UGT1A1 Polymorphism has a Prognostic Effect in Patients with Stage Ib or II Uterine Cervical Cancer and one or no Metastatic Pelvic Nodes Receiving Irinotecan Chemotherapy

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Hideki Matsuoka, Ryusuke Murakami, Kaoru Abiko, Ken Yamaguchi, Akihito Horie, Junzo Hamanishi, Tsukasa Baba, Masaki Mandai

Hideki Matsuoka
Kyoto Daigaku Igakubu Fuzoku Byoin

Ryusuke Murakami
Shiga General Hospital

Kaoru Abiko
Kyoto Daigaku Igakubu Fuzoku Byoin

Ken Yamaguchi
Kyoto Daigaku Rigaku Kenkyuka Rigakubu

Akihito Horie
Kyoto Daigaku Igakubu Fuzoku Byoin

Junzo Hamanishi
Kyoto Daigaku Igakubu Fuzoku Byoin

Tsukasa Baba
Iwate Ika Daigaku Fuzoku Byoin

Masaki Mandai
Kyoto Daigaku Igakubu Fuzoku Byoin
Prescreen

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Abstract

**Background** UGT1A1 is a predictive biomarker for the side-effects of irinotecan; irinotecan chemotherapy reduces the volume of tumors harboring UGT1A1 polymorphisms. We aimed to determine whether UGT1A1 polymorphisms can predict progression-free survival in patients with local cervical cancer treated with irinotecan.

**Methods** We retrospectively analyzed the data of 52 patients with cervical cancer treated at a single institution between 2010 and 2015. All patients were diagnosed with stage IB1, IB2, IIA, or IIB squamous cell carcinoma, underwent radical hysterectomy, and received irinotecan chemotherapy as neoadjuvant and/or adjuvant treatment. All patients were examined using UGT1A1 tests for measuring side-effects of irinotecan. Conditional inference tree and survival analyses were performed considering stage, age, UGT1A1 status, and the number of metastatic lymph nodes, to determine primary factors related to progression-free survival.

**Results** The tree-structured survival model determined high recurrence-risk factors related to progression-free survival. The most relevant factor was ≥ 2 metastatic lymph nodes (p = 0.003). The second most relevant was UGT1A1 genotype (p = 0.026). Among patients with ≤ 1 metastatic lymph node, those with UGT1A1 polymorphisms benefited from irinotecan chemotherapy and demonstrated significantly longer progression-free survival (p = 0.025) than those with wild-type UGT1A1.

**Conclusion** Irinotecan chemotherapy has the potential to benefit patients with cervical cancer, UGT1A1 polymorphism, and ≤ 1 metastatic lymph nodes.

Introduction

In 2018, cervical cancer caused approximately 311,000 deaths worldwide and was the fourth leading cause of cancer-related death in women [1]. Among women younger than 40 years, it is the second most common cancer and the third deadliest [2]. In Japan, 2,900 women die from cervical cancer every year, and the mortality of cervical cancer is increasing due to insufficient promotion of HPV vaccination and low rates of cancer screening [3]. It is important to decrease the morbidity and mortality of cervical cancer. In the Japan Society of Obstetrics and Gynecology’s annual patient report for 2015, the 5-year survival rates of the patients with stage I, II, III, and IV cervical cancer were 92.1%, 74.2%, 52.0%, and 29.8%, respectively [4].

The National Comprehensive Cancer Network guideline and the Japan Society of Gynecologic Oncology guidelines recommend concurrent chemoradiotherapy (CCRT) as adjuvant therapy for cervical cancer patients at high risk of recurrence after surgery [5, 6]. However, in Japan, adjuvant chemotherapy for local cervical cancer following radical hysterectomy is performed in about 13% of cervical cancer patients because of the severe adverse effects of adjuvant radiotherapy [3, 4]. Jung et al. reported that stage IB-IIA cervical cancer can benefit from adjuvant chemotherapy after radical hysterectomy, with fewer long-term complications and non-inferior therapeutic effect to adjuvant radiotherapy [7]. Matsuo et al. reported that postoperative systematic chemotherapy and CCRT have similar survival outcomes for clinical stage IB-IIB cervical cancer patients who undergo radical hysterectomy and are diagnosed with lymph node metastasis by histopathological findings. Chemotherapy is independently associated with lower rates of distant recurrence, but higher rates of local recurrence compared to CCRT [8]. Takekuma et al. reported that chemotherapy after surgery for high-risk patients had similar efficacy and a different toxicity profile from that of CCRT, associated with worse toxicity than chemotherapy [9]. In Japan, phase II trials have been conducted to determine the efficacy and toxicity of neoadjuvant chemotherapy (NAC) with irinotecan (CPT-11) and nedaplatin (NDP) followed by radical hysterectomy and adjuvant chemotherapy for locally advanced, bulky stage IB2-IIB cervical cancer [10–13]. Postoperative chemotherapy with irinotecan (CPT-11) and nedaplatin (NDP) without radiotherapy was also found to be very effective in high-risk patients with node-positive cervical cancer [14]. Abou-Taleb et al. reported that the CPT-11/NDP regimen shows favorable prognostic outcome and lower toxicities compared with CCRT [15]. In our institute, chemotherapy has mainly been used for adjuvant treatment when complete resection of the
cervical tumor is considered to have been achieved, even if high recurrence-risk factors are observed in postoperative pathological findings. We also administer chemotherapy using CPT-11 plus NDP for stage IB and II squamous cell carcinoma (SCC) of the uterine cervix.

In daily clinical practice, UGT1A1 genotyping is performed before treatment to estimate the degree of side-effects from CPT-11. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) glucuronidates an active metabolite of irinotecan, SN-38. UGT1A1 protein glucuronidates SN-38 more so than the other isoforms. Furthermore, UGT1A1 genotypes affect the pharmacokinetics of SN-38 and its associated toxicity [16]. Patients with UGT1A1 polymorphisms exhibit significantly higher response rates to NAC than those with wild-type UGT1A1 (79.5% vs. 49.5%, p < 0.05), suggesting that UGT1A1 may also serve as a highly potent marker for predicting the efficacy of NAC [17]. Therefore, we determined the influence of UGT1A1 polymorphism on the prognosis, specifically progression-free survival (PFS), of local cervical cancer patients treated with CPT-11/NDP, including in patients at high risk for recurrence. We also determined whether CPT-11/NDP was more effective as adjuvant chemotherapy in patients with UGT1A1 polymorphism by further stratification of patient risk factors.

**Methods**

**Patient registration**

Figure 1 shows the patient selection process. In total, 141 patients with stage IB-IIB uterine cervical cancer were treated at our hospital from 2010 to 2015. Forty-one patients treated with CCRT or surgery alone and 25 patients with histology other than SCC were excluded. We excluded three patients because they received chemotherapy other than CPT-11/NDP. We excluded 16 patients without a UGT1A1 test, three patients who refused adjuvant chemotherapy, and one patient who had positive margins in the resected tissue and was subsequently treated with CCRT as adjuvant treatment. The CPT-11/NDP regimen as neoadjuvant and/or adjuvant chemotherapy was used for all remaining patients (n = 52) due to patient risk factors. We included these 52 patients in further analyses in order to examine the relationship between the effectiveness of CPT-11/NDP and UGT1A1 genotype.

This retrospective study was approved by the institutional review board (approval number G531), and the requirement to obtain informed consent was waived; however, general written informed consent was obtained.

**Primary treatments**

Clinical staging was performed by internal examination before initial treatment. Lymph node metastasis was determined by postoperative histopathological diagnosis of surgical specimens. All patients underwent radical hysterectomy and received systematic pelvic lymphadenectomy. Patients with stage IIB (n = 26), IIA2 (n = 1), IB2 (n = 11), and IB1 (n = 1) disease with bulky tumors greater than 3.5 cm in size were also treated with neoadjuvant chemotherapy (n = 39, 75%). When intraoperative rapid diagnosis revealed pelvic lymph node metastasis, patients also received para-aortic lymphadenectomy.

The CPT-11/NDP regimen as NAC comprised intravenous administration of CPT-11 (60 mg/m²) on days 1 and 8 and NDP (80 mg/m²) on day 1 of a 21-day cycle. Two patients received one cycle of NAC and 37 patients received two cycles of NAC. The CPT-11/NDP regimen as adjuvant chemotherapy comprised CPT-11 (60 mg/m²) on days 1 and 15 and nedaplatin (60 mg/m²) on day 1 of a 28-day cycle. A total of six cycles, including NAC and adjuvant chemotherapy, was considered therapy completion. An average of 5.3 cycles of CPT-11/NDP were administered (six cycles, n = 35; five cycles, n = 8; four cycles, n = 6; three cycles, n = 1; two cycles, n = 1; and one cycle, n = 1). Only one patient received paclitaxel and carboplatin (four cycles) as adjuvant chemotherapy after 2 cycles of CPT-11/NDP as NAC due to a slight shrinkage ratio (20% decrease in tumor size).

UGT1A1 genotypes were detected from patients' blood. We divided patients into two groups: wild-type (*1/*1) and polymorphism (*1/*6, *1/*28, *6/*6, or *28/*28). For patients with heterozygotic polymorphisms (*1/*6 or *1/*28), we did not reduce the dose of CPT-11. Of four patients with homozygotic (*6/*6 and *28/*28) or compound heterozygotic (*6/*28) polymorphisms, we only reduced the dose of CPT-11 in one patient.
(50 mg/m$^2$). The other three patients received the normal dose of CPT-11 and were carefully followed. We assessed the side-effects using the Common Terminology Criteria for Adverse Events version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

**Follow-up**

All patients regularly underwent a physical examination, measurement of serum tumor markers, and imaging examinations, mainly computed tomography. Patients in this study were followed up until May 2019. The median follow up time was 60 months.

**Statistical analysis**

We analyzed the relationship between PFS and clinical variables, including age, FIGO stage I versus II, UGT1A1 genotype, and the number of metastatic lymph nodes. We used the statistical software R (version R-3.4.3, https://cran.ism.ac.jp/bin/macosx/, “The R Foundation for Statistical Computing”, Vienna, Austria). To identify the most important factors related to prognosis, conditional inference tree analysis was performed using the package “party” (https://cran.r-project.org/web/packages/party/index.html) with a univariate setting. Kaplan-Meier analysis and log-rank test were performed using the package “survival.” We used Fisher exact test for analysis of side effects. A p-value of less than 0.05 was considered statistically significant.

**Results**

**Background characteristics**

The clinical backgrounds of all 52 patients are listed in Table 1. The median patient age was 52.3 years old, and there were 24 patients with stage IB disease (46.2%; IB1: n = 13 and IB2: n = 11), two patients with stage IIA disease (3.8%; IIA1: n = 1 and IIA2: n = 1), and 26 patients with stage IIB disease (50%). Twenty-five patients (48.1%) had wild-type UGT1A1 (UGT1A1 *1/*1), 23 patients (44.2%) had a heterozygotic polymorphism (*1/*6 or *1/*28), and four patients (7.7%) had a homozygotic (three patients with *6/*6) or compound heterozygotic (one patient with *6/*28) polymorphism. Pathological findings revealed pelvic node metastasis in 12 patients (23.1%) and para-aortic node metastasis in two patients (3.8%). Age, FIGO stage, and number of metastatic lymph nodes were not different based on UGT1A1 genotype (Table 1).

| UGT1A1 | Total | UGT1A1 wild-type | UGT1A1 polymorphism (hetero/homo type) | p value |
|--------|-------|------------------|---------------------------------------|---------|
| number (%) | 52 | 25 (48.1%) | 23/4 (44.2%/7.7%) | |
| Age, years | Average (min-max) | 52.3 | 52.4 (36–64) | 52.1 (29–78) | 0.93 |
| FIGO stage | | | | |
| IB1-2 | 24 (46.2%) | 11 | 13 | 0.47 |
| IIA | 2 (3.8%) | 0 | 2 | |
| IIB | 26 (50.0%) | 14 | 12 | |
| Lymph node metastasis | None | 39 (73.1%) | 18 | 21 | 0.45 |
| Pelvic nodes | 11 (23.1%) | 5 | 6 | |
| Para-aortic nodes | 2 (3.8%) | 2 | 0 | |

Abbreviations: UGT1A1: UDP glucuronosyltransferase 1 family, polypeptide A1; FIGO: International Federation of Gynecology and Obstetrics.

**Tree-structured survival model**
We created a tree-structured survival model from our clinical variables to determine the most important factors related to PFS by univariate analysis. The primary determining prognostic factor for the risk of recurrence was two or more lymph node metastases upon pathological diagnosis (p = 0.003). The secondary stage found that UGT1A1 polymorphism led to significantly better PFS than wild-type UGT1A1 (p = 0.026) (Fig. 2). These findings suggest that a CPT-11/NDP regimen could be effective for patients with UGT1A1 polymorphism with one or no metastatic lymph nodes.

The relationship between PFS and lymph node metastasis

There was no significant difference in PFS between patients with and without lymph node metastasis (p = 0.22) (Fig. 3a). However, there was a tendency for better prognosis in patients without lymph node metastasis. Further, there was a significant difference in PFS between patients with no or one metastatic lymph node and those with more than one metastatic lymph node (p = 0.01) (Fig. 3b). Despite this limited analysis, we hypothesize that more than one metastatic lymph node might be a prognostic factor, as opposed to no or one metastatic lymph node.

The relationship between PFS and UGT1A1 genotype

There was no significant difference in PFS between patients with wild-type and polymorphic UGT1A1 (p = 0.21) (Fig. 3c). However, there was a tendency of better prognosis in patients with UGT1A1 polymorphism. When we limited analysis to patients with one or no metastatic lymph nodes, we found that patients with polymorphism had no recurrence and significantly longer PFS (p = 0.025) (Fig. 3d).

Kaplan-Meier survival curves of overall survival (OS) and PFS among clinical stages

The survival curves based on stage are shown in Fig. 4. The 3.5-year PFS rates were 92% in stage IB1 patients, 90% in stage IB2 patients, 100% in stage IIA patients, and 84% in stage IIB patients (Fig. 4a). OS curves based on stage are shown in Fig. 4b. The 3.5-year OS rates were 100% in stage IB1 patients, 100% in stage IB2 patients, 100% in stage IIA patients, and 96% in stage IIB patients.

Adverse events

We also analyzed adverse events of chemotherapy. Grade 3 and 4 neutropenia occurred in six patients with wild-type UGT1A1 (24%) and 15 patients with UGT1A1 polymorphism (55%). Neutropenia occurred significantly more frequently in patients with UGT1A1 polymorphism (p = 0.03). There was no significant difference in the incidence of other adverse events based on UGT1A1 genotype (Table 2). There was no treatment-related death.

| UGT1A1          | Wild-type (25 cases) | Polymorphism (hetero/homo, n = 23/4 cases) | p-value |
|-----------------|----------------------|--------------------------------------------|---------|
| Neutropenia     | 6                    | 15                                         | 0.03*   |
| Grade 3         | 5                    | 12                                         | 0.08    |
| Grade 4         | 1                    | 3                                          | 0.61    |
| Febrile neutropenia | 1                    | 1                                          | > 0.99  |
| Nausea (> Grade 3) | 1                    | 2                                          | > 0.99  |
| Diarrhea (> Grade 3) | 5                    | 3                                          | 0.46    |
| Anorexia (> Grade 3) | 0                    | 2                                          | 0.49    |

Discussion

This tree-structured survival model implied that patients should be stratified first by the number of metastatic
lymph nodes and second by UGT1A1 genotype to help to determine the risk of recurrence. We believe it may be valid to administer CPT-11/NDP chemotherapy for patients with one or no lymph node metastases and, secondarily, UGT1A1 polymorphism. A conditional inference tree is an effective way to determine and rank prognostic factors [18, 19].

We found that cervical cancer patients with one or no metastatic lymph nodes are less likely to experience recurrence after CPT-11/NDP therapy. It has been reported that the number of metastatic pelvic lymph nodes (≤ 3 vs. >3) is a significant prognostic factor in patients treated with radical surgery followed by postoperative CCRT. Further, no significant survival difference is observed between patients without metastasis and those with 1–3 metastatic lymph nodes [20]. Park and Bae reported that the 5-year OS rates for patients with stage IB-IIB cervical cancer and 0, 1, and ≥ 2 positive metastatic lymph nodes were 91, 80, and 47%, respectively (P = 0.006) [21]. Inoue and Morita reported that the 5-year OS rates for patients with stage IB-IIIB cervical cancer and 0, 1, 2–3, and ≥ 4 positive metastatic lymph nodes were 89, 81, 41, and 23%, respectively [22]. Sakuragi et al. reported that the cumulative 5-year OS rates for patients with 1 and ≥ 2 positive metastatic lymph nodes were 84.9 and 26.5%, respectively, with no significant difference between cumulative OS rates of patients with 0 and those with 1 positive node [23]. Therefore, ≥ 2 positive metastatic lymph nodes might be an important prognostic factor, rather than only lymph node positivity.

Chemotherapy and surgery may be useful for patients with one or no lymph node metastasis. Nevertheless, we need to consider CCRT as adjuvant therapy instead of chemotherapy alone for patients with two or more lymph node metastases. We consider that stratification of treatment based on the number of the lymph node metastases is preferable.

In patients who have radiation history, chemotherapy is the only course of treatment recommended when local recurrence is found in the vicinity of the pelvic cavity. We believe that secondary surgery or radiation therapy should be administered for local recurrence if patients have no history of radiation [11]. There are some arguments in support of chemotherapy or CCRT as initial adjuvant treatment after radical hysterectomy; however, the research is inconclusive. We also believe that consolidation chemotherapy might lead to a better prognosis for patients with locally advanced cervical cancer if they were initially treated with CCRT [24].

This study implied that the UGT1A1 polymorphism may also stratify patients and act as a predictive prognostic factor for the efficacy of CPT-11/NDP for cervical cancer patients. The UGT1A1 genotype has previously been implicated as a prognostic marker for CPT-11 therapy in colorectal cancer [25]. Some controversial studies have suggested a limited survival benefit in patients who were UGT1A1-poor metabolizers due to UGT1A1 polymorphisms [26, 27], although this association has been inconsistently reported [28].

In our study, about 50% of patients treated by chemotherapy experienced grade 3 or higher neutropenia, and 10% of patients experienced diarrhea and vomiting. Neutropenia and diarrhea are common adverse effects of CPT-11. The UGT1A1 genotype is known to be a useful predictor for adverse effects [29]. In our study, we divided patients into a wild-type group and a polymorphism group (*1/*6, *1/*28, *6/*6, *28/*28, and *6/*28), including a few patients with homozygotic or compound heterozygotic polymorphism (5.7% and 1.9%, respectively).

Patients with UGT1A1 polymorphisms tended to experience grade 3 or 4 neutropenia more frequently than patients with wild-type UGT1A1 (p = 0.03). This finding is consistent with reports that patients with UGT1A1 homozygotic (*6/*6 or *28/*28) and compound heterozygotic (*6/*28) polymorphisms tend to experience adverse effects of CPT-11[16, 30].

Our retrospective analysis revealed there was a significant difference in PFS between the UGT1A1 wild-type and polymorphism groups when we analyzed only patients with one or no lymph node metastases. Although we recommend CPT-11/NDP to patients with one or no lymph node metastases and UGT1A1 polymorphism, our data do not recommend this regimen to other patients. Nevertheless, we did not compare the efficacy and adverse effects of CPT-11/NDP to those of CCRT or other regimens, including paclitaxel/carboplatin or paclitaxel/cisplatin. Therefore, we should conduct a prospective study to test the more favorable prognostic effect of the CPT-11/NDP regimen for UGT1A1 polymorphism group compared to wild-type group in cervical cancer patients with one or no lymph node metastases after radical hysterectomy.
In conclusion, CPT-11/NDP may benefit patients with no or one metastatic lymph nodes and UGT1A1 polymorphism.

**Declarations**

**Ethics approval and consent to participate**

This retrospective study was approved by the institutional review board (approval number G531), and the requirement to obtain informed consent was waived; however, general written informed consent was obtained.

**Consent for publication**

Not applicable

**Availability of data and material**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Conception: T.B. ; Design of the work ; R.M. ; The acquisition and analysis ; H.M. and R.M.; Interpretation of data ; H.M. and R.M.; Writing - Drafting the work or substantively revising it: K.Y., K.A., A.H., J.H., T.B. and M.M.

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Figure 1

Stage IB–IIB cervical cancer (141 patients)

Surgery following chemotherapy (100 patients)

Histopathology: SCC (75 patients)

Exclusions:
- CCRT of RH alone
- Adenocarcinoma
- Small cell carcinoma
- Carcinosarcoma
- Glassy cell carcinoma

Other criteria:
- UGT1A1 testing
- Refused adjuvant CRT
Criteria for analysis: CPT-11/NDP for NAC and/or adjuvant therapy, UGT1A1 test examined (52 patients)

Figure 1

Patient selection process. CCRT: concurrent chemoradiotherapy; RT: radiotherapy; RH: radical hysterectomy; SCC: squamous cell carcinoma; CPT-11: irinotecan; NDP: nedaplatin; NAC: neoadjuvant chemotherapy; UGT1A1: uridine diphosphate glucuronosyltransferase 1A1
Figure 2

Tree-structured survival model. More than one metastatic lymph node was a primary determining prognostic factor (p value = 0.003). UGT1A1 polymorphism was a secondary determining high-risk factor for recurrence (p value = 0.026). PFS: progression-free survival; meta: metastasis; UTG1A1: uridine diphosphate glucuronosyltransferase 1A1; p < 0.05 *
Progression-free survival (PFS) in cervical carcinoma patients based on (a) lymph node metastasis (p = 0.22), (b) number of lymph node metastases (p = 0.01), (c) UGT1A1 genotype (p = 0.21), and (d) UGT1A1 genotype in patients with ≤1 metastatic lymph node (p = 0.025). UGT1A1: uridine diphosphate glucuronosyltransferase 1A1; p < 0.05 *
Figure 4
Survival in cervical cancer patients based on stage. (a) Progression-free survival (PFS) and (b) overall survival (OS).