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Usefulness of the Outpatient Chemotherapy Regimen of S-1 Followed by Weekly Paclitaxel for Far Advanced Gastric Cancer

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Summary. **To evaluate outpatient treatment, as well as the clinical effect of 1M tegafur-0.4M gimestat-1 M otastat potassium(S-1) followed by weekly Paclitaxel(PTX) for patients with far advanced inoperable gastric cancer, we analyzed retrospectively the appropriateness of outpatient anticancer chemotherapy from the standards of overall survival and time without symptom and toxicity(TWiST) as a quality- adjusted survival analysis. A total of 18 patients with advanced inoperable gastric cancer were treated with S-1 as first line single-agent chemotherapy from May 1, 2000 to September 30, 2000 at the Niigata City General Hospital. S-1 (60 mg-120 mg/m^2/orally twice daily on Days 1-28 followed by a 14 days rest / course) was repeated until progression of the disease. After the first line was completed, a second line, PTX (60 mg-80 mg/m^2/infused on Day 1/week, three weeks and withdrawal for a week), was started two weeks later. PTX was repeated until progression of the disease. No severe adverse events (≧National Cancer Institute Common Toxicity Criteria ((NCI-CTC) grade 3) were observed. The median survival time (MST) overall including the first line and second line was 295 days. The hospitalization period was 60.0 days throughout the median of the total hospital stay and the rate was 25.6% in overall survival. There was no significant difference by histological type, metastasis, liver metastasis, or peritoneal dissemination. The median duration of TWiST as quality-adjusted survival analysis was 353 days in good performance status (PS) and 72 days in poor PS. S-1 followed by weekly PTX for various advanced inoperable gastric cancers appears to be a promising, appropriate, and well-tolerated anticancer chemotherapy regimen in an outpatient setting.**

Key words — S-1, Paclitaxel, gastric cancer, quality of life, quality- adjusted survival analysis.

INTRODUCTION

Chemotherapy for far advanced inoperative gastric cancers has been to extend survival time in comparison with the best supportive care (BSC) [1,2,3,4]. Various gastric cancer chemotherapies have been tried, but no standardized chemotherapy for gastric cancer has yet been established. Until recently, gastric cancer was regarded as a poorly chemo-responsive cancer; however, some new generation chemotherapeutic regimens prove quite effective against gastric cancer. 1M tegafur-0.4M gimestat-1M otastat potassium (S-1) and Paclitaxel (PTX) are widely used in single-agent or combination therapies in far advanced inoperable gastric cancers. On the other hand, it has been generally accepted that anticancer chemotherapy for outpatients improves the quality of life (QOL) of patients. Our aim is to prevent the growth of the tumor so as to control the symptoms rather than to reduce the tumor size. S-1 and weekly PTX are suitable for home therapy because these therapies are acceptable chemotherapies for gastric cancer with high effectiveness and few adverse events, and are compatible with different types of anticancer agents. [5,6]. We therefore adopted a regimen of S-1 followed by weekly PTX. In this study, our primary goal was to calculate the overall

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Abbreviations– PTX, Paclitaxel; S-1, 1M tegafur-0.4M gimestat-1M otastat potassium; TWiST, time without symptom and toxicity.

survival period from the start of Chemotherapy to death, and we evaluated the appropriateness of the anticancer chemotherapy for far advanced inoperable gastric cancers in an outpatient setting by analyzing the overall survival, length of hospital stay, and the quality-adjusted survival analysis.

PATIENTS AND METHODS

We investigated 18 patients with far advanced inoperable gastric cancer. The patients were treated from May 1, 2000 to September 30, 2000 at the Niigata City General Hospital. These cases and their response assessments were classified by the `Japanese Classification of Gastric Carcinoma, 2rd edition[7,8]. The chemotherapy consisted of S-1 as the first line (60 mg-120 mg/m^2/intake on Days 1-28 and withdrawal on Days 29-35/course, repeated) and PTX as the second line (60 mg-80 mg/m^2/infused on Day 1/week for three weeks and withdrawal for a week). To avoid hypersensitivity reactions, the following short premedication was given to all patients one hour before PTX treatment: Dexamethasone 20 mg intravenously (iv), and Ranitidine 20 mg (iv). The first line was repeated until the response showed progression of the disease (PD); the second line started two weeks later after first line ended.

The evaluation of response to gastric cancer was based on the following specific criteria according to the `Japanese Classification of Gastric Carcinoma, 2rd edition[7,8]. Toxicity was evaluated by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. The performance status (PS) was evaluated by the Eastern Cooperative Oncology Group (ECOG) at the first day of treatment[9]. Overall survival time was measured from the first day of the treatment until death or the last day of follow-up period and estimated using the Kaplan-Meier method. Data were analyzed using Stat View J 5.0 (Stat View, Tokyo).

The impact of this treatment on QOL was assessed by the time without symptom and toxicity(TWiST) index, expressed as time without symptoms of treatment and disease, in relation to the individual length of progression-free survival. According to the calculation by Wiilemse PH et al.[10], this can be stated as:TWiST= overall survival – hospital admissions – (outpatient with symptom periods or periods of home IVH + outpatients treatment days) ×0.5 .

As there was no control arm or randomization, this report comprises a retrospective observation from our hospital.

Table 1. Characteristics of 18 patients treated with S-1 followed by weekly PTX

Gender	[male/female]	14/4
Age (year)	[median]	66.7
	Range	41-84
Stage	II /III/IV	1/0/17
Pathology	[diff./undiff.]	4/14
Performance status	[0/1/2/3/4/]	3/5/4/3/3

Table 2. Adverse events

	Grade 1	Grade 2	%Grade 3-
Nausea/vomiting	1	4	0
Anorexia	9	0	0
Stomatitis	2	0	0
Hair loss	6	2	0
Diarrhea	2	0	0
AST	1	0	0
ALT	1	0	0
Leukocytes	1	0	0
Netrophils	2	0	0
Hemoglobin	0	0	0
Platalets	0	0	0

RESULTS

Eighteen patients were enrolled in the present analysis. Fourteen men and four women, with a median age of 66.7 years (range 41-81), were treated at our hospital. The each PS 0, 1, 2, 3, 4 groups was 3, 5, 4, 3, 3 cases. The most appropriate case was PS 0, 1, 2 groups; however, six cases of PS 3, 4 groups were treated due to the express wishes of their families. One patient at stage II was an inoperable case, due to poor pulmonary function. All of the other cases were at stage IV. Two patients with pylorus stricture were treated after the insertion of a self expandable stent into the stricture (Table 1).

The median survival time (MST) as a whole including the first line and the second line was 295 days. No severe adverse events (NCI-CTC grade 3, 4) were observed (Table 2). There was no significant difference in classified MST by pathological type (Fig.1A), liver metastasis (Fig.1B), metastasis (Fig.1C), and peritoneal

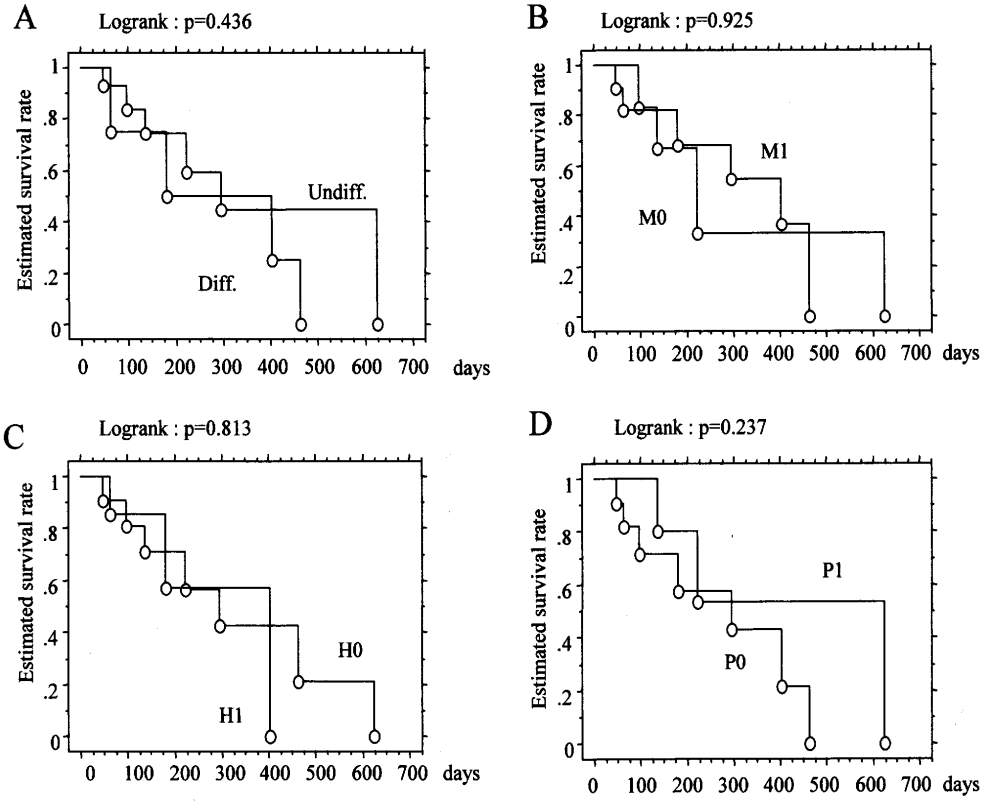

Fig 1. Examination of the two groups categorized by pathology and by the factors at stage IV. **A**. Overall survival rates of all patients with differentiated (diff) carcinoma or undifferentiated carcinoma (undiff). **B**. Overall survival rates of all patients with distant metastasis other than peritoneal, liver, or cytological metastasis (M1) and no other distant metastasis (although peritoneal, liver, or cytological metastasis may by present) (M0). **C**. Overall survival rates of all patients with liver metastasis (H1) or without liver metastasis (H0). **D**. Overall survival rates of all patients with peritoneal metastasis (P1) or without peritoneal metastasis (P0).

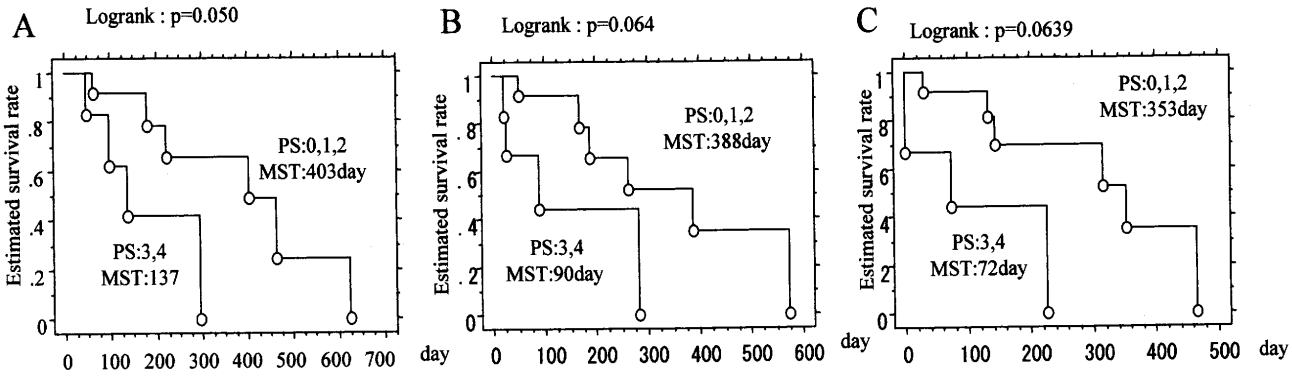

Fig 2. Examination of the two groups categorized by patient's status at the start of therapy. **A**. Overall survival rates of all patients with a PS of 0, 1, 2 and with a PS of 3, 4. **B**. Anticancer chemotherapy period of all patients with a PS of 0, 2, 3 vs. a PS of 3, 4. **C**. No chemotherapy period of all patients with a PS of 0, 2, 3 and with a PS of 3, 4.

dissemination (Fig.1D).

The MST of the only good PS 0,1,2 groups was 403 days. This MST was significantly longer than the MST of the poor PS 3,4 groups (Fig.2A). Naturally, the median of the anticancer chemotherapy period, good PS 0,1,2 groups was longer than the median of poor PS 3,4, groups (Fig.2B). The median duration of TWiST was 353 days in good PS 0,1,2 groups and 72 days in poor PS 3,4 groups.

The hospitalization period was 60.0 days throughout the median of the total hospital stay and the rate was 25.6% throughout the regimen.

DISCUSSION

Most S-1 treatment followed by weekly PTX can be conducted in an outpatient setting and a conventional therapy obtained better MST without any inferiority compared with other chemotherapies[11,12,13]. Also, this treatment may contribute to QOL improvement for the patient, mainly because of the outpatient treatment over the period when the symptoms have been stabilized.

Extension of the survival time is the final goals of cancer treatment; however, the tendency here is that the tumor-reducing effect corresponds to any of the representative guidelines and is considered as surrogate endpoint. Even the concept of aiming at longevity (=dormant) by proliferation control has been accepted in clinical practice as a treatment method on the basis of survival time[14].

Unfortunately, gastric cancer cannot be cured by chemotherapy only; therefore, the evaluation of overall survival including first line and further chemotherapy is clinically more important than the tumor-reducing effect. The QOL evaluation also needs to be clarified. From the clinical perspective, some objectives might include prolonging of the MST and TWiST.

One of the final goals of the cancer treatment is to improve the overall survival rate. If some therapies have equal effects, that therapy which improves QOL is the better therapy. A QOL survey is conducted with various scales. At present, the cancer specific scales often used in the West include EROTC QLQ-C30, and FACT-General. In Japan, the various rankings are made on the basis of the QOL-ACD that was set by the Kurihara Research Group of the Health and Welfare Ministry[15]. These scales are usually constricted by the core of the entire QOL scale and some modules: the type of cancer, degree of the disease, treatment differences, and symptoms. The important point to note is that reliability, appropriateness, and sensitivity of these psychological inspections are dependent on patient recognition of the survey vote. Therefore, in some patients with poor understanding, it was difficult to evaluate the survey feasibility. From now on, the impact of this treatment on QOL will be assessed by the TWiST index, expressed as Time Without Symptoms of Treatment and Disease, in relation to the individual length of progressive free survival and overall survival. TWiST is a quality-adjusted survival analysis encompassing such factors as the evaluation of participation with a possible healthy period so that the the result of multiplies the social activities[16,17]. TWiST objectively shows the possibility of a healthy outpatient period, maintaining social activities without symptoms. TWiST may be a suitable instrument for comparing the impact of different chemotherapy regimens in the outpatient setting[16,17].

S-1 followed by weekly PTX can provide regular survival irrespective of the variety of far advanced inoperable gastric cancers without a reduced TWiST. S-1 followed by weekly PTX for the far advanced inoperable gastric cancers seems to be one of the most promising, and appropriate well-tolerated anticancer chemotherapy regimens in the outpatient setting.

The evaluation from the perspective of quality-adjusted survival analysis is worth considering for chemotherapy for far advanced inoperable gastric cancers. In summary, S-1 followed by weekly Paclitaxel, for especially good PS patients, represents a reasonable standard anticancer chemotherapy regimen in the outpatient setting.

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