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ORIGINAL ARTICLE

Feasibility and efficacy of intraperitoneal docetaxel administration as salvage chemotherapy for malignant gynaecological ascites

H. Tsubamoto[1], S. Takeuchi[2], K. Ito[3], Y. Miyagi[4], S. Toyoda[5], K. Inoue[1], R. Kanazawa[1], Y. Hosoda[1] & H. Shibahara[1]

Departments of Obstetrics and Gynecology,[1]Hyogo College of Medicine, Nishinomiya, [2]Iwate Medical University School of Medicine, Morioka, [3]Kansai Rosai Hospital, Amagasaki, [4]Okayama Ohfuku Clinic, Okayama, and [5]Nara Prefectural Nara Hospital, Nara, Japan

Ovarian and endometrial cancers diagnosed at advanced stages are often associated with malignant ascites. This study aimed to determine the safety, feasibility and efficacy of intraperitoneal (IP) docetaxel (TXT) for the treatment of ascites. A phase I study, including nine patients, was undertaken to determine the maximum tolerable dose. Efficacy was retrospectively assessed in 18 patients treated with 40–70 mg/m^2 IP TXT between 2005 and 2012. In a phase I study, the dose was safely escalated to a maximum of 70 mg/m^2, at which level no patients had grade ≥3 haematological adverse events. In a retrospective study of 18 patients, seven had an Eastern Cooperative Oncology Group performance status of 3; 16 had prior paclitaxel administration and two, with doses of 40 and 70 mg/m^2, experienced a serological response and a decrease in paracentesis. Thus, palliative treatment of recurrent OC should be further studied with 40 mg/m^2 among more patients, and 70 mg/m^2 could be evaluated for first-line IP chemotherapy.

Keywords: Docetaxel, endometrial cancer, intraperitoneal chemotherapy, ovarian cancer, salvage chemotherapy

Introduction

Ovarian cancer (OC) is usually diagnosed at an advanced stage, and approximately 70% of patients are diagnosed with stage III or IV disease (Jemal et al. 2010). Standard initial management involves maximal cytoreduction, followed by chemotherapy with paclitaxel plus carboplatin (TC). Although the response rate (RR) to this regimen is approximately 60–80%, 50–75% of patients with advanced OC experience recurrence. Disease that progresses within 6 months of the last dose of a platinum-containing drug is considered to be platinum-resistant. The RR of these platinum-resistant patients to chemotherapy is low, and the primary goal of treatment in this population is the maintenance of quality of life through the prevention and control of symptoms. Intraperitoneal (IP) chemotherapy is a new paradigm for drug delivery in the treatment of advanced OC in order to achieve long-term survival by controlling peritoneal disease and malignant ascites.

Malignant ascites is the most prevalent symptom in advanced or recurrent OC and causes malnutrition, malcirculation and cachexia by compression of the intestines, diaphragm and lungs. Control of peritoneal disease and ascites prolongs patient survival. In endometrial cancer (EC), prognosis is poor in patients with advanced/recurrent disease, particularly in those with type 2 histology, such as serous and clear cell carcinomas and carcinosarcomas. A recent phase III trial supported the use of TC as the standard first-line regimen for EC (Miller et al. 2012), but no standard, second-line chemotherapy regimen has been identified. The Gynecologic Oncology Group (GOG) has tested IP chemotherapy in a phase I study (personal communication).

Docetaxel (TXT), an anti-mitotic, microtubule-stabilising chemotherapy, disrupts mitosis by promoting the assembly of abnormal microtubules and suppressing the depolymerisation of microtubule bundles to free tubulin. TXT monotherapy has shown efficacy in patients with recurrent OC and EC, with RRs of 20–40% and 23%, respectively (Francis et al. 1994; Kavanagh et al. 1996; Verschraegen et al. 2000; Katsumata et al. 2005). Palliative IP chemotherapy has been used in clinical practice (Markman et al. 2003) but has not been studied extensively as first-line chemotherapy. The decreased toxicity observed with IP TXT was thought to be attributable to the lower concentration of drugs reaching systemic circulation than that reaching the abdominal cavity, with patients showing a rapid response. A phase I study of intraperitoneal docetaxel (IP TXT) in 21 patients with peritoneal carcinomatosis (four with OC and 13 with prior chemotherapy) showed that the ratio of the areas under the curve for peritoneal and plasma concentrations across dose levels 40–156 mg/m^2 was approximately 152 and that a peritoneal concentration of >0.1 μm was maintained for 30 h (Morgan et al. 2003). Testing of the pharmacokinetics and toxicity of 45 mg/m^2 IP TXT in Japanese gastric cancer patients showed that the area under the curve was 85-fold higher for peritoneal than for plasma IP TXT, and the peak concentration was 200-fold higher in the peritoneum than in the plasma (Fushida et al. 2002). Although no objective responses were noted, one patient with OC had a decreased serum carbohydrate antigen (CA125) concentration after 3 cycles of treatment.

TXT-induced cell death has been found to be concentration dependent (Morse et al. 2005), and a phase III randomised trial in patients with advanced breast cancer reported a significant relationship between objective tumour response and TXT dose over a range of 60–100 mg/m^2 every 3 weeks. The highest dose (100 mg/m^2) showed the greatest activity, as determined by RR and time to progression (Harvey et al. 2006).

To extend these findings, we enrolled Japanese patients with recurrent OC or EC in a phase I trial (KCOG-0601) to determine the maximum tolerable dose (MTD) of IP TXT. Efficacy was

Correspondence: H. Tsubamoto, Department of Obstetrics and Gynecology, Hyogo College of Medicine, Mukogawa 1-1, Nishinomiya, Hyogo 663–8501, Japan. E-mail: tsuba@hyo-med.ac.jp

assessed by a multi-institutional retrospective study of IP TXT for the treatment of gynaecological malignant ascites.

Materials and methods

The primary endpoint of the phase I study was to determine the maximum tolerable dose of intraperitoneal administration of docetaxel. A retrospective study was conducted to assess the efficacy. These prospective and retrospective studies were approved by the Kansai Clinical Oncology Group and each Institutional Review Board.

Phase I study (KCOG-0601)

A multi-institutional, open-labelled, phase I study was performed to determine the MTD of IP TXT in the palliative treatment of malignant ascites in patients with recurrent gynaecological cancer. Inclusion criteria were: histologically confirmed epithelial OC; fallopian tube cancer (FC); primary peritoneal cancer (PPC) or EC; malignant ascites with peritoneal dissemination; and a relapse <6 months after previous platinum-based chemotherapy for OC, FC and PPC or relapse after first-line chemotherapy for EC. Other inclusion criteria were: receipt of ≤ 3 previous treatment regimens without TXT; completion of prior chemotherapy administration at least 3 weeks prior to recruitment; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; age of 20–75 years; adequate bone-marrow (white blood cell count $\geq 3{,}000/mm^2$, absolute neutrophil count $\geq 1{,}500/mm^2$, platelet count $\geq 100{,}000/mm^2$ and haemoglobin >9.0 g/dl); hepatic (serum aspartate aminotransferase or alanine aminotransferase ≤ 2 times the institutional upper limit of normal and total bilirubin ≤ 1.5 mg/dl) and renal (serum creatinine ≤ 1.5 mg/dl and blood urea nitrogen $\leq$ the institutional upper limit of normal) function; life expectancy of >3 months; provision of written informed consent. Patients were excluded if they had active, uncontrollable cardiac disease; interstitial pneumonitis; active inflammatory or collagen disease; or another active malignancy.

Before IP chemotherapy, malignant ascites were removed by temporary paracentesis or a placed intraperitoneal catheter. TXT was diluted in 1000 ml normal saline and administered by drip infusion for approximately 1 h. Dose levels 1, 2 and 3 were 50 mg/m^2, 60 mg/m^2 and 70 mg/m^2, respectively, with all patients starting at level 1. Dose level 3 was the maximum intravenous dose allowed by the Pharmaceutical and Medical Devices Agency in Japan. This exploratory study to determine the MTD was conducted according to the modified Fibonacci method. The dose level was increased, unless patients had a dose-limiting toxicity (DLT) by the end of the first cycle, in which case dose escalation was discontinued. This regimen was repeated every 3 weeks until disease progression, until the occurrence of unacceptable adverse events or at the discretion of the investigator. No dose escalation was permitted in individual patients. Chemotherapy-induced toxicity was graded according to the National Cancer Institute's common toxicity criteria (NCI-CTC) version 3.0. A DLT was defined as grade 3 or 4 thrombocytopenia, grade 3 or 4 febrile neutropenia or persistent grade 4 neutropenia for more than 4 days, or grade 3 or 4 non-haematological toxicities (excluding nausea and vomiting).

Retrospective study

A multi-institutional, retrospective study was performed to assess the feasibility and efficacy of IP TXT in the palliative treatment of malignant ascites in patients with recurrent gynaecological cancer. The medical charts of patients at each institution who received IP TXT between 2005 and 2012 were reviewed.

Adverse events after IP TXT were graded according to the NCI-CTC version 3.0. Efficacy was jointly evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) v. 1.1 and the serum CA125 concentration, as per the criteria of the Gynecologic Cancer InterGroup (GCIG) (Rustin et al. 2011). If stable disease could not be radiologically confirmed at ≥ 8 weeks, the patient was diagnosed as having progressive disease. A decrease in paracentesis was defined as prolongation of the interval before paracentesis for >30 days after IP TXT administration.

Results

Phase I study (KCOG-0601)

Between May 2007 and August 2010, nine patients were treated with IP TXT according to the study protocol. Eight patients had OC and one had PPC. Eight patients had the International Federation of Gynecology and Obstetrics (FIGO) stage III, and one had stage IV. Two patients had a PS of 0, and seven had a PS of 2 at enrolment. No patient experienced DLT, and the MTD was determined to be 70 mg/m^2 (level 3), although increased rates of anaemia and abdominal pain were observed at this level (Table I).

Retrospective study

Between May 2005 and March 2012, nine patients were administered IP TXT in daily practice and nine patients were enrolled in the KCOG-0601 phase I study. Of the 18 patients, 14 had OC, two had PPC and two had endometrial serous carcinoma. In addition to the nine patients who were enrolled in the phase I portion of this study, nine patients received 40 mg/m^2 IP TXT (Table II).

No patient had grade 3 or 4 haematological toxicity or febrile neutropenia or was treated with granulocyte colony-stimulating factor (G-CSF). One patient (50 mg/m^2) experienced grade 3 ileus, and one patient (70 mg/m^2) experienced grade 3 nausea (Table III). Two of the 18 patients, one receiving 40 mg/m^2 and one receiving 70 mg/m^2, showed a serological response and control of ascites. The RR, based on GCIG criteria, was 11.1% (95% confidence interval, CI: 0–25.6%). The RR based on the GCIG criteria among patients with OC and PPC was 12.5% (95% CI: 0–28.7%). After IP TXT, 12 patients received intravenous chemotherapy and six discontinued treatment.

Table I. Toxicities during the phase I trial ($n=9$).

		Level 1	Level 2	Level 3
Dose (mg/m^2)		50	60	70
n		3	3	3
Neutropenia	≥ Grade 1	0	0	0
Thrombocytopenia	≥ Grade 1	0	0	0
Anaemia	Grade 1	0	1	1
	Grade 2	0	0	2
	≥ Grade 3	0	0	0
Abdominal pain	Grade 1	0	1	2
Constipation	Grade 2	1	0	1
Ileus	Grade 3	0	0	1
Fatigue	Grade 2	0	1	1
Nausea	Grade 2	0	1	0
	Grade 3	0	0	1
AST elevation	Grade 1	0	2	0
ALT elevation	Grade 2	0	2	0

All toxicities were graded according to the National Cancer Institute's common toxicity criteria, v. 3.0. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table II. Background characteristics of patients who received intraperitoneal (IP) docetaxel (TXT) between 2005 and 2012 ($n = 18$).

Patients (n)	18
Age (years) (median, range)	62 (48–73)
Diagnosis	
Ovarian carcinoma	
High-grade serous	8
Endometrioid	3
Clear cell carcinoma	2
Carcinosarcoma	1
Primary peritoneal cancer	2
Endometrial carcinoma	
Endometrioid	1
Serous	1
FIGO stage	
III	17
IV	1
ECOG PS at IP administration	
0	2
1	0
2	9
3	7
Number of previous regimens	
1	5
2	11
3	2
Previous history of taxan administration	
Paclitaxel	16
Docetaxel	0
Naive	2
Platinum-free interval	
<1 month	3
1–6 months	7
≥ 6 months	8
Measurable lesions (RECIST 1.1)	12
Dose of docetaxel (mg/m^2)	
40	9
50	3
60	3
70	3
Method of IP	
Temporal paracentesis	12
Catheter placement	6

Measurable lesions were assessed by computed tomography before IP administration. FIGO, the International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors v. 1.1.

Table III. Adverse events in 18 patients during the 30 days after intraperitoneal chemotherapy.

	Patients			
			≥ Grade 2	
Adverse events	Grade 2 (n)	Grade 3 (n)	n	(%)
Constipation	3	0	3	17
Fatigue	3	0	3	17
Ileus	1	1	2	11
Abdominal pain	1	0	1	6
Nausea	0	1	1	6
Vomiting	1	0	1	6
Lymphoedema	1	0	1	6
Dehydration	1	0	1	6
ALT elevation	2	0	2	11

All toxicities were graded according to the National Cancer Institute's common toxicity criteria v. 3.0. No grade 3 or 4 haematological toxicities or febrile neutropenia were noted, and no treatment with granulocyte colony-stimulating factor was administered. ALT, alanine aminotransferase.

Response to IP TXT in a case of clear cell carcinoma of the ovary

A 72-year-old patient presented with stage IIIC OC. A macroscopic residual tumour of clear cell adenocarcinoma histology persisted after primary surgery. During the third cycle of first-line combination chemotherapy with irinotecan and cisplatin, the patient experienced abdominal distension and vomiting due to malignant ascites. She required paracentesis every other week. After providing informed consent for IP chemotherapy, she underwent paracentesis and received 40 mg/m^2 IP TXT. She also underwent paracentesis 2 and 5 months after the first IP chemotherapy. After the last dose of IP TXT, she did not have sufficient ascites for paracentesis for 6 months. During the 11 months after the first dose of IP TXT, the patient's total hospital stay was 6 days for paracentesis and IP TXT and the total dose of TXT was 120 mg/m^2.

Discussion

To improve the survival of patients with OC, it is necessary to identify an agent for effective second-line treatment after the gold standard first-line therapy of TC by intravenous administration. Dose-dense TC has been shown to improve overall survival compared with conventional, tri-weekly TC, but the 5-year survival rate was 60% at most (Katsumata et al. 2013). Most recurrent cases showed peritoneal disease with malignant ascites at the initiation of recurrence, resulting in protein loss into the abdominal cavity and gastrointestinal events, including ileus, which results in malnutrition and a vicious cycle of ascites-low albuminaemia cachexia syndrome.

It is well known that, in patients with recurrent OC, the platinum-free interval (PFI) is a factor of patient prognosis. A PFI shorter than 6 months is designated to reflect platinum-resistant disease, and patients showed RRs of over 20% to TXT, weekly paclitaxel and pemetrexed in GOG phase II trials. Two retrospective studies in patients with EC showed that PFI was prognostic for patient response (Sartori et al. 2003; Moore et al. 2010). In 48 patients with measurable, recurrent or persistent EC who received one prior chemotherapy regimen, paclitaxel showed an RR of 25%, but none of those patients had received prior platinum chemotherapy (Lincoln et al. 2003). Katsumata et al. (2005) reported that, among 13 patients who received prior chemotherapy, TXT was associated with an RR of 23%.

IP chemotherapy has been used for over 50 years in the management of OC and allows the unique opportunity to deliver increased doses of active agent directly to tumours that are predominantly confined to the peritoneal cavity. Platinum agents, such as cisplatin and carboplatin had 10–12 times higher areas under the curve with IP administration compared with intravenous administration for peritoneal concentrations. As for taxanes, paclitaxel and TXT showed nearly a thousand times higher area under the curve with IP administration (Markman et al. 1992; Markman et al. 1994). The ratio of peak peritoneal to plasma concentration of TXT was approximately 200:1 (Morgan et al. 2003).

Platinum-based IP chemotherapy has several advantages over intravenous chemotherapy in patients with platinum-sensitive disease, but is relatively ineffective in patients with platinum-resistant disease (Muggia et al. 1993). For tumours sensitive to TXT, increased dose intensities were reported to result in improved RRs (Hryniuk 1988). Higher concentrations were found to induce sustained mitotic arrest, followed by mitotic slippage and apoptosis. A randomised trial comparing weekly and tri-weekly TXT as adjuvant treatment for breast

cancer showed that disease-free survival was greater when 100 mg/m^2 TXT was administered every 3 weeks for 12 weeks than when 35 mg/m^2 was administered weekly for 12 weeks (Sparano et al. 2008).

Considering the fact that paclitaxel was administered as first-line chemotherapy in most of the patients with OC or EC, TXT was considered because it is cross-resistant but effective to some extent (Verschraegen et al. 2000). Therefore, IP TXT was considered promising in the control of malignant ascites in patients with recurrent OC and EC.

In this study, IP TXT controlled ascites and reduced serum CA125 levels in two OC patients without measurable disease. The RR among patients with OC and PPC was 12.5%, based on GCIG criteria, with no patient with measurable disease showing a response. Evidence of gross disease is strongly associated with a poor response to first- and second-line IP chemotherapy (Markman et al. 2009). The patient involved in the presented case of response had ovarian clear cell carcinoma. Clear cell carcinoma of the ovary is a histological subtype of EC that accounts for 5% of all ECs diagnosed in Western countries; this subtype is resistant to treatment with conventional anti-cancer cytotoxic agents (Sugiyama et al. 2000; Crotzer et al. 2007; Chan et al. 2008; Orezzoli et al. 2008). The median overall survival for individuals with recurrent or persistent disease is 7–11 months (Kajiyama et al. 2012). In this study, first-line chemotherapy with irinotecan and cisplatin was administered according to our previous report (Adachi et al. 1999). Progression-free survival of 11 months in cases of platinum-refractory disease is extraordinary, and only three administrations of low-dose TXT maintained the patient's quality of life with less toxicity and cost. Two patients with EC received first-line doxorubicin plus cisplatin, second-line TC and third-line IP TXT. One patient with a serous adenocarcinoma progressed during TC treatment, and another with grade 1 endometrioid carcinoma had persistent disease during TC treatment. Neither patient showed improvement during IP TXT treatment.

IP TXT has been studied extensively in gastric cancer patients with peritoneal carcinomatosis (Fushida et al. 2002; Morgan et al. 2003). A recent study showed that first-line IP TXT at 40–60 mg/m^2 is safe in gastric cancer patients when combined with oral chemotherapy (Fujiwara et al. 2012; Fushida et al. 2013). First-line IP administration of paclitaxel and carboplatin in patients with OC did not result in grade 3 or 4 peripheral neuropathy or alopecia (Takano et al. 2008; Krasner et al. 2007). Of 18 patients who underwent a second look operation, 14 (78%) showed a complete pathological response. IP chemotherapy with taxane and carboplatin may be a promising first-line approach.

Our study had several limitations, in that it was retrospective to assess the safety and efficacy, with a small sample size. Nevertheless, IP TXT was promising in its less toxicities and efficacy. Our results showed that second-line or palliative treatment of recurrent OC should be further studied with 40 mg/m^2 IP TXT. Furthermore, 70 mg/m^2 IP TXT could be evaluated for first-line IP chemotherapy.

Ethical approval

The phase I and retrospective studies were approved by the Kansai Clinical Oncology Group (http://www.kcog.jp/) and the institutional review boards of each participating institute.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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