厚生労働科学研究費補助金

がん臨床研究事業

高度リンパ節転移を伴う進行胃癌の根治を目指した術前化学療法＋拡大手術法の確立

平成22年度　総括研究報告書

研究代表者　佐野　武

平成 23（2011）年 4 月

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研究代表者　佐野　武　　財団法人癌研究会有明病院　上部消化管担当部長

本研究は多施設共同の臨床試験であり、個々の分担研究者固有の研究はないため、本総括研究報告書がすべてを代表するものとする

研究要旨：高度リンパ節転移を有する胃癌に対し、Docetaxel＋CDDP＋S-1 というわが国独自の 3 剤併用療法による downstage と、専門施設による拡大リンパ節郭清を伴う胃切除術を加えて治癒率の向上をめざすという第 II 相試験を計画している。プロトコールがほぼ完成し、50 例の症例登録に向けて準備中である。本治療の効果と安全性が確認されれば、現在の暫定標準とされている S-1＋CDDP を対照とする第 III 相試験を行う予定である。

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A. 研究目的

高度リンパ節転移を伴う胃癌では、たとえ肉眼的治癒切除が行えたとしても予後は極めて不良である。しかし、遠隔転移、腹膜播種などの切除不能因子を有する進行胃癌と異なり、強力な術前化学療法と拡大手術の組み合わせにより治癒できる可能性がある。本試験は、このような対象に対してこれまで積み重ねてきた第 II 相試験をさらに発展させ、術前化学療法と拡大手術の最良の組み合わせ治療を確立することを目的とする。

高い奏効率が報告されている Docetaxel＋CDDP＋S-1（DCS）というわが国独自の 3 剤併用療法を用い、さらに専門施設による

拡大リンパ節郭清を伴う胃切除術を行うという、わが国のみで行い得る高度な治療法である。

B. 研究方法

JCOG 胃がんグループによる多施設共同第 II 相臨床試験としてスタートする。上腹部造影 CT にて高度リンパ節転移陽性（第 2 群リンパ節転移が一塊となって腫瘤を形成する Bulky N2 と、第 3 群大動脈周囲リンパ節 No.16a2/b1 転移のどちらか、または両方）と診断された症例を対象とし、DCS 療法を 2 コース行った後、腫瘍縮小効果を RECIST で評価し、手術を行う。治癒切除を目指し、D3 郭清を伴う胃切除を行う。術後は S-1 補助化学療法を 1 年間行う。

主評価項目は術前化学療法による奏効割合、副次評価項目は 3 年生存割合、5 年生存割合、根治切除割合、治療完遂割合、組織学的奏効割合、有害事象発生割合とする。平成 23 年度早々にプロトコールを完成させ登録を開始する。平成 24 年度末までに 50 例を集積し、安全性・有効性が認められれば、現在暫定標準とみなされる術前 S-1 + CDDP を対照として、第 III 相試験を開始する予定である。

C. 研究結果

平成 22 年度は、班会議を通じて JCOG 胃がんグループの参加外科医・腫瘍内科医と協議しつつプロトコール作成を行った。DCS 療法の投与スケジュールについては、当初金沢大学外科のレジメンを採用する計画であったが、臨床腫瘍学的標準化の立場から、すでに第 2 相試験が論文報告されている北里大学レジメンを用いることとなった。

対象および治療効果判定方法については、これまで行ってきた二つの第 2 相試験との比較性を保つためにこれらと同一の基準を用いることとした。

リンパ節郭清の程度に関しては大きな議論となった。治療前に大動脈周囲リンパ節 No.16 が腫大している症例に関してはこれを切除する D3 郭清を行うことで問題はないが、No.16 に腫大がなく、第 2 群のみが大きく腫大している Bulky N2 症例で D3 を行うべきか否かで意見が伯仲した。最終的には、やはり従来の試験との比較性を保つことも念頭に、全例 D3 を行うことで意見の統一をみた。

JCOG プロトコール審査委員会の審査を経て改訂を行い、最終審査を待つ段階となった。

D. 考察

T1 胃癌の予後は極めて良好で、T2、T3 胃癌の手術成績も高く、S-1 補助化学療法がこれをさらに改善している。一方、切除不能因子（腹膜播種や遠隔転移）を有する胃癌の予後は未だに極めて不良で、現在の化学療法にはこれを治癒せしめるパワーはない。この境界域にあると考えられるのが①スキルス型浸潤を示す腫瘍と②高度リンパ節転移を有する腫瘍である。これらは、肉眼的治癒切除が行えたとしても予後は不良（3 年生存割合 15-20%）であり、術後補助化学療法の効果も不十分である。

①に対しては現在すでに S-1+CDDP による術前化学療法の効果を検証する第 III 相試験（JCOG 0501）が進行中であるが、②は比較的頻度が低く、かつ侵襲を伴う高度

なリンパ節郭清手技を要求されるため、慎重に第 II 相試験が行われつつあるのが現状である。ところが最新の試験（JCOG 0405）では予想をはるかに上回る治癒切除達成率と 3 年生存割合が示されており、②は実は高い治療効果の望める対象であることが明らかになってきた。化学療法レジメンと拡大手術の最良の組み合わせを確立するには、質の高い第 II 相試験とこれに続く多施設共同の第 III 相試験が必須である。

JCOG 胃がん外科グループでは、高度リンパ節転移を有する胃癌に対しまず CDDP + CPT-11 と D3 郭清手術による第 II 相試験（JCOG 0001）を行ったところ、54.5%の臨床奏効割合と期待閾値を上回る 27%の 3 年生存割合を達成したものの、治療関連死が 3 例発生して試験が中止となった（Yoshikawa, Br J Surg, 2009）。同じ対象に対して S-1 + CDDP と D3 郭清手術を行った JCOG 0405 では、臨床奏効割合 64.7%、根治切除割合 82.4%を達成し、かつ 3 年生存割合 59%という成績が得られた。本研究では、DCS というわが国独自の強力な 3 剤併用療法を用いることで、さらに高い治癒をめざす。

平成 23 年 4 月より、JCOG 胃がんグループは再編成され、54 の医療機関を含む大きなグループとなった。本試験参加予定施設に年間登録可能症例数の予測をきいたところ、50 例の登録は 1 年以内に終了する可能性が示されている。

E. 結論

高度リンパ節転移を有する胃癌に対し、現時点では術前 S-1 + CDDP と D3 胃切除（JCOG 0405）で得られた成績が最良である。本研究では、さらに生存期間の改善を目指して DCS という強力な術前化学療法と拡大郭清手術を行い、これまで極めて予後不良と事実上諦められていた症例の多くに治癒をもたらすことが期待される。

今日のわが国の胃癌は、確実に治る早期癌と、非治癒因子を持つ高度進行癌に 2 極化されつつあると言われるが、この境界領域にある本研究対象患者の予後が改善すれば、わが国のみならず世界の胃癌治療全般の底上げにつながる。また、このような毒性の強い化学療法と拡大手術の組み合わせ治療が、外科医を中心とするグループで安全に施行可能であることが示されれば、腫瘍内科医が絶対的に不足するわが国の胃癌患者にとって朗報となろう。

F. 健康危機情報

本研究では該当する危機情報はなかった。

G. 研究発表

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H. 知的財産権の出願・登録状況

特に予定していない。

研究成果の刊行・発表に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Fukagawa T, Katai H, Saka M, Morita S, Sasajima Y, Taniguchi H, Sano T, Sasako M.	Significance of lavage cytology in advanced gastric cancer patients.	World J Surg	34	563-568	2010
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World J Surg
DOI 10.1007/s00268-009-0355-1

World Journal of Surgery

Significance of Lavage Cytology in Advanced Gastric Cancer Patients

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Abstract

Background Lavage cytology positive (Cy1) is well known as a poor prognostic factor in advanced gastric cancer patients. However, the optimal therapeutic strategy for patients with Cy1 has not yet been established. The aim of this study was to evaluate the clinical significance of Cy1 for the purpose of establishing a suitable therapeutic strategy.

Methods The data of 996 consecutive advanced gastric cancer patients who underwent gastrectomy between 1992 and 1998 at the National Cancer Center Hospital were retrospectively studied.

Results The 2- and 5-year survival rates of the patients who underwent gastrectomy without any other noncurative factors besides Cy1 were 25.3 and 7.8%, respectively. When the analysis was limited to type 4 advanced gastric cancer patients, none of the patients with Cy1 survived for more than 40 months.

Conclusions The prognosis of gastric cancer patients with Cy1 is very poor. Some patients show long survival after standard gastrectomy with D2 lymph node dissection; however, the prognosis of type 4 gastric cancer patients with Cy1 is so poor that multimodality therapy, including perioperative chemotherapy, is essential.

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Introduction

Recently, standard therapeutic strategies have been established for gastric cancer patients based on the results of some clinical trials [1–3]. The treatment outcomes of early gastric cancer patients are now favorable [4] due to the remarkable progress in endoscopic treatments [5, 6] and minimally invasive surgery, including function-preserving gastrectomy [7] and laparoscopic gastrectomy [8]. However, many surgeons believe that the treatment outcomes of advanced gastric cancer patients remain poor.

Peritoneal dissemination is one of the most frequent modes of metastasis in advanced gastric cancer. The possibility of cure in patients with this metastasis is considered to be low because no effective curative therapy has been established so far. Even after curative surgery in patients without evidence of peritoneal dissemination at the time of the operation, many patients develop peritoneal recurrence, which is extremely difficult to overcome [9].

The majority of patients showing lavage cytology-positive (Cy1) intraoperatively develop peritoneal recurrence [9]. Cy1 can be interpreted as a state in which free cancer cells are floating in the abdominal cavity, with small peritoneal foci already established in the peritoneum [10]. However, despite Cy1 being recognized as a definite predictive factor for peritoneal recurrence of gastric cancer[11–13], no effective treatment strategies have been established for Cy1 gastric cancer patients. In some cases prolonged survival has been achieved, even in Cy1 patients. When the analysis is limited to patients with type

Published online: 07 January 2010

4 advanced gastric cancer, however, the prognosis of Cy1 seems to be particularly severe [14].

In this study, the exact relevance of Cy1 and the clinical outcomes of these patients were evaluated based on data from a large-volume center of gastric cancer patients. This is expected to be helpful for developing a suitable new therapeutic strategy for this condition.

Patients and methods

The data of 996 consecutive patients who underwent gastrectomy between 1992 and 1998 for advanced gastric cancer that invaded the gastric wall deeper than the muscularis propria, as assessed by histopathological examination performed after the surgery at the National Cancer Center Hospital, were studied retrospectively. All patients underwent partial or total gastrectomy with lymph node dissection. Basically, patients with peritoneal dissemination underwent simple gastrectomy with minimum dissection; other patients underwent standard dissection. Patients with preoperative, clinically definitive peritoneal dissemination, i.e., ascites, hydronephrosis, and colonic stenosis by barium enema study, were not included in this study. Both the patients with diffuse peritoneal dissemination detected at surgery and those with locally resectable peritoneal dissemination were included in this study.

The former Japanese Classification of Gastric Carcinoma defined peritoneal dissemination as P0, P1, P2, and P3 according to its extent, while the current classification (13th) is P0 and P1: with or without. All patients were classified according to the Japanese Classification of Gastric Carcinoma. Macroscopic features of advanced gastric cancer are classified as type 0: superficial, flat tumors; type 1: polypoid tumors; type 2: ulcerated tumors; type 3: ulcerated tumors without definite limits; type 4: diffusely infiltrating carcinomas; and type 5: nonclassifiable carcinomas. For the purpose of the present analysis, the patients were divided into two groups based on the macroscopic features of type 4 gastric cancer and others.

Cytopathology

Cytological samples were obtained just after laparotomy. Approximately 100 ml of sterile saline was instilled into the pouch of Douglas and then aspirated. The samples were subjected to cytocentrifugation onto slide glasses at 1700 rpm for 60 s at room temperature. The slides were then fixed in 95% ethanol, followed by Papanicolaou and alcian blue stains. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010,Tokyo, Japan), and also for epithelial antigen using the BerEP4 antibody (DAKOPATTS, Glostrup, Denmark). Two to three cytotechnologists and cytopathologists independently examined all the slides to arrive at a diagnosis by consensus. A patient was considered to have positive peritoneal cytology (Cy1) if adenocarcinoma cells were detected, regardless of the number of cells. In cases where atypical cells were present but could not be definitely identified as cancer cells, the peritoneal cytology was estimated as class 3, or indeterminate. Basically, lavage cytology was carried out intraoperatively for advanced gastric cancer cases. The data of cytology in this article, recorded in our database, is the final result confirmed by immunohistochemistry several days after surgery.

Statistical analysis

Statistical analysis was carried out using SPSS software version 11.5 (SPSS Inc., Chicago, IL). The Kaplan–Meier method was used for constructing the survival curves, and the log-rank test was used for evaluating the statistical significance of differences between the survival curves.

Results

Among the 996 cases included in our study, cytological examination was performed in 779 (Table 1). Cytological examination was positive for cancer cells mainly in advanced gastric cancer patients in whom the tumor had invaded outside the serosal surface (T3) or directly invaded adjacent organs (T4) (Table 1).

As expected, many of the patients with peritoneal dissemination (P1) were cytology-positive (Cy1) but 27 patients with peritoneal dissemination (P1) were cytology-negative (Cy0) (Table 2).

Among the 996 consecutive patients, 217 patients who did not undergo cytological examination and 13 whose cytological examination revealed an indeterminate result were excluded from the analysis; in addition, 65 patients who had distant metastasis to the liver, lung, and supraclavicular lymph nodes were also excluded. The remaining

Table 1 Correlation between cytological examination and the depth of the tumors

	T2 (MP)	T2 (SS)	T3	T4	Total
Cy0	78	156	251	56	541
Cy1	1	5	137	82	225
Indeterminate	0	0	9	4	12
Undone	105	58	44	10	217
	184	219	441	152	996

MP muscularis propria, *SS* subserosa, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 2 Correlation between the results of cytological examination and presence/absence of peritoneal dissemination

	P0	P1	Total
Cy0	514	27	541
Cy1	101	124	225
Indeterminate	8	5	13
Undone	196	21	217
	819	177	996

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 3 Number of patients per peritoneal dissemination and cytology type of tumors

	Type4	Other Types	Total
P0Cy0	53	432	485
P0Cy1	33	55	88
P1Cy0	9	13	22
P1Cy1	61	45	106
	156	545	701

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

701 patients were divided into four groups: (1) peritoneal dissemination-negative and cytology-negative (P0Cy0), (2) peritoneal dissemination-negative and cytology-positive (P0Cy1), (3) peritoneal dissemination-positive and cytology-negative (P1Cy0), and (4) peritoneal dissemination-positive and cytology-positive (P1Cy1). The number of patients in each category is given in Table 3.

Survival

The overall survival curves of the four groups are shown in Fig. 1. The prognosis of the patients with P1 and/or Cy1 was worse than that of the patients with P0Cy0. The prognosis of the P0Cy1 patients was better than that of the P1Cy1 patients ($p = 0.0002$, log-rank). The median survival time of the P0Cy1 patients was 12 months. The 2-year and 5-year survival rates in the P0Cy1 patients were 25.3% (95% confidence interval [CI] = 16.2–34.4%), and 7.8% (95% CI = 2.0–13.5%) (Table 4). Five (5.7%) of the 88 P0Cy1 patients survived for more than 5 years without evidence of recurrent disease.

The 88 P0Cy1 patients consisted of 33 patients with type4 gastric cancer and 55 with other types of gastric cancer. The survival of P0Cy1 patients with type 4 gastric cancer was significantly worse than that of the patients with other types of gastric cancer, as shown in Fig. 2 ($p = 0.0072$, log-rank). The median survival time was 10 months. The 2-year survival rate was 12.1% (95% CI = 0.12–22.1%) (Table 4). None of the patients survived for more than 40 months. Among the 88 P0Cy1 patients, 51 patients received postoperative adjuvant chemotherapy, mainly based on fluorouracil, while 35 did not, although this was not randomized. There was no information about adjuvant therapy for two patients who had moved to other hospitals soon after surgery. There was no significant difference in the survival curves between the P0Cy1 patients who received and did not receive adjuvant chemotherapy ($p = 0.1238$, log-rank) (Fig. 3).

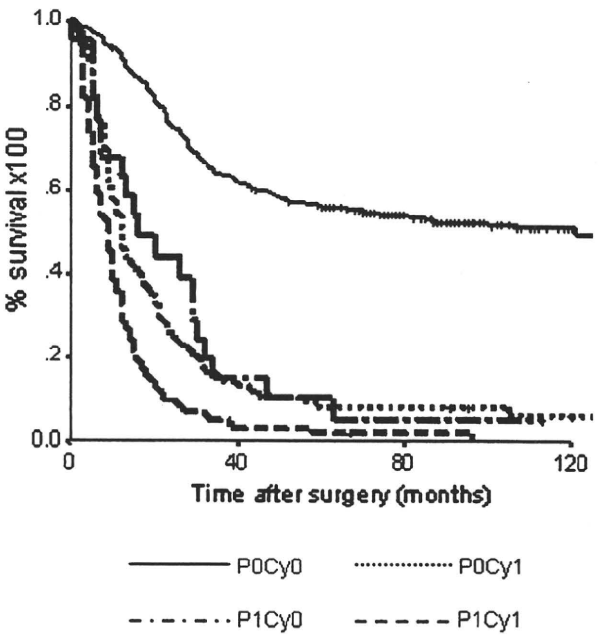

Fig. 1 Overall survival curves of gastric cancer patients (P0Cy0, P0Cy1, P1Cy0, and P1Cy1) are shown. The survival of P0Cy1 patients was poor but better than that of P1Cy1 patients ($p = 0.0002$)

Discussion

Lavage cytology-positive (Cy1) is most commonly encountered among gastric cancer patients with deeply invading tumors that extend outside the gastric wall [9, 15]; therefore, it is thought that the cancer cells escape from the surface of the tumors into the intraperitoneal cavity [16]. This is not clearly supported by some experiments, but Cy1 may reflect systemic spread of the tumor cells via the lymphatic pathway, which can cause retroperitoneal invasion, hydronephrosis, and rectal stenosis [17].

The prognosis of the patients who are found at the time of surgery to show peritoneal dissemination is expectedly very poor. The indication of mass reductive or palliative surgery should be evaluated by clinical trial [18], but it is regarded, by consensus, that gastric cancer patients with

Table 4 Survival rate and median survival time of P0Cy1 gastric cancer patients per type of tumor

	1 year	2 years	3 years	5 years	MST
P0Cy1					
All ($n = 88$)	46.0 (35.5–56.5)	25.3 (16.2–34.4)	13.8 (6.5–21.0)	7.8 (2.0–13.5)	12 (9.7–14.3)
Type 4 ($n = 33$)	45.5 (28.5–62.4)	12.1 (0.1–22.1)	0	0	10 (6.8–13.2)
Others ($n = 55$)	51.9 (38.5–65.2)	33.3 (20.8–45.9)	22.2 (11.1–33.3)	12.5 (3.5–21.5)	13 (7.6–18.4)

MST median survival time in months (95% confidence interval)

Values are % (95% confidence interval)

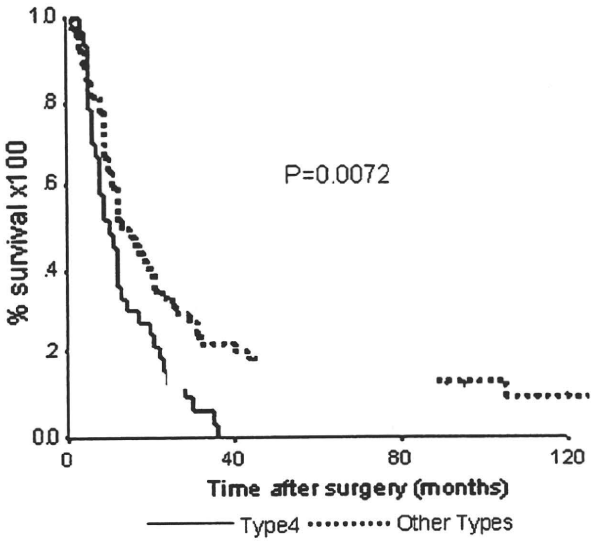

Fig. 2 The survival of P0Cy1 patients with type 4 advanced gastric cancer was significantly worse than that of patients with other types of advanced gastric cancer ($p = 0.0072$)

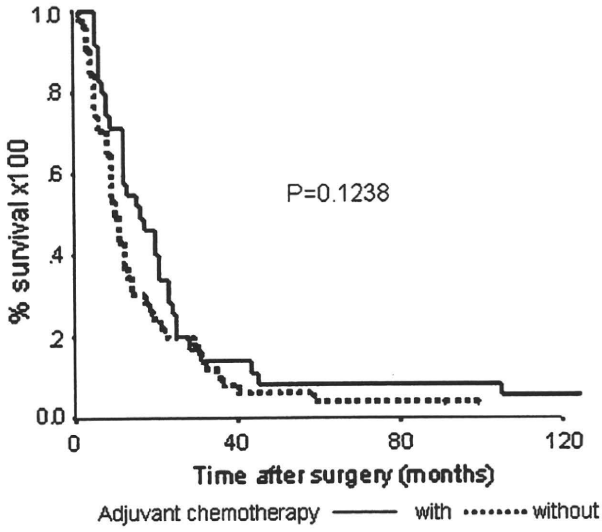

Fig. 3 There was no significant difference in the survival curves between P0Cy1 patients treated/not treated by adjuvant chemotherapy ($p = 0.1238$)

definite peritoneal dissemination are not suitable candidates for gastrectomy.

Cytological examination of intraperitoneal lavage fluid is performed in many institutions in Japan. In some institutions the result is confirmed intraoperatively, while in others it is confirmed on the following day. Cy1 is now included as one of the factors defining Stage IV in the Japanese classification of gastric carcinoma [19] because the prognosis of these patients with Cy1 is poor. However, the knowledge of a patient being Cy1 alone does not seem to be sufficient to decide on the therapeutic procedure [20]. The current consensus is that gastric cancer patients with intraoperatively confirmed Cy1 undergo standard gastrectomy and postoperative adjuvant chemotherapy [21]. Extended lymph node dissection and resection of other organs have gradually become less frequent in these patients. The efficacy of adjuvant chemotherapy with S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) after curative surgery has been reported [3]; however, no satisfactory postoperative adjuvant chemotherapy regimen for gastric cancer patients with Cy1 has been established. In our study, adjuvant chemotherapy using agents other than S-1 yielded no survival benefit. At our institution, S-1 was given as adjuvant chemotherapy to the patients, mainly after the end of the study period. In a future article we shall report on the efficacy of adjuvant chemotherapy with S-1 in gastric cancer patients with Cy1 compared with that in the subjects of this study as the historical control.

In this study, the 5-year survival rate of gastric cancer patients with P0Cy1 was 7.8%. This poor result must be interpreted as suggesting that previously used treatment, including surgery alone, was not suitable for these patients [22]. If those patients undergo surgery first, more intensive adjuvant chemotherapy would be needed. Currently, S-1 is given to these patients as adjuvant therapy [21, 23], but is S-1 monotherapy sufficient? A feasibility study of S-1 plus platinum as adjuvant therapy is ongoing (data not published); however, compliance with this therapy may not be favorable due to the unstable postoperative status of the gastric cancer patients. It is quite natural to expect that preoperative chemotherapy might be useful for those patients [24].

In order to carry out preoperative chemotherapy, information on Cy1 must be confirmed by staging laparoscopy [25]. In Japan, staging laparoscopy has been popular, but it may be difficult for it to be routinely performed in every advanced gastric cancer patient at every institution. Definitive evidence on the efficacy of preoperative chemotherapy, such as that from the MAGIC trial [26], is mandatory for encouraging the use of this therapy in Japan.

When only type 4 advanced gastric cancer patients are included in the analysis, the prognosis of those with Cy1 is extremely poor. No patient survived for more than 40 months after surgery in this study. The survival curve of the patients with P0Cy1 was almost the same as that of the patients who were found to have peritoneal dissemination (P1Cy1) at the time of the surgery (data not shown). The indication for gastrectomy for these patients must be discussed [27]. No surgeon performs gastrectomy for linitis plastica with peritoneal dissemination, except for palliating stenosis or bleeding. The former therapeutic strategy of immediate surgery and adjuvant chemotherapy has a less curative power for these patients with such a poor prognosis, and preoperative chemotherapy should be tried. Controlled arm may be the chemotherapy without surgery [28]. Information on Cy1 is necessary for determining the therapeutic strategy in patients with type 4 advanced gastric cancer, therefore, staging laparoscopy must be carried out first.

The patients with peritoneal dissemination are not always cytology-positive. The survival of P1Cy0 patients is better than that of P1Cy1 patients (Fig. 1) ($P = 0.0028$, log-rank). When the analysis is limited to type 4 gastric cancer, the survival of P1Cy0 patients is also better than that of P0Cy1 and P1Cy1patients (not shown), but the sample size (P1Cy0: $n = 9$) is too small for statistical evaluation. The P1Cy0 patients with local disseminated nodules may be the subset that can benefit from intraoperative chemotherapy.

In conclusion, curative treatment has been scarce for gastric cancer patients with Cy1 until now. The prognostic benefit of adjuvant chemotherapy with S-1 has been expected for years, but more intensive adjuvant chemotherapy, preoperative chemotherapy, and intraperitoneal chemotherapy [29] also warrant trials. The prognosis of type 4 gastric cancer patients with Cy1 is especially poor; therefore, it is recommended that such patients be treated at large-volume institutions with new therapeutic strategies developed based on clinical trials.

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Cancer Chemother Pharmacol
DOI 10.1007/s00280-010-1432-8

ORIGINAL ARTICLE

Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer

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Received: 25 April 2010 / Accepted: 13 August 2010

Abstract
Purpose To evaluate the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III gastric cancer after curative resection.
Methods Japanese patients with stage III gastric cancer who underwent gastrectomy with D2 lymph node resection were enrolled. Treatment consisted of 3 cycles of S-1 (80 mg/m^2/day, b.i.d.) for 21 days followed by a 14-day rest, and cisplatin (60 mg/m^2 iv) on day 8. After that, S-1 monotherapy was given on days 1–28 every 6 weeks until 1-year postsurgery. After protocol amendment, the first chemotherapy cycle consisted of S-1 monotherapy; cisplatin was added to cycles 2, 3, and 4, followed by S-1 monotherapy up to 1-year postsurgery. The primary endpoint was the completion rate of three cycles of S-1 plus cisplatin.

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Published online: 01 September 2010

Results A total of 63 enrolled patients have been evaluated. Grade 3/4 toxicities included neutropenia (40%), anorexia (28%), and febrile neutropenia (4%) before protocol amendment ($n = 25$), and neutropenia (37%), anorexia (8%), and febrile neutropenia (3%) after amendment implementation ($n = 38$). Excluding ineligible cases, treatment completion rates were 57% (12/21) before and 81% (30/37) after the protocol amendment.

Conclusions The amended S-1 plus cisplatin is more feasible than the original protocol because of early dose reduction of S-1 prior to cisplatin addition and greater recovery time from surgery prior to cisplatin. This treatment should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

Gastric cancer (GC) remains a major health problem with approximately 8,03,000 deaths worldwide in 2004, although the mortality rate has steadily decreased in recent years [1]. The primary treatment for GC is surgery, which is almost always curative in early GC (stage I) patients, who have a >90% 5-year survival rate. However, locally advanced (stage II–III) GC often recurs, even after curative resection is performed. Therefore, it is very important to develop adjuvant chemotherapy regimens that can improve survival in GC patients with stage II–III disease after surgical resection.

Until recently, several randomized controlled trials of postoperative adjuvant chemotherapy for GC were conducted [2–12]. Although most of them have failed to show clinical benefit in particular multi-agent anthracycline or cisplatin-based regimens, a recent meta analysis showed that postoperative adjuvant chemotherapy was associated with reduced risk of death compared with surgery alone [13].

S-1 (TS-1, Taiho Pharmaceutical Co.) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil) [14] approved in Japan, Korea, Singapore, and China for GC. In 2007, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial demonstrated the efficacy of S-1 for stage II–III GC patients who underwent curative resection with D2 lymphadenectomy [15]. S-1 improved the 3-year overall survival (OS) rate from 70.1% for surgery alone to 80.1%, with a low incidence of adverse events and good compliance with treatment for 3 months in 87.4% and for 6 months in 77.9%. However, the 3-year OS rates in stage IIIA and stage IIIB patients receiving S-1 were 77.4 and 63.4%, respectively, which are less satisfactory compared with the rate for stage II (90.7%). Therefore, further investigation into more effective treatments for patients with stage III GC is urgently needed.

Meanwhile, for metastatic or recurrent GC, the phase III trial comparing S-1 alone to S-1 plus cisplatin (S-1 Plus cisplatin vs. S-1 In RCT In the Treatment for Stomach cancer; SPIRITS trial) showed that S-1 plus cisplatin resulted in a significantly higher response rate, longer progression-free survival (PFS), and longer OS [16]. Another phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial) showed that S-1 plus cisplatin was associated with fewer toxic effects and demonstrated noninferiority compared with infusional fluorouracil and cisplatin [17]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent GC, as well as a candidate for an experimental arm in the next adjuvant chemotherapy trial.

Before comparing S-1 monotherapy with S-1 plus cisplatin in a phase III trial, we first evaluated the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III GC after curative resection, to confirm that S-1 plus cisplatin can safely be used.

Patients and methods

Eligibility criteria

The following eligibility criteria were employed: (1) histologically proven adenocarcinoma of the stomach; (2) ≥ D2 lymphadenectomy, with complete resection of the primary tumor (R0 surgery); (3) stage IIIA/IIIB disease (T2, N2; T3, N1–2; or T4, N0–1 [Japanese classification]); (4) ECOG performance status 0–1; (5) age 20–75 years; (6) no prior chemotherapy or radiotherapy; (7) able to be enrolled 4–8 weeks after surgery; (8) sufficient oral food intake; (9) adequate organ function (white blood cells [WBCs] $\geq 3{,}000/mm^3$ and $\leq 1{,}20{,}000/mm^3$, neutrophils $\geq 1{,}500/mm^3$, hemoglobin ≥8.0 g/dl, platelets $\geq 1{,}00{,}000/mm^3$, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels ≤100 IU/l, total serum bilirubin ≤2.0 mg/dl, serum creatinine concentration ≤1.2 mg/dl, estimated creatinine clearance ≤60 ml/min, normal electrocardiogram); and (10) written informed consent obtained from the patient. Disease stage was classified according to Japanese Gastric Cancer Association guidelines [18]. The protocol was approved by the institutional review board at each participating center.

Treatment and toxicity assessment

Treatment according to the original protocol was begun 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin ("S-1+ cisplatin [SP] step") followed by S-1 monotherapy ("S-1 step") up to 1 year after surgery. In the "SP step", each cycle consisted of 40 mg/m^2 of S-1 taken orally twice daily for 21 days plus a 2-hour infusion of 60 mg/m^2 of cisplatin on day 8. Each cycle was administered at 5-week intervals. In the "S-1 step", 40 mg/m^2 of S-1 was taken orally twice daily as monotherapy for 28 days at 6-week intervals. All patients received 5-HT3 antagonists and dexamethasone on administration of cisplatin as antiemetics.

Patients were assessed before registration, on days 1, 8, and 15 during the "SP step", and every 2 weeks during the "S-1 step". The baseline assessment included physical examination and laboratory tests. Patients were monitored for adverse effects throughout the treatment period, in addition to receiving follow-up for treatment-related adverse effects. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

For adverse effects, the subsequent chemotherapy cycle was delayed until patient recovery, which included the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, hemoglobin $\geq$8.0 g/dl, platelets >75,000/mm^3, AST or ALT levels $\leq$100 IU/l, total serum bilirubin level $\leq$2.0 mg/dl, and serum creatinine concentration <1.5 mg/dl. Nonhematological toxicities, excluding stomatitis, alopecia, pigmentation changes, nail changes, and watery eyes, were required to be grade 0/1. Cisplatin administration was delayed and administered within 1 day of recovery of the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, platelets >75,000/mm^3, and serum creatinine <1.5 mg/dl. Both S-1 and cisplatin doses were reduced in the event of grade 4 leukopenia or neutropenia, grade 3/4 thrombocytopenia, serum creatinine $\geq$1.5 mg/dl, or other drug-related nonhematological grade 3/4 toxicities. For level −1 dose reduction, S-1 was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, or from 80 to 50 mg/day, while cisplatin was reduced from 60 to 50 mg/m^2. Dose reduction was permitted twice. When dose-limiting toxicities as described previously occurred again at level −2 (S-1 reduced from 100 to 80 mg/day or from 80 to 50 mg/day [if the −1 level of S-1 was already 50 mg, the patient was withdrawn from the study]; cisplatin administration reduced from 50 to 40 mg/m^2), the patient was withdrawn from the study. A patient was also withdrawn from the study whenever the beginning of the subsequent cycle was delayed by toxicity for more than 3 weeks. When cisplatin administration was delayed beyond day 15, the cisplatin portion of the cycle was skipped.

Protocol amendment

During enrollment, some toxicity was reported during the first cycle of SP, especially neutropenia and anorexia. To minimize patient risk, the Data and Safety Monitoring Committee recommended that patient enrollment be halted and that an interim analysis be conducted using the first 25 registered cases (see "Results"). After the analysis, we decided to amend the protocol.

Treatment according to the amended protocol was begun 4–6 weeks after surgery as in the ACTS-GC trial, and consisted of the following: (1) The first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 monotherapy was administered up to 1 year after surgery; (2) The dose of S-1 in the first SP cycle was reduced in case of severe toxicity during the first cycle of S-1 monotherapy; (3) The criterion for delaying cisplatin administration was changed from a neutrophil count of <1,500/mm^3 to <1,200/mm^3; (4) Dexamethasone was recommended for treatment-induced nausea with 20 mg on day 8 (the day of cisplatin administration) and 16 mg on days 9 and 10.

Statistical analysis

The primary endpoint was the rate of completion of 3 cycles of S-1 plus cisplatin; secondary endpoints were the rate of completion of 2 cycles of S-1 plus cisplatin, the proportion of patients receiving treatment according to protocol, and adverse events. Treatment completion was defined as administration of S-1 for more than 14 days in each cycle plus administration of cisplatin. Completion rate of S-1 plus cisplatin was evaluated in all eligible patients. Toxicity was evaluated among patients who received more than one cycle of S-1 plus cisplatin.

In the present trial, the rate of treatment completion was expected to be lower than compliance in the ACTS-GC trial because of the addition of cisplatin. Moreover, if the rate of treatment completion using 3 cycles of S-1 plus cisplatin were lower than 50%, this regimen would be considered inappropriate for adjuvant therapy and would not be evaluated in a phase III trial. Assuming a null hypothesis of 50% for the rate of completion of 3 cycles and an alternative hypothesis of 70%, and using a 1-sided alpha of 0.1 and a statistical power of 0.1, it is necessary to enroll a minimum of 44 patients. Therefore, the target enrollment was 50 patients, in order to make accommodations for ineligible patients.

After protocol amendment, a minimum of 33 patients is needed for a 1-sided alpha of 0.1 and a statistical power of 0.2. Therefore, 38 more patients were added to allow for ineligible patients. Statistical analysis was performed independently for patients enrolled before and after amendment.

Table 1 Patient characteristics

Characteristic	Original ($n = 25$)	Amended ($n = 38$)
Median age, years (range)	60 (47–72)	62 (40–74)
Gender		
Male	16	25
Female	9	13
PS (ECOG)		
0	17	26
1	8	12
Pathological type		
Intestinal	14	5
Diffuse	11	33
Type of gastrectomy		
Total	8	13
Distal	16	25
Proximal	1	0
T stage		
pT1	2	0
pT2	8	9
pT3	14	28
pT4	1	1
N stage[a]		
pN0	1	0
pN1	10	8
pN2	14	30
Cancer stage[a]		
IB	1[b]	0
II	2[b]	0
IIIA	17	16
IIIB	5	21
IV	0	1[b]

Original before protocol amendment, *Amended* after protocol amendment, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

[a] Japanese classification; [b] excluded after enrollment

Table 2 Toxicities

Toxicities	Original ($n = 25$)				Amended ($n = 38$)			
	All		Grade 3/4		All		Grade 3/4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
(A) Hematological toxicities								
Leucopenia	19	(76)	1	(4)	26	(68)	2	(5)
Neutropenia	20	(80)	10	(40)	30	(79)	14	(37)
Anemia	23	(92)	5	(20)	35	(92)	3	(8)
Thrombocytopenia	10	(40)	1	(4)	17	(45)	1	(3)
Febrile Neutropenia	1	(4)	1	(4)	1	(3)	1	(3)
(B) Nonhematological toxicities								
Anorexia	23	(92)	7	(28)	34	(89)	3	(8)
Nausea	17	(68)	2	(8)	31	(82)	1	(3)
Vomitting	7	(28)	0	(0)	8	(21)	0	(0)
Diarrhea	13	(52)	0	(0)	24	(63)	1	(3)
Fatigue	17	(68)	0	(0)	34	(89)	2	(5)
Stomatitis	2	(8)	0	(0)	8	(21)	0	(0)
AST	5	(20)	0	(0)	10	(40)	0	(0)
ALT	5	(20)	0	(0)	8	(36)	0	(0)
Total bilirubin	6	(30)	0	(0)	22	(22)	0	(0)
Creatinine	5	(20)	0	(0)	11	(10)	0	(0)

Original before protocol amendment, *Amended* after protocol amendment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Results

Patient characteristics

From August 2007 to July 2009, 63 patients (25 patients in the original protocol/38 patients in the amended protocol) were accrued from 5 Japanese hospitals. To date, all 63 patients have finished the "SP step" and have been evaluated. Clinical characteristics are summarized in Table 1. The median age was 60/62 (original/amended protocol) years (range, 47–72/40–74 years), and the following types of resection were performed: total gastrectomy ($n = 8/13$), distal gastrectomy ($n = 16/25$), and proximal gastrectomy ($n = 1/0$). In the original protocol, 17 patients had stage IIIA disease and 5 had stage IIIB disease; whereas 16 had stage IIIA and 21 had stage IIIB disease in the amended protocol. After enrollment, 4 patients were deemed ineligible during the original protocol because of confirmed stage II disease ($n = 2$), stage IB disease ($n = 1$), and cancer other than GC ($n = 1$), and 1 patient was considered ineligible during the amended protocol because of pathological stage IV ($n = 1$) disease.

Toxicity

A total of 202 cycles from the 63 cases were assessable for toxicity (Table 2). Under the original protocol ($n = 25$), neutropenia was the most common hematological toxicity, with grade 3/4 neutropenia observed in 10 patients (40%). Additional grade 3/4 hematological toxicities included anemia in 5 patients (20%), and leucopenia, thrombocytopenia, and febrile neutropenia in 1 patient (4%) each. Grade 3/4 anorexia was the most frequent nonhematological toxicity ($n = 7$ [28%]), followed by nausea ($n = 2$ [8%]). There was no grade 3/4 creatinine elevation seen.

Under the amended protocol ($n = 38$), the frequency of grade 3/4 neutropenia was similar to the original; it was seen in 14 patients (37%). Grade 3/4 anemia decreased to 3 patients (8%), and the frequencies of grade 3/4 leukopenia ($n = 2$

[5%]), thrombocytopenia ($n = 1$ [3%]), and febrile neutropenia ($n = 1$ [3%]) were also similar to the original. Among nonhematological toxicities, grade 3/4 anorexia was remarkably reduced to 3 patients (8%) and nausea also decreased to 1 patient (3%). The incidences of grade 3/4 fatigue and diarrhea slightly increased to 2 (5%) and 1 (3%) patients, respectively. There was no grade 3/4 creatinine elevation seen. There were no treatment-related deaths occurring within 30 days after completion of "SP step" treatment.

Compliance

As mentioned previously, 4 and 1 patients were determined to be ineligible after enrollment in the original and amended protocols, respectively, and therefore 21 and 37 patients were analyzed for compliance, respectively. Under the original protocol, 57% (12/21; 95% CI 34–78%) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 76% (16/21; 95% CI 53–92%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 57% (12/21; 95% CI 34–78%). Of note, 6/21 (29%) patients did not complete the first cycle of the "SP step". Reasons for not completing the first cycle included neutropenia on the day of cisplatin administration (day 8) in 3 patients, anorexia in 2 patients, and infection in 1. Dose reductions of S-1 and cisplatin were required once in 9 (43%) and 8 (38%) patients, respectively, and twice in 1 (5%) and 1 (5%) patients, respectively. There were 6 patients (29%) withdrawn from treatment as follows: 3 because of toxicity (neutropenia), 2 because of patient refusal of additional treatment because of toxicity, and 1 because of refusal of additional treatment for other reasons.

Under the amended protocol, 81% (30/37; 95% CI 65–92%; $P < 0.001$ under the null hypothesis) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 95% (35/37; 95% CI 82–99%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 78% (29/37; 95% CI 62–90%). The number of patients not completing the first cycle of the "SP step" was remarkably decreased to only 1 (3%) patient. There were 10 (27%) patients requiring S-1 dose reduction after the first chemotherapy cycle of S-1 monotherapy. Dose reductions of S-1 and cisplatin were required once in 12 (32%) and 8 (22%) patients, respectively, and twice in 7 (19%) and 6 (16%) patients, respectively. Withdrawal of treatment occurred in 2 (5%) patients as follows: one because creatinine elevation did not recover and the other because of patient refusal of additional treatment because of toxicity.

The relative dose intensities (RDIs) of S-1 were 0.67 in the original and 0.78 in the amended protocol, and for cisplatin were 0.65 and 0.81, respectively.

Discussion

To the best of our knowledge, this is the first report on a safety analysis of S-1 plus cisplatin treatment for stage III GC patients who have undergone curative resection with D2 lymphadenectomy. The overall frequencies of major toxicities under the original protocol were almost similar to those of the SPIRITS trial [16] (neutropenia 40 vs. 40%; anemia 20 vs. 26%; and anorexia 28 vs. 30% in this study and the SPIRITS trial, respectively). However, the completion rate of 3 cycles of S-1 plus cisplatin as a primary endpoint (57%) and RDI of S-1 or cisplatin were unexpectedly low in this study. Among the 9 patients who could not complete the 3 cycles of S-1 plus cisplatin, 6 patients could not complete treatment even during the first cycle, mainly because of neutropenia on day 8 and anorexia. We found that toxicity of chemotherapy was more likely to occur during the first cycle.

Therefore, to improve the completion rate of the treatment, we decided to amend the protocol by establishing S-1 monotherapy as the first cycle of chemotherapy, followed by 3 cycles of S-1 plus cisplatin. Although it might be possible that efficacy is decreased by changing the first cycle to S-1 monotherapy, we prioritized complying with postoperative adjuvant chemotherapy, which might also be important in improving survival [19, 20].

In our amended protocol, not only was cisplatin administration omitted in the first cycle, but also the dose of S-1 in subsequent combination cycles was reduced if there were severe toxicities during the "first-cycle" administration of S-1 monotherapy. In addition, the neutropenia count for delaying cisplatin administration was also changed, from $<1{,}500/mm^3$ to $<1{,}200/mm^3$. As a result, 81% of patients achieved treatment completion with 3 cycles of S-1 plus cisplatin with improved RDIs of both S-1 (0.78 from 0.65) and cisplatin (0.81 from 0.65). The frequency of grade 3/4 anorexia and nausea also decreased, from 28 to 8% and 8 to 3%, respectively, although we do not use Substance P inhibitor in both protocol because it was not approved in Japan at that time.

The actual cause of the poor compliance during the early post-gastrectomy course in this study was not discovered. There are several reports about the effect of gastrectomy on S-1 pharmacokinetics [21–23], although this issue remains controversial. Kim et al. reported that total gastrectomy significantly increased the maximum concentration and the areas under the curves of plasma fluorouracil and 5-chloro-2,4-dihydroxypyridine (CDHP) after S-1 administration, which may be one explanation for the toxicity seen in this study [23]. Additionally, there may be a hidden cause, such as relatively poor nutritional status due to gastrectomy, although this study included patients with sufficient oral intake and adequate organ function.

Although this was not a randomized study, in comparison with the original protocol, the amended protocol was more feasible, with a higher completion rate and higher RDIs. Relapse-free survival and overall survival were not reached in this study; therefore, it is difficult to speculate that the addition of 3 cycles of cisplatin might improve the prognosis compared with S-1 alone. Now in Japan, another feasibility study of S-1 plus docetaxel as postoperative adjuvant chemotherapy is ongoing [24]. The addition of any other agent to S-1 as an adjuvant chemotherapy needs to be validated in a randomized phase III trial with S-1 as the control arm.

In conclusion, the postoperative adjuvant S-1 plus cisplatin regimen of the amended protocol is more feasible than the original protocol, because of (1) early dose reduction of S-1 prior to cisplatin addition (2) greater recovery time from surgery prior to cisplatin. It should be regarded as a feasible experimental arm for the next adjuvant phase III trial comparing this S-1 plus cisplatin regimen and S-1 alone as adjuvant chemotherapy for stage III GC patients who have undergone curative resection with D2 lymphadenectomy.

Acknowledgments We thank Mr. Yushi Nagai and Ms. Michiyo Tada for help in collecting and organizing the database. We received no financial support.

Conflicts of interest T. Sano has received lecture fees from Taiho Pharmaceutial (Tokyo, Japan). All other authors declared no conflicts of interest.

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World J Surg (2010) 34:555–562
DOI 10.1007/s00268-010-0396-5

World Journal of Surgery

Predictive Factors Improving Survival After Gastrectomy in Gastric Cancer Patients with Peritoneal Carcinomatosis

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Published online: 16 January 2010

Abstract

Background The aim of this study was to review prognosis following gastrectomy for gastric cancer patients with synchronous peritoneal carcinomatosis and to identify predictive factors for improving survival after gastrectomy in this setting.

Methods Records of all patients who underwent gastrectomy for gastric cancer with peritoneal dissemination in our center between 1993 and 2004 were reviewed.

Results Data of 101 patients who underwent gastrectomy for gastric cancer with peritoneal dissemination were available. Peritoneal dissemination was classified as P1, metastasis to the adjacent peritoneum in 34 patients; P2, a few scattered metastases to the adjacent peritoneum in 13 patients; and P3, numerous metastases in 54 patients. Nineteen patients sustained 21 adverse events. Overall survival was significantly improved for those in the P1 and P2 groups compared with that for the P3 group (median of 18 months and 15 months vs. 9 months; $P < 0.001$). Seven factors were significant for overall survival: peritoneal carcinomatosis, peritoneal lavage cytology, macroscopic type, resection margin, extent of lymph node dissection, curative potential of gastric resection, and chemotherapy, including perioperative and postrecurrent chemotherapy. In multivariate analysis, two factors were identified as independently associated with poor survival: P3 disease ($P = 0.002$) and absence of chemotherapy ($P = 0.009$). Univariate analysis of gastric cancer patients with P1 or P2 carcinomatosis revealed only tumor differentiation to be significant.

Conclusions Gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors are likely to have an improved survival after gastrectomy. We emphasize that patients with good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates before embarking on palliative systemic chemotherapy alone.

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Introduction

Gastric cancer disseminates by hematogenous, lymphatic, and direct implants on peritoneal surfaces. Peritoneal dissemination is the most frequent pattern of metastasis and recurrence in patients with gastric cancer [1–3]. Patients (10–20%) investigated for potentially curative resection of gastric cancer will have peritoneal seeding at the time of abdominal examination, and some patients with gastric cancer will present with peritoneal carcinomatosis [4–6].

Traditionally, there was a mutual agreement in the oncology community that those patients with gastric peritoneal dissemination were incurable [7]. Results of published studies have indicated a median survival of about 6 months [8, 9]. Despite improvements in systemic chemotherapy, gastric cancer patients with peritoneal dissemination generally have poor survival, and although palliative systemic chemotherapy has shown encouraging tumor response rates, there has been no improvement in survival [10–12]. Positive effects of palliative gastric cancer resection on survival have been previously demonstrated in patients with peritoneal carcinomatosis [5, 6, 13–17] but surgical strategies for these patients remain controversial.