厚生労働科学研究研究費補助金

がん臨床研究事業

がんの腹膜播種に対する標準的治療の確立に関する研究に関する研究

－臨床研究実施チーム－（H17－がん臨床－002）

平成17年度総括研究報告書

主任研究者　白尾　国昭

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Ⅰ. 総 括 研 究 報 告 書

厚生労働科学研究費補助金（がん臨床研究事業）

総括研究報告書

がんの腹膜播種に対する標準的治療の確立に関する研究

－臨床研究実施チームの整備－

分担研究者　　白尾　国昭　　国立がんセンター中央病院　医長

研究要旨：本研究は腹膜播種を伴う進行胃がんを対象にMTX-5-FU時間差療法と5-FU単独持続静注療法の第Ⅲ相無作為化比較試験を行い、標準的治療法を確立することを目的とする。腹膜播種を伴う胃がんに対する臨床研究は国内外ともに報告がなく、本研究の結果が期待される。

A．研究目的

腹膜播種を伴う進行胃がん（腹膜播種を伴う術後再発胃がんを含む）を対象にMTX-5-FU時間差療法と5-FU単独持続静注療法の第Ⅲ相無作為化比較試験を行い、標準的全身化学療法を確立する。

B．研究方法

Primary endpointは全生存期間、Secondary endpointは登録時経口摂取可能例が経口摂取不能となるまでの期間（経口摂取可能生存期間）、登録時経口摂取不能例における経口摂取改善割合、有害事象発生割合、重篤な有害事象発生割合とした。

対象症例は以下の通りである。

（1）組織学的に腺癌であることが確認されていること

（2）切除不能または術後再発胃癌症例であること

（3）腹膜転移を有すること。腹膜転移の診断は注腸/小腸造影またはCTで行い、画像上明らかに指摘可能病変が存在すること。

（4）測定可能病変の有無は問わない。

（5）年齢：20歳以上、75歳以下。

（6）performance status (ECOG): 0, 1, 2

（7）胃癌に対して外科治療および本試験登録24週以前に終了した術後補助化学療法以外、いかなる治療法も行われていない症例。

（8）胃癌以外の悪性腫瘍に対して、抗癌剤による化学療法または放射線療法の既往がない。

（9）主要臓器機能が十分に保たれていること。

（10）登録前１４日以内に輸血を行っていない症例。

（11）本試験の参加に関して、同意が患者本人より文書で得られていること。

治療法は以下の通りである。

(1)　5-FU持続静注療法：

5-FU 800 mg/m2/day: 5日間（120時間：day 1-5）持続静注を４週１コースとして増悪まで繰り返す。

(2)　MTX+5-FU時間差療法：

MTX, 100 mg/m2/day　急速静注（day1）

5-FU, 600mg/m2/day　急速静注（day 1: MTX投与３時間後）

ロイコボリン　10mg/m2 x 6 静注または経口　(day 2-3, MTX投与24時間後より開始、６時間ごとに６回投与)

以上を、１週１コースとして増悪まで繰り

返す

＜倫理面への配慮＞

ヘルシンキ宣言および我が国の「臨床研究に関する倫理指針」に従い以下を遵守する。

1)プロトコールの IRB（倫理審査委員会）承認が得られた施設からしか患者登録を行わない。

2)全ての患者について登録前に十分な説明と理解に基づく自発的同意を本人より文書で得る。

3)データの取り扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティーを確保しプライバシー保護を厳守する。

4)研究の第三者的監視：JCOG を構成する他の研究班の主任研究者等と協力して、臨床試験審査委員会、効果・安全性評価委員会、監査委員会を組織し、研究開始前および研究実施中の第三者的監視を行う。

C．研究結果

本研究はすでに、厚生労働科学研究費（効果的医療技術の確立推進臨床研究事業・大津班）により平成 14 年から開始されている。現在順調に登録が行われており、平成 18 年 2 月の時点で 170 例が登録された。当初 160 例を予定していたが、予定症例数を計 236 例（各治療群 118 例）に変更し、現在登録中である。平成 18 年度には予定症例の登録を終了する見込みである。

D．考察　E．結論

登録終了後 1 年の追跡期間終了後、最終解析を実施する予定であるが、最終解析の結果をもとに、さらなる治療成績の向上を目指し、次期第三相試験を計画したい。なお、平成 17 年度より、腹膜転移を伴う胃がんの二次治療に関する比較第二相試験（JCOG0407：best available 5-FU vs weekly Taxol：がん研究助成金指定研究 14 指-3 大津班）が実施されており、その結果も考慮にいれ、次期第三相試験を計画する予定である。

F．健康危険情報

特記すべきことなし。

G．研究発表

1．論文発表

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H．知的財産権の出願・登録状況（予定含）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅱ．研究成果の刊行物・別刷

Clinical Application of Immunoreactivity of Dihydropyrimidine Dehydrogenase (DPD) in Gastric Scirrhous Carcinoma Treated with S-1, a New DPD Inhibitory Fluoropyrimidine

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Abstract. *Background: A highly specific antibody against recombinant human dihydropyrimidine dehydrogenase (DPD) has been developed to immunohistochemically assess DPD expression in tumors. A new oral DPD inhibitory fluoropyrimidine (DIF), S-1, is reportedly effective against gastric scirrhous carcinoma. Patients and Methods: In this study, the relationship between immunoreactivity to DPD in biopsy specimens and the effects of chemotherapy were investigated in 61 patients treated with first-line fluoropyrimidine-based chemotherapy (S-1:DIF, 5-FU:non-DIF) for gastric scirrhous carcinoma. Results: The response rate was significantly higher in patients with DPD-positive tumors than in those with DPD-negative tumors in the S-1 group (45.5%, 10.0% : $p<0.05$), as compared to the 5-FU group (0%, 5.6%: $p=0.398$). According to the median survival time, there was no significant difference between patients with DPD-positive tumors (364 days) and those with DPD-negative tumors (406 days; $p=0.626$) in either the S-1 group or the 5-FU group (181 days and 256 days, respectively; $p=0.543$). Conclusion: This study indicates that S-1 may be effective even in gastric scirrhous carcinoma with a high level of DPD activity.*

Borrmann-type-4 gastric cancer, clinically synonymous with gastric scirrhous carcinoma, is generally resistant to systemic chemotherapy. This type of gastric cancer is characterized by diffuse malignant lesions with indistinct borders, and is usually diagnosed at a very advanced stage. High rates of lymph node metastasis, invasion of neighboring structures and peritoneal dissemination pose a great challenge for medical care. The outcome is usually poor, with 5-year survival rates ranging from 0% to 20% (1). Although most gastric scirrhous carcinomas are resistant to conventional 5-fluorouracil (5-FU)-based regimens, several recent case studies have reported a good response to S-1 (2, 3) Many studies have demonstrated that dihydropyrimidine dehydrogenase (DPD) is a biomarker for response in patients treated with 5-FU-based chemotherapy (4-7). DPD is a rate-limiting enzyme in the metabolism of 5-FU, and its expression by tumors is thought to attenuate the response to 5-FU (8-10). Since more than 80% of the administered dose of 5-FU is degraded in the liver by DPD to fluorinated β-alanine, the level of DPD activity is also a major determinant of 5-FU toxicity (11).

Recently, encouraging clinical results have led to the development of a new generation of oral fluoropyrimidines, commonly referred to as DPD inhibitory fluoropyrimidines (DIF) (12, 13). S-1 is a combined preparation consisting of 1 M tegafur, 0.4 M 5-chloro-2,4-dihydroxypyridine (CDHP), and 1 M potassium oxonate (Oxo). CDHP is a potent inhibitor of DPD, approximately 180 times more active than uracil in inhibiting DPD *in vitro*, and maintains prolonged 5-FU concentrations in plasma and tumors (14-16) Oxo protects against 5-FU-induced gastrointestinal toxicity. Two phase II studies of S-1 monotherapy in patients with metastatic gastric cancer yielded response rates of about 50%, with minimal toxicity (17-19). S-1 is now used to treat advanced gastric cancer as a single agent or in combination with other anticancer agents, including cisplatin, CPT-11, paclitaxel and docetaxel (20).

A technique using highly specific antibodies against recombinant human DPD (rhDPD) has been developed to immunohistochemically assess DPD expression in tumors (21-23) and thereby predict the clinical response to 5-FU-based chemotherapy. Several studies have examined the relationship between the DPD immunoreactivity of tumors

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Key Words: Gastric scirrhous carcinoma, S-1, dihydropyrimidine dehydrogenase (DPD), DPD inhibitory fluoropyrimidines (DIF).

and the response to oral fluoropyrimidines, but the clinical impact of DPD activity on response remains unclear for new drugs such as S-1, and there are no reports on the treatment of gastric scirrhous carcinoma. In this study, intra-tumoral levels of DPD were assessed immunohistochemically using anti-DPD polyclonal antibodies, and the relationship between the immunoreactivity of DPD and the antitumor effects of S-1 were investigated. We propose that S-1 might circumvent the resistance to 5-FU in gastric scirrhous carcinoma with a high level of DPD activity. Our aim was to clarify the differences between the antitumor activities and mechanisms of action of S-1 as a DIF and 5-FU as a non-DIF.

Patients and Methods

Patients. Sixty-one patients with Borrmann-type-4 gastric scirrhous carcinoma, who received S-1 or 5-FU as first-line chemotherapy at the National Cancer Center Hospital (Tokyo, Japan) between February 2000 and January 2003, were studied retrospectively. Thirty-one patients were given S-1 and 30 were given 5-FU. Tumor biopsy specimens were obtained from all patients before chemotherapy.

Treatment schedule and evaluation of response. S-1 was administered at a dose of 40 mg/m^2 of body surface area (BSA) twice daily in one of the following doses: 40 mg (BSA<1.25 m^2), 50 mg (1.25 m^2≤BSA <1.50 m^2), or 60 mg (BSA ≥1.50 m^2). S-1 was given for 28 consecutive days, followed by a 14-day rest period. This period was defined as one course of treatment. S-1 was purchased from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) in the form of 20 and 25 mg capsules. 5-FU (800 mg/m^2/day) was administered as a 5-day (120 h) intravenous continuous infusion, repeated every 28 days, comprising one course of treatment.

Both treatments were continued until tumor progression, unacceptable toxicity, or refusal by the patient to continue further therapy. The response of measurable target lesions to chemotherapy was objectively evaluated according to the WHO criteria after each course of treatment. The response of primary lesions was also evaluated according to the roentgenographic and endoscopic criteria proposed by the Japanese Research Society of Gastric Cancer for "c-lesions" (24). Complete response (CR) was defined as the disappearance of all invasive findings. Partial response (PR) was defined as a decrease of 50% or greater in the affected area on X-ray films after barium administration, obtained in the same position as that before treatment. Progressive disease (PD) was defined as a 25% or greater increase in lesions or the appearance of new lesions. Responses not falling into any of these categories were classified as stable disease (SD). The survival time was calculated from the start date of the first course of treatment to the date of death or to the final date of confirmed survival.

Immunohistochemical examination. DPD immunoreactivity in the tumor biopsy specimens was examined with the use of an anti-recombinant human DPD polyclonal antibody (diluted at 1:1000, The Second Cancer Laboratory, Taiho Pharmaceutical Co., Ltd., Saitama, Japan). The tissues were routinely fixed in 10% formalin and embedded in paraffin wax. Sections 3 μm thick were cut and mounted on aminopropyltriethoxysilane-coated slides, and were deparaffinized with xylene and rehydrated in graded ethanol. Endogenous peroxidase activity was quenched with 0.3% hydrogen peroxidase in methanol for 30 min at room temperature. Representative specimens were evaluated by the following antigen retrieval procedure. Three types of soaking solutions were employed: 10 mM citrate buffer, pH 6.0, 10 mM citrate buffer, pH 7.0 and 1mM EDTA solution, pH 8.0. After pressure cooking, the sections were left at room temperature for 30 min. The sections were incubated with polyclonal antibody against DPD overnight at room temperature. The specificity of this antibody has been reported previously (21). After rinsing in phosphate-buffered saline (PBS), pH 7.2, the sections were incubated with universal immunoperoxidase polymer, anti-mouse and rabbit (Histofine Simple Stain MAX PO, Nichirei, Tokyo, Japan), at room temperature for 30 min. The reaction products were visualized in 50 mM Tris-HCl buffer, pH 7.6, containing 50 mg/dl diaminobenzidine tetrahydrochloride and 0.006% hydrogen peroxidase. The nuclei were lightly counterstained with Mayer's hematoxylin, and the specificity of immunostaining with the polyclonal antibody was checked by preabsorption experiments using representative samples. Before immunostaining, the diluted antibody was combined with recombinant human DPD (Taiho Pharmaceutical Co., Ltd.) at final concentrations of 0.01, 0.1, 1.0 and 10 μg/ml, at 37°C for 1 h. As a positive control, we employed tumor tissue obtained from a xenograft of the human pancreatic cancer cell line MIAPaCa-2 in nude mice, established to have high DPD expression. Negative

Table I. *Patient characteristics in both regimen (S-1 : DIF, 5-FU : non-DIF) groups.*

Characteristics	S-1	5-FU	*p*-value
Total noumber of patients	31	30	
Age, years, median (range)	53.7 (30-73)	58.2 (39-70)	0.387
Gender (men/women)	16/15	18/12	0.592
ECOG performance status			
0	10	4	0.214
1	20	22	
2	1	4	
Histological type			
Intestinal type	2	1	0.978
Diffuse type	29	29	
Number of organs involved			
1	8	12	0.151
2	17	11	
3	6	7	
Site of metastatic disease			
Peritoneum	29	16	0.117
Distant lymph nodes	17	20	0.672
Liver	9	12	0.867
Lung	2	2	0.978
Others	3	5	0.330
Surgery (total gastrectomy)			
yes	17	11	0.126
no	14	19	
Treatment duration, days, median (range)	217 (27-767)	76 (25-258)	0.006
Number of chemotherapy cycles, mean (range)	5.0 (1-16)	2.4 (1-5)	0.045

controls were prepared by substituting PBS for the primary antibody (Rabbit Immunoglobulin Fraction: DAKO ENVISION). The slides were counterstained with hematoxylin.

Evaluation of immunostaining. Immunohistochemical staining intensity was semiquantitatively graded (– to 3+) on the basis of the proportion of positively-stained cancer cells in the lesions: –, negative; 1+, less than 1/3 of cancer cells positive; 2+, from 1/3 to less than 2/3 of cancer cells positive; 3+, 2/3 or more of cancer cells positive. A staining intensity of – to 1+ was considered negative, and that of 2+ to 3+ was considered positive. Immunohistochemical staining was evaluated independently by four investigators blinded to clinical outcomes. Any disagreement was resolved by consensus.

Statistical analysis. The statistical significance of the relationships of DPD immunoreactivity and TS immunoreactivity to the patients' responses to chemotherapy was evaluated with χ^2-tests. Survival curves were calculated with the Kaplan-Meier method and analyzed with the use of log-rank tests.

Results

Patients' characteristics. The patients' characteristics are provided in Table I. Thirty-four men and 27 women, with a median age of 55 years (range, 30-73 years) were included. Fifty-six patients (91.8 %) had a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale, and all patients received S-1 or 5-FU chemotherapy as first-line treatment, including preoperative neoadjuvant chemotherapy.

DPD immunoreactivity. DPD immunoreactivity was diffusely distributed in the cytoplasm of tumor cells, with some differences in staining intensity within a given tumor. All grading patterns of DPD immunoreactivity using anti-recombinant human DPD polyclonal antibody are shown in Figure 1 .

Immunoreactivity and response to chemotherapy. The overall response rate was 22.6% (7/31) in the S-1 group and 3.3% (1/30) in the 5-FU group. Positive rates for DPD were, respectively, 35.5% (11/31) in the S-1 group and 40.0% (12/30) in the 5-FU group. Response rates were 45.5% (5/11) in patients with DPD-positive tumors and 10% (2/20) in those with DPD-negative tumors ($p=0.044$) in the S-1 group, as compared with 0% (0/12) and 5.6 % (1/18) ($p=0.398$), respectively, in the 5-FU group.

Relationship between survival and DPD activity. The median survival time of all patients was 340 days (S-1: 393 days, 5-FU: 226 days). The median survival times were 364 days in patients with DPD-positive tumors and 406 days in those with DPD-negative tumors in the S-1 group ($p=0.626$), as compared with 181 days and 256 days, respectively, in the 5-FU group ($p=0.543$). The median survival time did not differ significantly between patients with DPD-positive tumors and those with DPD-negative tumors in either treatment group.

Discussion

Our study indicates that S-1 may be effective in the treatment of gastric scirrhous carcinoma with higher DPD activity. Several studies focusing on human cancer cell lines have suggested that intratumoral DPD levels, assessed on the basis of either enzymatic activity or mRNA expression, are good predictors of the response to 5-FU-based chemotherapy (25-27). Previous studies have also shown that inhibition of intratumoral DPD increases sensitivity to 5-FU, and that thymidylate synthase (TS) overexpression plays a major role in the resistance. Here, we focused on the antitumor effect of S-1 as a newly-developed DIF, and examined the correlation with a DIF antitumor effect and a biomarker (DPD). Immunohistochemical analysis has several important advantages over measuring protein and mRNA levels, since it is labor-saving, low-cost and can be used for tissue specimens fixed in formalin. We believe that it would be valuable to establish a simple and reliable method to assess DPD expression in biopsy specimens, since this is the only available material capable of providing information on the biological properties of tumors before chemotherapy. Antibodies against DPD have recently become available for immunohistochemical analysis, and studies have shown that DPD immunoreactivity correlates with DPD activity and the level of mRNA expression in cancer tissue. Cancer cells that express higher levels of DPD are considered more resistant to 5-FU and may be unresponsive to chemotherapy. However, our findings suggest that S-1 may be effective against gastric scirrhous carcinoma with higher DPD activity. Although there was no significant difference in median survival time between DPD-positive patients and -negative patients in the S-1 group ($p=0.626$) as compared with those of the 5-FU group ($p=0.528$), S-1 showed a higher response rate in tumors with a high DPD activity ($p<0.05$). These results indicates that S-1 could be more effective in gastric scirrhous carcinoma patients resistant to 5-FU only and with high DPD activity. One remarkable point was that all patients who responded to S-1 in the DPD-positive group showed shrinkage of primary lesions. Although DPD has been documented as an important determinant of chemosensitivity to 5-FU, most previous studies have found that the levels of DPD mRNA, protein and activity in tumors are unrelated to outcome. Our results, which showed no correlation of the DPD score in biopsy specimens with survival or time to progression, are in agreement with these findings.

In tumors with low DPD activity, inhibition of DPD by CDHP did not enhance cytotoxicity, even if tumor DPD activity was further reduced. In contrast, maximum

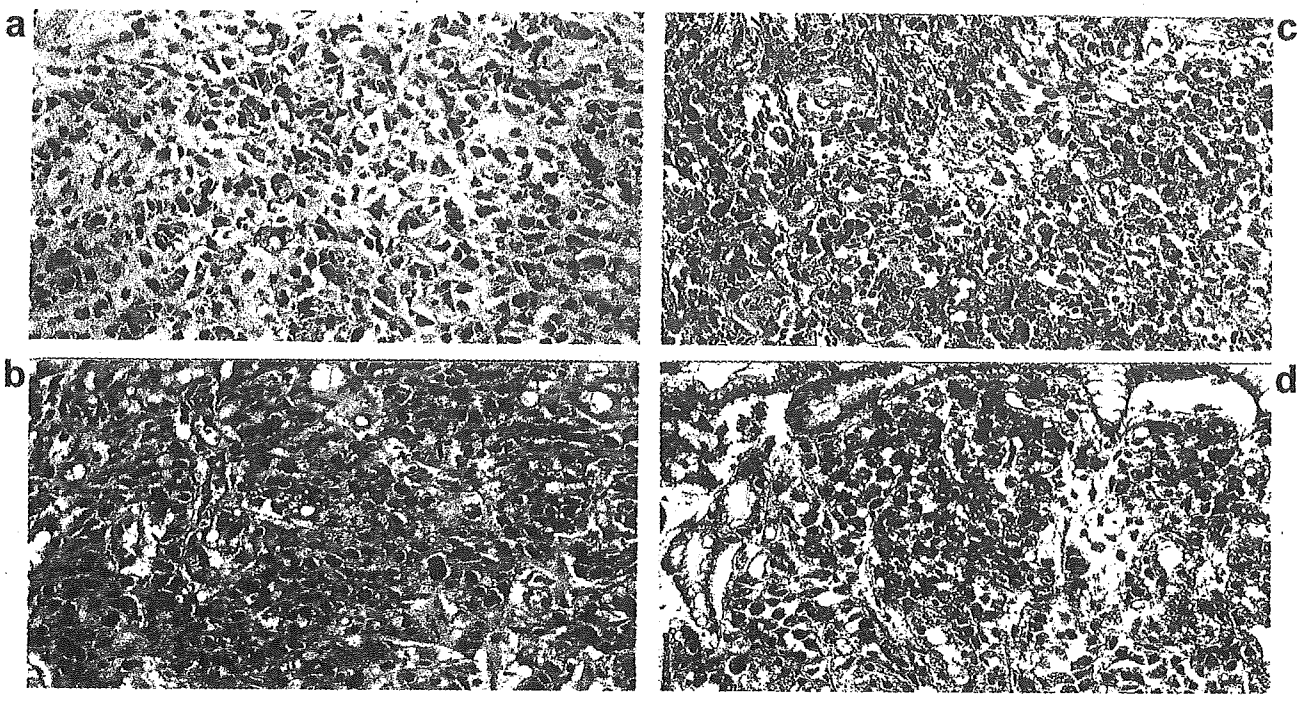

Figure 1. *All grading pattern of immunohistochemical staining for DPD with polyclonal antibody (x400 magnification). Positive staining for DPD is observed in the cytoplasm of cancer cells, with some differences in staining intensity within a given tumor. (a. DPD -, b. DPD 1+, c. DPD 2+, d. DPD 3+). A staining intensity of – to 1+ was considered negative, and that of 2+ to 3+ was considered positive.*

enhancement of the antitumor effect of S-1 would be expected in patients whose tumors have high DPD activity (28). Although the proportion of intratumoral DPD activity inhibited by CDHP is not clinically known, S-1 is expected to show antitumor effects, regardless of the status of intratumoral DPD. Similar to our results, several recent case studies have reported that S-1 is associated with shrinkage of primary lesions of Borrmann-type-4 gastric scirrhous carcinoma (2, 3). Although the mechanism of the response of primary lesions to S-1 remains unclear, strong inhibition of DPD, resulting in prolonged active concentrations of 5-FU in plasma and tumors, may be responsible for the shrinkage of these lesions.

In conclusion, our results suggest that S-1 may be effective against gastric scirrhous carcinoma, even in tumors with high levels of DPD activity. The relationship between DPD and the clinical response to other chemotherapeutic regimens should be investigated to determine whether intra-tumoral DPD activity is useful for selecting the best suited chemotherapeutic regimen. Further immunohistochemical studies on DPD with larger numbers of patients will hopefully contribute to the development of tailor-made DIF-based regimens designed to optimize response.

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ORIGINAL ARTICLE

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A phase I/II study of nedaplatin and 5-fluorouracil with concurrent radiotherapy in patients with T4 esophageal cancer: Japan Clinical Oncology Group trial (JCOG 9908)

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Abstract
Background. Nedaplatin is an analogue of cisplatin with less nonhematologic toxicity. The combination of nedaplatin and 5-fluorouracil showed a promising response rate in a previous phase II study for metastatic esophageal cancer. The purpose of this study was to determine a recommended dose and to evaluate the efficacy of nedaplatin and 5-fluorouracil combined with concurrent radiotherapy.
Methods. Eligibility criteria included squamous cell carcinoma of the thoracic esophagus; T4 disease without distant organ metastasis; age 20–70 years; performance status 0–2; and adequate organ functions. Patients received two cycles of nedaplatin (80 mg/m^2 or 90 mg/m^2) on day 1 and continuous infusion of 5-fluorouracil 800 mg/m^2/day on days 1–5, every 5 weeks with concurrent radiotherapy 60 Gy in 30 fractions.
Results. Between December 1999 and April 2002, 26 patients were accrued. The recommended dose of nedaplatin was 90 mg/m^2. Common grade ≥3 toxicities included leukopenia 9, neutropenia 5, thrombocytopenia 4, esophagitis 4, and esophageal fistula 3. Three of 26 patients achieved complete response (12%; 95% confidence interval, 2%–30%). With a minimum follow-up of 26 months for surviving patients, the median survival time was 12 months (95% confidence interval, 9–22 months), and the 2-year overall survival was 31% (95% confidence interval, 13%–49%).
Conclusions. This combined therapy is active with acceptable toxicity, however, the survival figure remains poor. Further investigation into more effective treatment is needed.

Key words Esophageal neoplasms · Drug therapy · Radiotherapy · Clinical trial

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Introduction

Esophageal cancer has become an important disease in the fight against cancer. In recent years, the number of patients with stage I disease has been increasing, but most patients are diagnosed with advanced disease and their prognoses are still daunting.

Over the last decade, chemoradiotherapy (CRT) for esophageal cancer has revealed promising results [1,2]. After the report of an intergroup randomized controlled trial (Radiation Therapy Oncology Group 85-01) that compared CRT with radiotherapy alone, the combined-modality treatment became a standard for patients with esophageal cancer who received nonsurgical treatment [3,4]. Most reports of CRT used cisplatin (CDDP) and fluorouracil (FU) with concurrent radiotherapy, and this combination is thought to be standard [1–6].

Nedaplatin (NDP; *cis*-diammine-glycolatoplatinum), a novel second-generation platinum compound, has shown promising antitumor activity with less nephrotoxicity, gastrointestinal toxicity, and neurotoxicity than CDDP in some preclinical and clinical studies [7–11]. The combination of NDP and FU also showed promising results in a phase II study for metastatic esophageal cancer [12]. Following the results of this phase II study, we decided to investigate this combination with concurrent radiotherapy in locally advanced disease. To determine a recommended dose and to evaluate the efficacy of NDP and FU combined with concurrent radiotherapy, we conducted a phase I/II study in patients with T4 (according to the International

Union Against Cancer tumor-node-metastasis system, 1997) esophageal cancer.

Patients and methods

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven squamous cell carcinoma of the thoracic esophagus; clinical tumor-node-metastasis system T4 disease without distant organ metastasis but supraclavicular and celiac nodes metastases were allowed; age, 20–70 years; performance status (PS; based on the Eastern Cooperative Oncology Group scale), 0–2; adequate hematologic [white blood cell count (WBC) count ≥ 4000/mm^3, platelet count ≥ 100000/mm^3, and hemoglobin ≥ 9.5 g/dl], hepatic [aspartate amino transferase (AST) and alanine amino transferase (ALT) level ≤ 2.5 times the upper limit of normal, and total bilirubin ≤ 1.5 mg/dl], and renal (creatinine ≤ 1.2 mg/dl and creatinine clearance ≥ 50 ml/min) functions; PaO_2 ≥ 70 torr; no esophageal fistula; no pleural and pericardial effusion; and no serious comorbidity. All patients gave written informed consent in accordance with institutional review boards.

Pretreatment evaluation

Pretreatment evaluation included history and physical examination; complete blood cell count; serum chemistries; chest radiograph; barium swallow; endoscopy of the esophagus; computed tomography (CT) scan of the neck, the chest, and the abdomen; and electrocardiogram. Endoscopic ultrasonography of the esophagus was optional. Bronchoscopy was performed if tracheobronchial involvement was suspected and surgical resection was under consideration. The tracheobronchial tree was judged to be involved if the tumors extended into the lumen or caused deformity of the lumen. The descending aorta was judged to be involved if the contact angle of the tumor was 90° or greater on the CT scan. Metastatic lymph nodes were defined if they were ≥1 cm in longest diameter on any imaging.

Treatment details

The treatment consisted of two cycles of NDP (level 1, 80 mg/m^2; level 2, 90 mg/m^2) on day 1 and continuous infusion of FU 800 mg/m^2/day on days 1–5, every 5 weeks, with concurrent radiotherapy at 60 Gy in 30 fractions over 6 weeks. The dose level of NDP was set referring to the results of a preceding phase I/II study in patients with metastatic esophageal cancer (data not shown). The second cycle of chemotherapy was set in the 6th week referring to a CDDP/5-FU chemoradiation regimen used in our institutions [5]. Radiotherapy was delivered with megavoltage equipment using anterior/posterior opposed fields up to 40 Gy including the primary tumor and the metastatic lymph nodes. An additional dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique or multiple fields. The clinical target volume for the primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally, and the clinical target volume for the metastatic nodes was the same as the gross tumor volume. The planning target volumes for the primary tumor and the metastatic lymph nodes were determined with 0.5- to 2-cm margins, taking account of setup variations and internal organ motion. Elective nodal irradiation was not intended in this study. Lung heterogeneity corrections were not used.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) [13]. Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 3 months for the first years and every 6 months thereafter: physical examination, toxicity assessment, complete blood cell count, serum chemistry profile, endoscopy of the esophagus, and CT scan of the neck, the chest, and the abdomen. Biopsy of the primary tumor site was routinely performed at each follow-up examination. Pulmonary function test, electrocardiogram, and cardiac ultrasound were performed when indicated.

Response assessment

Complete response (CR) for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared with negative biopsy and lasted for ≥4 weeks.

Responses of the metastatic lymph nodes were assessed using the World Health Organization response criteria for measurable diseases. Briefly, CR was defined as the complete disappearance of all measurable and assessable disease for ≥4 weeks. Uncertain CR (uCR) was defined when small nodes (≤1 cm) persisted with no evidence of progression for ≥3 months after completion of treatment, and it was also included in CR.

Patterns of failure

Patterns of failure were defined as the first site of failure. Local/regional failure included the primary tumor and

regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Study design and statistics

Two dose levels were set following the results from a preceding phase I study for metastatic esophageal cancer. A recommended dose for phase II was determined using the conventional 3 × 3 method. Dose-limiting toxicities (DLTs) were defined as follows: treatment-related death; grade 4 thrombocytopenia; grade 4 vomiting; PS 3; grade 3 febrile neutropenia persisting ≥4 days; and grade 3 nonhematologic toxicities excluding anorexia, nausea, vomiting, esophageal fistula, esophagitis, and infection due to esophageal fistula. It was also regarded as DLT if radiotherapy could not be completed within 60 days or if protocol treatment could not be completed because of any adverse event. For exploratory evaluation of the efficacy of this treatment, the sample size for phase II part was determined following the assumption that a CR rate of less than 20% would not be promising and a CR rate of 40% or greater with α error of 0.10 and β error of 0.20 would warrant further investigation of this regimen. Taking into account that 10% of the patients may be ineligible, the total sample size including phase I part was determined to be 25 to 40. Survival was measured from the first day of treatment. Death from any cause was included as an event in the overall survival, and any failure and any cause of death were included as events in the progression-free survival. The overall and the progression-free survival curves were calculated by the Kaplan–Meier method [14].

Results

Patient population

Between December 1999 and April 2002, 26 patients were enrolled in the study: 3 patients at level 1 and 23 patients at level 2. Their median age was 60 years (range, 45–69 years), 25 were male, and 1 was female. Patient and tumor characteristics are summarized in Table 1.

Table 1. Patient and tumor characteristics

Number of patients	26
Age	
Median	60
Range	45–69
Sex	
Male	25
Female	1
Performance status	
0	14
1	12
Location	
Ut	13
Mt	12
Lt	1
TNM	
T4	26
N0	5
N1	21
M0	17
M1a	5
M1b	4
Stage	
III	17
IV	9
Involved sites in T4	
Aorta	4
Bronchial tree	19
Both	3

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; TNM, tumor-node-metastasis classification

Treatment compliance and toxicity

One of 3 patients in the level 1 group and none of the first 3 patients in the level 2 group experienced DLT, and level 2 was determined to be the recommended dose. In total, including patients in the phase II part, 3 of 23 patients in the level 2 group experienced DLT. Twenty-four patients completed the protocol treatment, and 2 patients in the level 2 group could not complete the treatment due to DLT. Eight patients had treatment delay before delivering the second cycle of chemotherapy as a result of hematologic toxicity in 7 patients and pneumonia caused by esophageal fistula in 1 patient. The median overall treatment time of radiotherapy was 44 days (range, 42–56 days), and 21 patients completed radiotherapy within 49 days.

Common grade 3 or greater acute toxicities were leukopenia, 9 (35%); neutropenia, 5 (19%); thrombocytopenia, 4 (15%); esophagitis, 4 (15%); and esophageal fistula, 3 (12%). There was no treatment-related death. The toxicity profile is shown in Table 2. As of the date of this analysis, 1 case with grade 3 pericardial effusion, 1 with grade 3 pleural effusion, and 2 with esophageal stenosis were observed as late toxicities.

Response and survival

Of all 26 registered patients, 3 achieved CR with a CR rate of 12% [95% confidence interval (CI), 2%–30%]. With a minimum follow-up period of 26 months for surviving patients, the median survival and the 1- and 2-year survivals were 12 months (95% CI, 9–22 months), 50% (95% CI, 31%–69%), and 31% (95% CI, 13%–49%), respectively (Fig. 1). The median progression-free survival and the 1-year progression-free survival were 6 months (95% CI, 5–8 months) and 27% (95% CI, 10%–44%), respectively. Two of 3 CR patients and 6 of 23 non-CR patients survived more than 2 years.

Patterns of failure

At the time of this analysis, 22 of 26 patients (85%) showed tumor progression, and 4 patients (15%) were alive without disease progression. The patterns of first failure were local/

Table 2. Acute toxicities[a]

	Level 1 ($n = 3$)					Level 2 ($n = 23$)					Total
	Grade					Grade					≥Grade 3 (%)
	0	1	2	3	4	0	1	2	3	4	
Hemoglobin	0	3	0	0	0	1	13	9	0	0	0
Leukocytes	0	0	2	1	0	1	3	11	7	1	35
Neutrophils	0	0	2	1	0	4	7	8	3	1	19
Platelets	2	0	0	1	0	8	7	5	2	1	15
Creatinine	3	0	0	0	0	22	1	0	0	0	0
Performance status	1	2	0	0	0	4	16	3	0	0	0
Infection	2	0	0	1	0	14	2	5	2[b]	0	12
Diarrhea	1	2	0	0	0	17	5	1	0	0	0
Esophagitis	1	2	0	0	0	5	11	3	4	0	15
Esophageal fistula	3	–	–	0	0	20	–	–	3	0	12
Mucositis/stomatitis	3	0	0	0	0	14	4	3	2	0	8
Nausea	2	1	0	0	0	10	10	3	0	0	0
Vomiting	2	1	0	0	0	14	7	2	0	0	0
Dyspnea	3	0	0	0	0	21	0	2	0	0	0
Pneumonitis	3	0	0	0	0	22	0	1	0	0	0

[a] National Cancer Institute–Common Toxicity Criteria version 2
[b] Both cases were caused by esophageal fistula

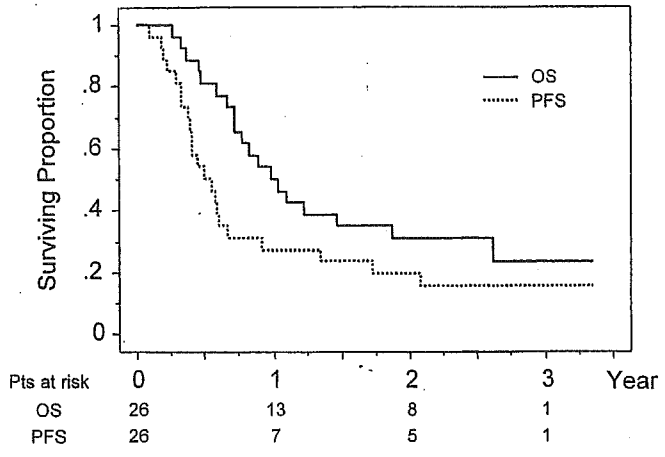

Fig. 1. Overall survival (*OS*) and progression-free survival (*PFS*) for all patients (*Pts*) enrolled in this study

regional only, 12 (46%); local/regional and distant, 3 (12%); and distant only, 7 (27%). Four patients developed local/regional progression after the occurrence of distant metastasis, and two patients developed distant metastasis after local/regional failure. In total, 19 (73%) patients developed local/regional failure and 12 (46%) patients developed distant failure.

Discussion

In the past decade, chemoradiotherapy consisting of CDDP and FU with concurrent radiotherapy has become a standard of care in selected patients with unresectable locally advanced esophageal cancer. Ohtsu et al. [5] reported median progression-free survival, median survival, and 1-year overall survival in patients with T4 and/or M1 lymph node disease as 6 months, 9 months, and 41%, respectively. Grade ≥3 toxicities were also reported as follows: leukopenia, 24%; anemia, 24%; thrombocytopenia, 17%; esophagitis, 15%; and esophageal fistula, 10%. In our study, median progression-free survival, median survival, and 1-year survival were 6 months (95% CI, 5–8 months), 12 months (95% CI, 9–22 months), and 50% (95% CI, 31%–69%), respectively. Grade ≥3 toxicities were observed as follows: leukopenia, 31%; thrombocytopenia, 15%; esophagitis, 15%; and esophageal fistula, 12%. These results seemed comparable with CDDP and FU with concurrent radiotherapy, showing that the treatment regimen of NDP and FU with concurrent radiotherapy is effective in selected patients with T4 disease. However, these survival figures are far from satisfactory, and patterns of failure showed that about three-fourths of patients developed local/regional failure and about one-half of patients developed distant failure. We should make further efforts to improve local control and to prevent distant metastasis.

The dose-escalation strategy of radiotherapy was one way but was not proven to be effective in the INT 0123 study [15], and current approaches of escalating dose of radiotherapy with CDDP and FU could achieve incremental benefit but seem to have reached a plateau. Different combinations with a novel cytotoxic drug are another way to improve survival. Paclitaxel is active for both adenocarcinoma and squamous cell carcinoma of the esophagus. A phase II trial of paclitaxel in patients with advanced esophageal cancer showed a 34% response rate in adenocarcinoma and a 28% response rate in squamous cell carcinoma [16]. There is evidence of synergism between paclitaxel and CDDP or FU [17], and paclitaxel combined with CDDP and FU in patients with advanced esophageal cancer was tested in a phase II study [18]. This trial showed a 46% response rate in adenocarcinoma and a 50% response rate in squamous cell carcinoma. These encouraging results led to trials

employing induction chemotherapy followed by concurrent chemoradiotherapy with paclitaxel, CDDP, and FU, but the advantage of this approach has yet to be proven.

Recently, molecular targeted drugs have been enthusiastically investigated in various malignant diseases [19–22]. Epidermal growth factor receptor is one of the targets, and this has been shown to be effective in patients with head and neck cancer when combined with radiotherapy in a phase III study [23]. It seems reasonable to investigate whether the combination of these agents has a survival impact for esophageal cancer.

There is another concern about the response criteria in the treatment of esophageal cancer. We employed response criteria using endoscopy for the primary tumor, which seemed to be reliable in patients who received nonsurgical treatment [6]. In this trial, the CR rate obtained was far less than expected, and this treatment regimen should be deemed ineffective according to the predefined hypothesis. However, 2 of 3 CR patients and 6 of 23 non-CR patients survived more than 2 years, 3 of these 6 non-CR patients did not show any disease progression, and the median survival obtained was not worse than historical data. This discrepancy suggests that the CR criteria used in this trial was not applicable to T4 disease and thus the CR rate failed to be a surrogate endpoint for survival. We think that overall survival will be appropriate as a primary endpoint in future phase II trials for this patient population.

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