is therefore of crucial importance to develop new chemotherapy options to improve the outcomes of patients with advanced or recurrent endometrial cancer. The response rate of single-agent chemotherapy in patients with endometrial cancer ranges between 4% and 27% [9–19].

Irinotecan hydrochloride (CPT-11) is an anticancer drug developed in Japan that acts as a topoisomerase I inhibitor. CPT-11 has been shown to be an effective treatment for a variety of solid tumors resistant to other cytotoxic agents [20]. In vitro, CPT-11 was effective against 4 endometrial cancer cell strains [21], with sensitivity differences among tumor histological subtypes [22].

Although phase II clinical trials of other topoisomerase I inhibitors, such as nogitecan hydrochloride (topotecan), have been performed in patients with endometrial cancer [13, 23], there are currently no phase II clinical trials assessing the anti-tumor activity and safety of CPT-11 as a single agent for the treatment of advanced or recurrent endometrial cancer. Its demonstrated efficacy in vitro [21], which is considered 75% accurate as a predictor of clinical efficacy [22], as well as its effects on other gynecological cancers [24], make CPT-11 a promising candidate for single-agent chemotherapy in patients with advanced or recurrent endometrial cancer.

We report the results of a phase II clinical trial investigating for the first time the efficacy of CPT-11 as a single chemotherapy agent in patients with advanced or recurrent endometrial cancer.

2. Patients and methods

This study was approved by the Kurume University Ethics Committee and was registered at the University Hospital Medical Information Network (UMIN) (protocol number: UMIN00017097). All patients signed an informed consent form to participate in the clinical trial.

2.1. Eligibility

Eligible patients had advanced, recurrent uterine cancer, as confirmed by endometrial biopsy or surgical histopathology, with measurable lesions; a previous treatment history including no >2 regimens, for which at least 4 weeks had elapsed since the administration of chemotherapy and radiotherapy (or no effect had been seen), and at least 2 weeks had elapsed since the administration of an antimetabolite, hormone, or immunotherapy (or no effect had been seen); an age of at least 20 years; a performance status (ECOG) ranging between 0 and 2; they had undergone had a previous imaging study no >28 days; an expected survival of at least 3 months; adequate bone marrow, liver, and kidney functions 1 week before registration, as based on the following variables: neutrophil count ≥1500/mm^3, thrombocyte level 100,000/mm^3, hemoglobin level ≥9 g/dl, total bilirubin ≤1.5 mg/dl, AST and ALT ≤2.5 times the upper limit of the reference range, and serum creatinine within the reference range.

Patients were excluded from the study if they had one or more of the following conditions: sarcoma or carcinosarcoma; previous treatment with topoisomerase I inhibitors; impaired liver or kidney function; hypersensitivity to the drug; multiple active cancers; a diagnosis or suspected diagnosis of clinically problematic infectious diseases; poorly controlled hypertension or diabetes or clinically significant electrocardiographic abnormalities; clinically relevant heart disease; severe pulmonary disease (interstitial lung disease, lung fibrosis, advanced emphysema, etc.); a previous history of clinically relevant mental disorder, central nervous system damage, or cerebrovascular neuropathy; fresh bleeding of the gastrointestinal tract, paresis of the intestine, intestinal obstruction, peptic ulcer, or diarrhea; pleural effusion, ascites, or pericardial fluid requiring removal; or evidence or suspected evidence of brain metastasis. Patients were also excluded if they were receiving atazanavir sulfate or continuous systemic administration (oral or intravenous) of steroids, or if they were or intended to be pregnant or breastfeeding. Any other patients for whom the principal investigator judged the study treatment to be inappropriate were also excluded.

2.2. Study design and treatment plan

The treatment was administered in cycles of 28 days, where 100 mg/m^2 of irinotecan hydrochloride, diluted in 500 ml of saline, 5% glucose solution, or another electrolyte solution, was administered on days 1, 8, and 15 of a 4-week cycle. The treatment was administered as an intravenous drip infusion over the course of 90 min. Concomitant supportive therapy consisted of 5-HT$_3$ (antiemetic) administration.

While the goal was to achieve a result with no >2 cycles per patient, the treatment was continued until a response was achieved, unless there was a worsening of the primary disease, severe adverse events, refusal by the patient, or a decision to terminate by the attending physician.

2.3. Management of toxicity

The treatment dose was reduced on the occurrence of any grade 3 or higher adverse events, excluding nausea/vomiting, hair loss, loss of appetite, and fatigue. The dose was reduced when the first course of treatment was delayed for >8 days because of toxicity. If any adverse effects occurring in the previous treatment course met the dose reduction criteria, the current course was started at a reduced dose. If the reduced dose did not satisfy the criteria to start subsequent treatment courses, treatment was postponed until confirmation of recovery. Dose reduction was limited to two times, each of which represented a reduction of 20 mg/m^2.

Treatment was discontinued if one or more of the following criteria were met: the primary disease was exacerbated after the onset of treatment; grade 4 nonhematologic toxicity occurred; there were toxicity symptoms that did not resolve after two dose reductions; there were adverse effects that required postponing the treatment for >2 weeks; the attending physician determined that treatment should be discontinued owing to the occurrence of adverse effects.

Treatment was also discontinued at the patients' request because of adverse effects (this information was registered and considered in the study's results) or personal reasons such as relocation, and if the patient was excluded from the study because of reasons such as disease exacerbation between registration and beginning of treatment, protocol violation, changes in the pathological diagnosis, or if the attending physician considered treatment continuation impossible or inadequate.

Given that genetic polymorphisms of uridine diphosphoglucuronate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1), are associated with an increased risk of CPT-11-related adverse events [25], gene polymorphism tests were performed.

The *UGT1A1* genotypes *6 and *28, known to be associated with irinotecan-induced neutropenia [26, 27], were evaluated by genotyping in all registered patients. Patients were divided into three genotype groups: wild-type (wt/wt), heterozygous (*6/wt, *28/wt), and homozygous (*6/*6, *28/*28, *6/*28).

2.4. Immunohistochemistry

As predictors of CPT-11 efficacy, the biomarkers estrogen receptor (ER) and progesterone receptor (PR), topoisomerase 1 (TOPO1), excision repair cross-complementation group 1 (ERCC1) and group 2 (ERCC2), and X-ray repair cross-complementing group 1 (XRCC1) were immunohistochemically investigated in tumor samples as described previously [28, 29].

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