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Safety and effectiveness of docetaxel combined with S-1 for patients with incurable recurrent squamous cell carcinoma of the head and neck

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Summary. *Background and aim of the work:* Therapeutic options for patients with advanced platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) are limited. The aim of this study was to determine whether docetaxel (DOC) combined with S-1 (a 5-fluorouracil derivative) is a safe and effective alternative therapy for recurrent, incurable SCCHN that can be administered on an outpatient basis. *Methods:* We retrospectively investigated the therapeutic outcome and adverse effects of this treatment in 14 patients ineligible for platinum-based therapy because of renal dysfunction, poor overall health, and refractory disease. The patients included 13 men and 1 woman (median age, 64 years; range, 45-79 years). The primary tumor sites were the larynx (n = 6), oropharynx (n = 5), and hypopharynx (n = 3). DOC was administered intravenously for 3-4 weeks at 20-30 mg/m^2, and S-1 was administered orally twice daily for 2 weeks at 80-120 mg/day followed by rest for 1-2 weeks. *Results:* Grade ≤2 hematotoxicity manifesting as leukopenia (n = 3), neutropenia (n = 2), and anemia (n = 4) was observed. Non-hematotoxic adverse effects were grade 2 fatigue (n = 2) and anorexia (n = 1); 1 patient had a grade 4 anaphylactic reaction. The median survival time was 10 months; survival rates after 6 months and 1 year were 64.3% and 32.7%, respectively. *Conclusions:* The DOC and S-1 regimen caused mild adverse effects and is therefore feasible for ambulatory administration as a salvage treatment for SCCHN patients ineligible for platinum-based chemotherapy.

Key words: squamous-cell carcinoma of the head and neck, Docetaxel, 5-fluorouracil

«Sicurezza ed efficacia di docetaxel combinato con S-1 per pazienti con carcinoma squamocellulare ricorrente e incurabile della testa e del collo»

Riassunto. *Premesse e scopo dello studio:* Le opzioni terapeutiche per il carcinoma squamocellulare avanzato platino-resistente della testa e del collo (SCCHN) sono limitate. Lo scopo del presente studio è di determinare se l'impiego di docetaxel (DOC) combinato con S-1 (un derivato del 5-fluorouracile) sia una terapia alternativa sicura ed efficace per pazienti con SCCHN ricorrente, incurabile in regime ambulatoriale. *Metodi:* Abbiamo indagato retrospettivamente i risultati terapeutici e gli effetti collaterali di questo trattamento in 14 pazienti non idonei alla terapia a base di platino. I siti primari dei tumori erano laringe (6 casi), orofaringe (5 casi) e laringofaringe (3 casi). DOC è stato somministrato per via endovenosa per 3-4 settimane a 20-30 mg/m^2, S-1 è stato somministrato oralmente 2 volte al giorno a 80-120 mg al giorno per 2 settimane seguite da una pausa di 1-2 settimane. *Risultati:* È stata osservata tossicità ematica di grado ≤2 manifestatasi come leucopenia (3 casi), neutropenia (2 casi) e anemia (4 casi). Tossicità non ematica si è presentata come affaticamento di grado 2 (2 casi) e anoressia (1 caso); 1 paziente ha avuto una reazione anafilattica di grado 4. Il tempo medio di sopravvivenza è stato di 10 mesi; il tasso di sopravvivenza dopo 6 mesi e 1 anno è stato rispettivamente del 64,3% e del 32,7%. *Conclusioni:* Il regime con DOC e S-1 ha causato effetti collaterali moderati

ed è perciò applicabile ambulatorialmente come trattamento di salvataggio per pazienti con SCCHN non idonei alla chemioterapia a base di platino.

Parole chiave: carcinoma squamocellulare della testa e del collo, Docetaxel, 5-fluorouracile

Introduction

In addition to surgery and radiotherapy, chemotherapy based on platinum-containing drugs such as cisplatin plays an important role in the treatment of squamous cell carcinoma of the head and neck (SCCHN). A combination of radiotherapy with cisplatin-based chemotherapy is a standard non-surgical treatment for locally advanced SCCHN, and has also been commonly used as an adjuvant chemotherapy regimen for postoperative high-risk groups (1, 2). However, 20–30% of patients develop local relapse and distant metastasis after the primary treatment (3). In this case, chemotherapy with double-agent platinum is usually offered as a second-line treatment (4), with the exception of patients with renal dysfunction, a poor general condition, or resistance to platinum drugs. It is then difficult to select the appropriate treatment strategy because platinum-refractory disease is also characterized by resistance to other cytotoxic agents. The current treatment is based on chemotherapy agents with an activity mechanism different from that of platinum compounds. As such, non-platinum single-agent therapy with docetaxel (DOC) or S-1 is frequently used (5, 6). S-1 (Taiho Pharmaceutical, Japan) is a novel oral fluoropyrimidine derivative based on biochemical modulation of 5-fluorouracil (5-FU); it consists of a mixture of tegafur, 5-chloro-2,4-dehydroxypyrimidine, and potassium oxonate in a molar ratio of 1:0.4:1. S-1 has enhanced efficacy and lower toxicity than conventional 5-FU derivatives and can be administered chronically on a daily basis, offering the potential for more convenient outpatient treatment (7).

Because SCCHN is usually incurable, the goal of treatment is to accomplish prolonged survival while maintaining quality of life. This study focused on identifying a safe and effective alternative therapy for recurrent, incurable SCCHN that can be administered on an outpatient basis, without interrupting daily life and achieving preferable survival time. We retrospectively reviewed the adverse reactions and therapeutic outcome of ambulatory salvage treatment with DOC and S-1 as a non-platinum double-drug regimen in 14 patients with recurrent SCCHN ineligible for platinum-based therapy.

Methods

A total of 14 patients were examined, all with recurrent SCCHN, who received salvage combination chemotherapy with DOC and S-1 on an outpatient basis from February 2004 to April 2012. The eligibility criteria were as follows: a) histologically confirmed SCCHN; b) incurable disease due to recurrence or metastasis, which was unresectable; and c) failure of a standard platinum-based chemotherapy regimen. The platinum regimens used in our institution consisted of cisplatin 80 mg/m^2 administered intravenously (IV) on day 1 and 5FU 1,000 mg/body administered via continuous infusion for 5 days (CDDP/5-FU) when creatinine clearance (CCr) was over 60 ml/min. When CCr was under 60 ml/min, we administered carboplatin at an area under the curve (AUC) of 4 or 5 on day 1 and 5FU 800 mg/body for 5 days (CBDCA/5-FU). The male/female ratio was 13:1 (median age, 64 years; range 45-79 years). The Eastern Cooperative Oncology Group (ECOG) performance status (PS), which describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability, was 0 (indicating full activity without restriction) for 6 patients and 1 (restricted in physically strenuous activity but able to carry out light work) in 8 patients. The study design was approved by the institutional committee of Hyogo Cancer Center. Because in rare cases DOC can cause anaphylactic shock, it was initially administered on an inpatient basis and subsequently as an outpatient treatment. Primary sites were

the larynx (n = 6), oropharynx (n = 5), and hypopharynx (n = 3) (Table 1). The observation period was defined as the time from the start of salvage therapy until the last day of follow-up (median, 10 months; range 3-32 months) or death. The overall survival rate was estimated from the beginning of salvage treatment by the Kaplan-Meier method. Data was analyzed using the JMP software (SAS, JMP, Version 9.0, Cary, NC).

The drug administration protocol was as follows: DOC was delivered intravenously at a dose of 20-30 mg/m^2 for 3-4 weeks and S-1 was administered orally twice a day for 2 weeks followed by 1-2 weeks of rest, according to the body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; 1.25 m^2 ≤ BSA < 1.50 m^2, 100 mg/day; BSA ≥1.50 m^2, 120 mg/day. This schedule was repeated every 3-4 weeks until intolerable adverse reactions or conspicuous disease progression.

Of the 14 patients, 4 had local recurrence, 4 had lymph node metastasis, and 8 had distant metastasis, including overlapping cases of recurrence and metastasis. The primary treatment included surgery (8 patients) and radiation therapy (6 patients). Prior to this regimen, 12 patients underwent first-line chemotherapy treatment that included induction chemotherapy or concurrent chemoradiotherapy. Renal function was evaluated on the basis of CCr: CCr was >60 ml/min in 5 patients and <60 ml/min in 9. The reasons for consent to the current therapeutic protocol included: a) outpatient treatment (9 patients; 7 refused more intense chemotherapy with platinum-based agents on the ground of painful previous experience such as malaise, nausea, and vomiting, and 2 refused hospital admission); b) poor physical status (3 patients; 2 developed renal dysfunction and 1 was ineligible for platinum-based chemotherapy because of cardiac failure); c) platinum therapy-refractory status, defined as a relapse within 6 months after platinum drug-based chemotherapy (2 patients).

Table 1. Summary of patient characteristics.

	Number	(%)
Total	14	
Mean age, Y(range)	64 (45-79)	
Sex		
Male	13	92.8
Female	1	7.2
Performance status		
1	6	42.8
0	8	57.2
Follow-up, M(range)	10 (3-32)	
Primary site		
Larynx	6	42.9
Hypopharynx	3	21.4
Oropharynx	5	35.7

Results

The median number of times the regimen was administered was 5.5 times (range, 1-42 times). The median duration of administration was 236 days, which corresponded to approximately 8 months. The range was 0-944 days, wherein the anaphylactic reaction accounted for zero days. The median amount of total DOC received was 142.5 mg/body (range, 30-1,050 mg/body).

The most severe observed hematological toxicity was grade ≤2 and manifested as leukopenia (3 patients), neutropenia (2 patients), and anemia (4 patients). Adverse effects were assessed on the basis of the criteria of Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Non-hematotoxic adverse effects included grade 2 fatigue (2 patients) and anorexia (1 patient). One patient developed grade 4 anaphylaxis (Table 2). Because DOC was initially administered during hospitalization, the patient with anaphylaxis received appropriate care, avoiding any serious accident.

The median survival time (MST) was 10 months. The 6-month overall survival rate was 64.3% and the 1-year rate was 32.7%. Tumor response to treatment was assessed by using computed tomography or magnetic resonance imaging according to the criteria of the World Health Organization (1979). One patient had a partial response (PR), 1 developed stable disease (SD), and 8 had progressive disease (PD); 4 patients were not subjected to imaging tests (Figure 1).

As shown in Table 3, univariate analysis was performed for the following variables: performance status (PS), renal function (CCr), site, recurrence/metastasis, induction chemotherapy, and platinum-refractory factors. No significant differences were found.

Table 2. Toxicity.

	Gr 1	Gr 2	Gr 3	Gr 4	% (Gr 3 over)
Leucocyte	10	3	0	0	**0**
Neutrophil	4	2	0	0	**0**
Hemoglobin	11	6	0	0	**0**
Platelet	1	0	0	0	**0**
Fatigue	4	2	0	0	**0**
Appetite	5	1	0	0	**0**
Febrile neutropenia	-	-	0	0	**0**
Anaphylactic reaction	-	-	0	**1**	**7.10%**

Table 3. Univariate analysis.

Variable	P value
Age (<70y vs ≥70y)	0.0245*
PS (ECOG) (0 vs 1)	0.6191
Renal function(≥60 vs <60)	0.0885
Site (Oropharyngeal vs other)	0.1621
R/M site (distant vs not)	0.8371
ICT (with vs without)	0.8278
RFI (since last platinum):(<6 m vs ≥6 m)	0.4646

* Statistically significant

Discussion

In our department, DOC-based chemotherapy has been administered since 2004. The combination therapy with DOC, cisplatin, and fluorouracil (5-FU) or DOC single-agent therapy was adopted on a trial-and-error basis (6, 8). According to the treatment results, the DOC dose for outpatient administration has been reduced to below 60 mg/m^2 because of frequent episodes of neutropenia, which is also in agreement with previous findings indicating that DOC induces neutropenia in a dose-dependent manner. Inuyama *et al.* reported that in a clinical study on 63 patients who resumed DOC treatment at a dose of 60 mg/m^2 every 3-4 weeks, grade ≥3 leukopenia and neutropenia were observed in 59.7% and 79% of patients, respectively (9); based on these results, neutropenia was considered a criterion for dose-limiting toxicity. Since S-1 was approved for the treatment of gastric cancer in 1999, it has been used in combination with DOC as a chemotherapeutic regimen for advanced or recurrent gastric cancer. In a phase I clinical trial, DOC plus S-1 combination chemotherapy of advanced or recurrent gastric cancer produced a significant response rate (RR) of 71.4% and demonstrated a good safety profile, as evidenced by low-grade hematological or non-hematological adverse effects in the patients who received 40 mg/m^2 DOC on day 1 and 80 mg/m^2 S-1 for 2 weeks every 3 weeks (10). Our regimen was based on this protocol.

In 2011, a phase III START clinical trial was conducted in patients with advanced and recurrent gastric cancer treated with the following regimen: Arm A, 40 mg/m^2 S-1 twice daily for 2 weeks every 3 weeks and

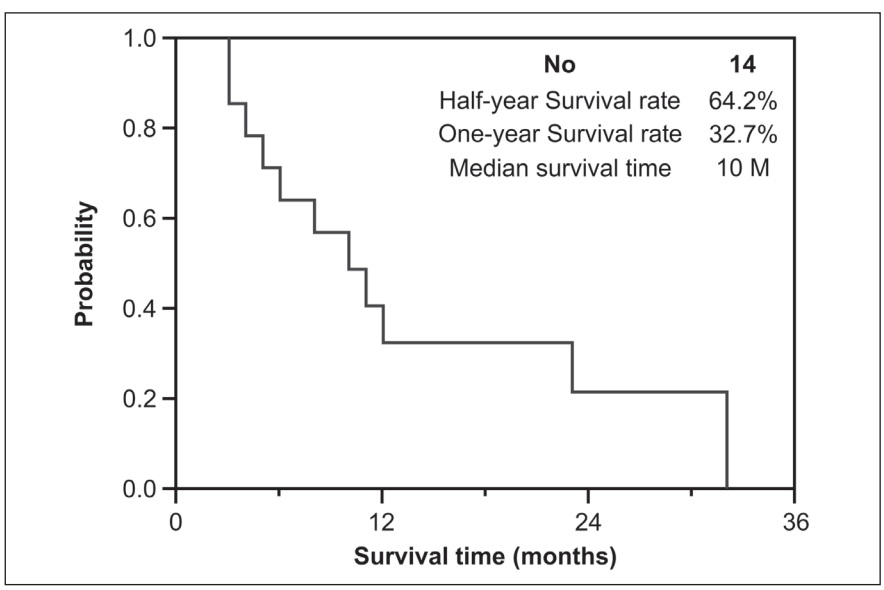

Figure 1. Overall Survival rate and Response rate estimated using the Kaplan-Meier method.

40 mg/m^2 DOC on day 1; and Arm B, S-1 for 4 weeks every 6 weeks (11). S-1/DOC did not meet the primary criteria of overall survival (OS); however, other clinical response criteria such as time-to-progression and OS in the non-measurable disease group indicated that S-1/DOC was significantly superior to S-1 alone. Although that trial did not offer any guidance regarding the treatment of distinct carcinoma, it presented valuable safety data showing that grade 3 (or more) neutropenia was permissible at approximately 30%, which was used in our study protocol. In our investigation, we did not observe hematotoxicity above grade 2 or other adverse effects (with the exception of 1 case of an anaphylactic reaction). These findings indicate the feasibility of using this regimen on an outpatient basis for the treatment of SCCHN patients ineligible for platinum-based therapy owing to renal dysfunction, poor general condition, or platinum resistance.

Our treatment protocol resulted in a median survival time (MST) of 10 months (Figure 1). Previous studies have shown that double-platinum chemotherapy for recurrent or metastatic SCCHN resulted in 30% RR and 6–9-month MST (11-15); with single-agent DOC treatment, the MST was 4.5 months (9). On the other hand, the studies on platinum-refractory SCCHN reported an RR of 0% to 10% and MST of 3-6 months (16-20). Platinum-drug resistance has been established as a poor prognostic factor. Vermorken *et al.* demonstrated an increase in MST by 3 months after the application of a triple-drug regimen consisting of a platinum agent, 5-FU, and cetuximab (21), which has the potential to be more widely used as a novel strategy for the treatment of SCCHN (Table 4).

Our study was conducted retrospectively and adds only limited evidence for the treatment efficacy of DOC combined with S1. There was a discrepancy between an MST of 10 months and a low RR of 7.1%; however, an MST of 10 months may be considered a clinically relevant benefit. Another limitation is that in 4 cases, the RR was not estimated and no routine imaging tests were conducted after two rounds of treatment, as they should be in a clinical study.

Conclusions

The results of our study demonstrate that the DOC plus S-1 regimen has mild toxicity and few adverse effects; if DOC is administered during hospitalization to cope with any anaphylactic reaction, this treatment is feasible for subsequent ambulatory administration as a salvage treatment for patients with advanced SCCHN

Table 4. Clinical investigation in HNSCC.

Study	Regimen	Number	Response Rate%	Median Survival Time (months)
R/M HNSCC				
Morton, 1985 (Phase II trial)	BSC vs BLM vs CDDP+BLM vs CDDP	117	n.a.(1) vs 14% vs 21% vs 13%	CDDP arms vs others 4.3M vs 1.8M
Dreyfuss, 1999 (Phase II study)	DOC 100mg/m^2	22	20.80%	4.5M
Inuyama, 1999 (Late phase II study)	DOC 60mg/m^2	63	22.20%	-
Forastiere, 1992 (Randomized study)	FP vs CBDCA/5-FU vs MTX	277	32% vs 21% vs 10%	6.6M vs 5.0M vs 5.6M
Vermorken, 2008 (Phase III trial)	Cetuximab +FP vs FP	442	36% vs 20%	10.1M vs 7.4M
Platinum-refractory HNSCC				
Vermorken, 2007 (Phase II trial)	Cetuximab	103	13%	5.9M
Herbst, 2005 (Phase II trial)	Cetuximab + CDDP	96	10%	6.5M
Zenda, 2007 (Retrospective date)	DOC 60mg/m^2	20	10%	4.6M
Leon, 2003 (Retrospective date)	Chemotherapy only	43	0%	3.6M

(1) not available

BSC: Best Suppositive Care; BLM: bleomicina; CDDP: cisplatino; FP: fluoropyrimidina; CBDCA: carboplatino; 5-FU: 5-fluorouracile; MTX: methotrexate

who are ineligible for platinum-based chemotherapy because of renal dysfunction, poor general condition, or platinum-drug resistance.

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