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Safety and Anti-tumor Effects of Docetaxel Plus Cisplatin in Intermediate- and High-risk Endometrial Cancer

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Safety and Anti-tumor Effects of Docetaxel Plus Cisplatin in Intermediate- and High-risk Endometrial Cancer

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Abstract. *Background: Endometrial cancer (EC) has a poor prognosis due to drug resistance. Patients and Methods: We evaluated the safety and efficacy of adjuvant combination chemotherapy with docetaxel plus cisplatin ((DP) docetaxel, 70 mg/m^2; cisplatin, 60 mg/m^2; every 28 days) in EC patients at intermediate-risk (IR) or high-risk (HR) for recurrence. Results: Sixty-four patients diagnosed with EC were enrolled. Stage-I, -II, -III and -IV disease was noted in 23, 7, 28 and 6 patients, respectively. Histopathological analyses revealed that 56, 3, 1 and 4 patients had endometrioid, serous, clear-cell or "other" types of carcinoma. Grade-3/4 hematologic toxicities were found at 80% and 95% in patients in IR and HR groups, respectively. In IR and HR groups, mean progression-free (PFS) survival was 69.5 and 29.5, while overall survival (OS) was 59.6 and 47.5 months, respectively. Conclusion: DP may be clinically safe and useful treatment for EC.*

In 2013, the number of patients with newly diagnosed endometrial cancer (EC) was 49,560 and the annual number of deaths due to EC was 8,190 (1). The annual report of the International Federation of Gynecology and Obstetrics (FIGO) in 2013 revealed that (based on the FIGO classification from 1988) 26,5313, 973, 1048 and 255 patients had Stage-I, -II, -III and -IV EC and that overall survival (OS) at 5 years was 90%, 78%, 62% and 21%, respectively (2). Accordingly, advanced EC has been recognized as carrying a poor prognosis.

Histology reveals that EC comprises four types: "endometrioid", "serous", "clear-cell carcinoma" and "other". The prognosis of endometrial cancer is dependent upon histological subtypes and clinical characteristics (clinical stage, metastatic lesions). Risk of recurrence is divided into three categories (low, intermediate, high) according to these prognostic factors (3); EC treatment is initiated according to these three categories.

Primary treatment of EC is surgery: a hysterectomy and bilateral salpingo-oophorectomy with/without dissection of pelvic and para-aortic lymph nodes. Postoperatively, patients are treated with chemotherapy regimens (platinum-containing compounds, taxanes) dependent upon recurrence risk (4). However, whether cisplatin or carboplatin and paclitaxel or docetaxel should be combined is not known.

To ascertain the safety and efficacy of anticancer agents in patients with intermediate-risk (IR) or high-risk (HR) EC, we undertook adjuvant chemotherapy with docetaxel and cisplatin (DP).

Patients and Methods

Patients. This retrospective investigation assessed 184 patients with newly-diagnosed EC between 2005 and 2012. Patients underwent peritoneal washing, a total hysterectomy, radical hysterectomy, bilateral salpingo-oophorectomy or pelvic lymphadenectomy and dissection of para-aortic lymph nodes for EC. We reclassified 184 patients according to guidelines for EC set by the FIGO in 2008. Risk of EC recurrence was based on 2013 guidelines set by the Japan Society of Gynecologic Oncology (JSGO). Patients with uterine sarcoma were excluded from our study.

Criteria for inclusion into groups. Criteria for inclusion into the IR group were: (i) endometrioid adenocarcinoma G1 or G2 and ≥50% myometrial invasion; (ii) endometrioid adenocarcinoma G3 and ≤50% myometrial invasion; (iii) serous adenocarcinoma or clear-cell adenocarcinoma and no myometrial invasion; (iv) no cervical invasion; (v) venous or lymphatic invasion; (vi) no distant metastasis.

Criteria for inclusion into the HR group were: (i) endometrioid adenocarcinoma G3 and ≥50% myometrial invasion; (ii) serous adenocarcinoma or clear-cell adenocarcinoma and myometrial invasion; (iii) spread to uterine adnexae, serosa or the cardinal ligament; (iv) cervical invasion; (v) invasion of the vaginal wall; (vi) metastasis into pelvic or para-aortic lymph nodes; (vii) vesical or rectal invasion; (viii) peritoneal dissemination; (ix) distant metastasis.

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Key Words: Endometrial cancer, safety, efficacy, docetaxel, cisplatin.

Treatment schedule. Patients received DP (docetaxel, 70 mg/m^2; cisplatin, 60 mg/m^2) every 28 days. Treatment was continued until disease progression or treatment completion. Treatment in the IR group was three cycles and six cycles in the HR group. Study treatment was delayed if any of the following were encountered on the scheduled day of administration or previous day: neutrophil count <1,500/mm^3; platelet count <75,000/mm^3; aspartate aminotransferase >100 IU/l; alanine aminotransferase >100 IU/l; total bilirubin >1.5 mg/dl; serum creatinine >1.50 mg/dl; grade-3 or grade-4 peripheral neuropathy; proteinuria grade ≥2; hemorrhage; stomatitis; fatigue and/or diarrhea.

Evaluation of efficacy and safety. Primary endpoint was prevalence of completion of scheduled chemotherapy, progression-free survival (PFS) and OS. Secondary endpoints were grade 3/4 toxicity and treatment response. Toxicity was assessed according to the Common Toxicity Criteria of the National Cancer Institute v4.0 (Japanese version issued by the Japan Clinical Oncology Group).

Results

Patients' characteristics. Twenty patients were placed in the IR group and 44 in the HR group according to the risk factors for EC recurrence. Patients' characteristics are shown in Table I. Median age of the IR group was 58 (range=42-73) years and that of the HR group was 58 (range=34-78) years. All patients had an Eastern Cooperative Oncology Group performance status of zero.

In the IR group, all patients had Stage-I disease (FIGO classification 2008). In this group, according to histopathologic analyses, 4 patients had endometrioid adenocarcinoma grade 1 (Stage-IB disease), 9 patients had endometrioid adenocarcinoma grade 2 (Stage-IB disease) and 7 patients had endometrioid adenocarcinoma grade 3 (Stage-IA disease).

In the HR group, according to FIGO 2008, 3 patients had Stage-I disease, 7 patients had Stage-II disease, 28 patients had Stage-III disease and 6 patients had Stage-IV disease. In this group, according to histopathological analyses, 36 had endometrial carcinoma, 3 had serous or mucinous adenocarcinoma, 1 patient had clear-cell adenocarcinoma and 2 patients had "other" type of adenocarcinoma.

Adverse events. Table II shows the prevalence and types of adverse events. Hematologic toxic events were the main major severe adverse events in both groups. In IR and HR groups, grade 3/4 hematologic toxicities (including neutropenia) were found in 80% and 95% of subjects, respectively. Grade-3 diarrhea occurred in 2 patients (10%) in the IR group and in 2 patients (5%) in the HR group. Neuropathy or nephropathy was not observed in either group.

Treatment completion. All patients in the IR group completed DP treatment. Among the 44 patients in the HR group who received DP treatment, 39 (89%) completed the treatment. Treatment was discontinued in 5 patients at the patient's discretion (1 case) and because new lesions developed (4 cases) during DP treatment.

Table I. *Clinical characteristics of patients*.

	Intermediate-risk (n=20)	High-risk (n=44)
Age (mean [range])	58 [42-73]	58 [34-78]
Performance status (n)		
0	20	44
Histology (n)		
Endometrioid adenocarcinoma		
G1	4	15
G2	9	12
G3	7	9
Serous adenocarcinoma	0	3
Clear-cell adenocarcinoma	0	1
Mucinous adenocarcinoma	0	2
Undifferentiated carcinoma	0	1
Mixed carcinoma	0	1
Stage (n)		
Ia/Ib	8/12	1/2
II	0	7
IIIa/IIIb/IIIc	0/0/0	9/2/17
IVa/IVb	0/0	0/6

Response. PFS and OS were estimated using the Kaplan–Meier method (Figure 1A and B). In the IR and HR groups, mean PFS was 69.5 and 29.5 (log rank test, p=0.00312), whereas mean OS was 59.6 and 47.5 months (log rank test, p=0.00527), respectively.

One patient in the IR group had EC recurrence. She had metastasis in pelvic lymph nodes 13 months after the final course of DP. In her recurrent lesion, cancer cells (which were undifferentiated and produced granulocyte colony-stimulating factor) transformed into an extremely malignant phenotype.

No recurrence was found in the 3 patients with Stage-I disease in the HR group. In the HR group, 4 patients had EC recurrence during DP treatment. One patient with Stage-IIIA disease and grade-1 endometrioid adenocarcinoma discontinued treatment of her own volition; she had no new lesions at 65 months. The remaining 4 patients had EC recurrence during DP treatment. One patient (case number 1; clinical Stage-IIIA and grade-3 endometrioid adenocarcinoma) had new lesions in the peritoneal cavity and lungs after the third course of chemotherapy. One patient (case number 2; clinical Stage IIIC1 and grade-3 endometrioid adenocarcinoma) had new lesions in the peritoneal cavity after the fifth course of chemotherapy. The third case (clinical Stage IIIC2 and grade-1 endometrioid adenocarcinoma with partial grade-3 endometrioid adenocarcinoma) had a metastatic lesion in para-aortic lymph nodes after the third course of

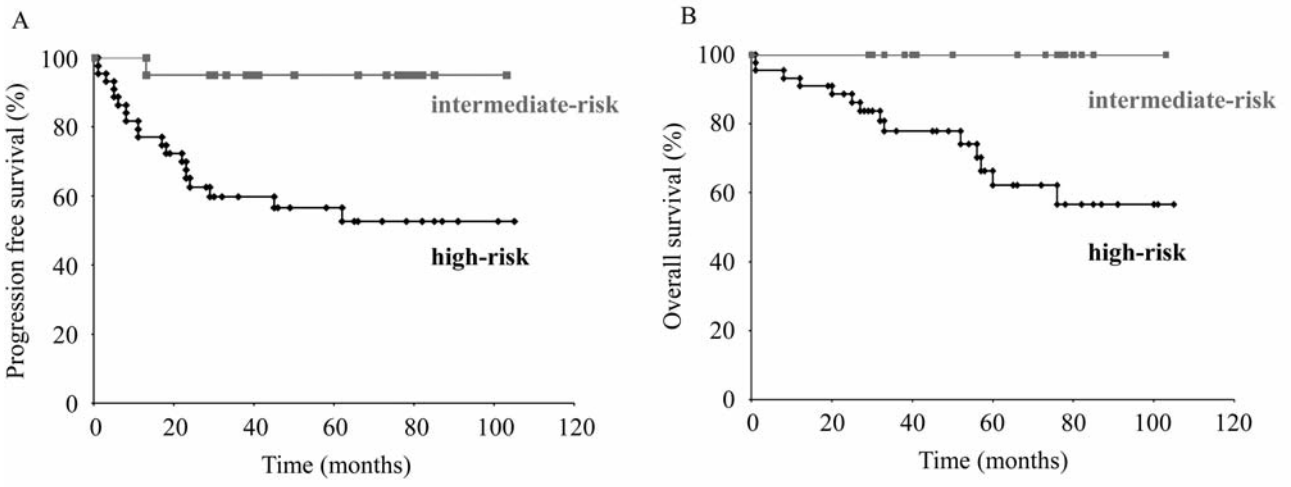

Figure 1. *Progression-free survival (A) and overall survival (B) in the two groups of intermediate-risk (gray line) and high-risk (black line). (A) The mean progression-free survival in the intermediate- and high-risk groups was 69.5 and 29.5 months, respectively (p-value for the log rank test=0.00312). (B) The mean overall survival in the intermediate- and high-risk groups was 59.6 and 47.5 months, respectively (p-value for log rank test=0.00527).*

Table II. *Adverse events.*

	Intermediate-risk (n=20)				High-risk (n=44)			
	Grade				Grade			
	1	2	3	4	1	2	3	4
Neutropenia		4	1	15		2	8	34
Aminotransferase increase		1				2		
Diarrhea			2			2	2	
Ileus						1		
Nausea	1				3			
Stomach pain					1			
Allergic reaction	1							

chemotherapy. The fourth patient (clinical Stage IIIC2 and grade-3 endometrioid adenocarcinoma) suffered recurrence with peritoneal carcinomatosis and died soon afterwards due to intestinal obstruction. In 3 patients with serous-type carcinomas, 1 patient with clear-cell carcinoma and 5 cases with other types of carcinoma, no recurrence was found even at the advanced stage.

Discussion

We investigated the efficacy and safety of DP treatment in EC patients according to the risk factors for EC recurrence set by the JSGO. Prevalence of completion of DP treatment in IR and HR groups was high. Neutropenia was the main severe adverse event (excluding fever or infectious events) in both groups. Prevalence of recurrence was 1 in 20 patients (5%) in the IR group and 4 in 44 patients (9%) in the HR group. Two large studies have focused on differences in the efficacy of chemotherapy between doxorubicin and cisplatin (AP) and doxorubicin (A) alone (5, 6). Those studies reported that the response to AP was increased significantly compared with that of A without, however, any significant difference in survival found between AP and A.

In the GOG 177 study, a combination of paclitaxel, doxorubicin and cisplatin (TAP) was compared with that of AP as adjuvant chemotherapy in 287 patients with advanced EC or recurrent EC (7). Response, OS and PFS in patients treated with TAP were improved significantly compared with those treated with AP. Thirty-nine percent of patients treated with of TAP had grade-2/3 peripheral neurotoxicity, compared

with 5% of patients who received AP. Treatment with TAP and AP was tolerated with regard to hematologic adverse events.

Sovak *et al*. reported on the efficacy of adjuvant chemotherapy using paclitaxel and carboplatin (TC) in patients who had optimal cytoreduction of Stage-III and -IV EC (8). TC treatment was well-tolerated and 3-year disease-specific survival in these patients was 56%. However, treatment was very heterogeneous: 21% of patients received external-beam radiation, 10% had vaginal brachytherapy, while the remainder underwent individualized treatment.

In a small retrospective study, Hidaka *et al*. compared patients receiving cisplatin, doxorubicin and cyclophosphamide (CAP) with those receiving TC (9). Three-year PFS and OS was 50% and 75%, respectively, in the TC group, and 38% and 50%, respectively, in the CAP group. Patients receiving TC suffered fewer toxic effects than those receiving CAP.

In the present study, DP treatment did not induce neurotoxicity or nephrotoxicity and treatment due to adverse events was not interrupted. Nevertheless, the prevalence of neutropenia was very high. Our study cohort was heterogeneous but the prognosis seemed to be favorable. A randomized study comparing treatment of AP, DP or TC for patients with advanced or recurrent EC (JGOG2043) is in progress and should provide sufficient information for EC treatment.

During the past 30 years, EC has been classified broadly into two subtypes on the basis of histologic characteristics, expression of hormone receptors and histologic grade (10). This dual classification started to become incorporated into clinical decision-making algorithms to stratify high-risk patients; however, its prognostic value is limited because ≈20% of patients with grade-1 (type-I) endometrioid adenocarcinoma relapse and ≈50% of patients with non-endometrioid (type-II) EC do not suffer recurrence (10). In addition, how 15%-20% of patients with high-grade endometrioid adenocarcinoma should be divided in this dual model is not clear (11, 12).

In the present study, 1 patient with intermediate risk for recurrence (clinical Stage IB and grade-1 endometrioid adenocarcinoma) relapsed with an extremely malignant phenotype at a distant metastatic lesion. In addition, 4 patients with grade-3 endometrioid adenocarcinoma suffered recurrence, whereas patients with specific histologic subtypes did not suffer recurrence.

Recently, it has become increasingly clear that EC comprises of a range of diseases with distinct genetic and molecular features (12-15). Development of a novel therapeutic agent for various subtypes would improve clinical outcome.

Conclusion

Our results suggest that DP is a therapeutically safe and useful regimen. Data from the present study could aid in development of novel molecular-targeted agents for EC treatment.

Conflicts of Interest

No potential conflicts of interest are disclosed.

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(This text is a combination of advice and suggestions contributed by Editors, Authors, Readers and the Managing Editor of AR).