の多彩な薬理作用を理解する上で極めて重要なペプチドである．両ペプチドの大きな違いは産生部位であり，CGRP は主に神経終末など神経組織，ADM は主に上皮細胞，平滑筋細胞など非神経組織である．大建中湯が腸管粘膜上皮細胞と感覚神経終末を刺激することで，ADM と CGRP および，受容体関連因子が動員され血流増加が起こることが解明された（図 3）．

次に，構成成分の薬効解析を進めるため，腸管上皮培養細胞を用いた．腸管上皮細胞が ADM を産生することを確認し，大建中湯によって濃度依存性に ADM 産生が起こった．生薬では山椒と乾姜が ADM を産生することを確認した．さらに山椒と乾姜の主成分のランダム試験を行った結果，hydroxy-α-sanshool と 6-shogaol が薬効成分であることが判明した．

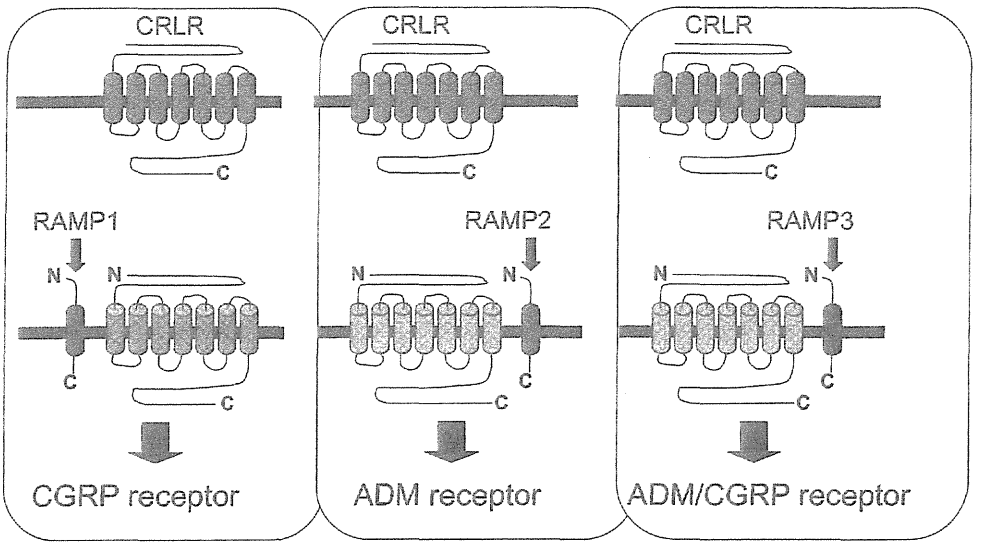

図 2　カルシトニン・ファミリー・ペプチド受容体の成熟化
未成熟受容体 CRLR（calcitonin receptor-like receptor）の成熟化に RAMP（receptor activity-modifying membrane protein）が必須で RAMP1 が成熟化に関与すると CGRP 受容体になるが，RAMP2，RAMP3 が成熟化に関与すると CGRP と同じカルシトニン・ファミリー・ペプチドであるアドレノメデュリン ADM（adrenomedullin）の受容体に変化する．

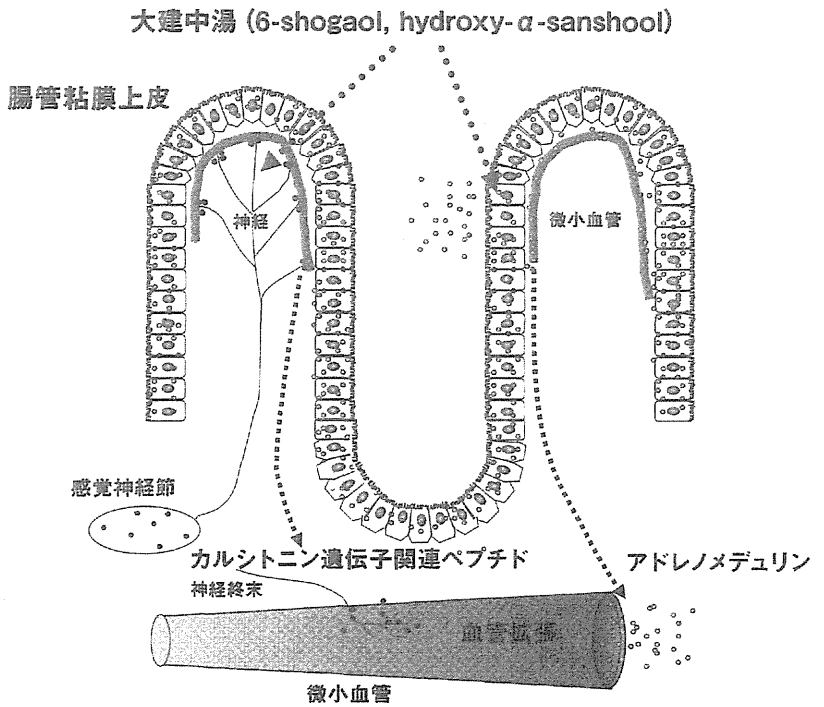

図 3　大建中湯と腸管血流
大建中湯が腸管粘膜上皮細胞と感覚神経終末を刺激することでアドレノメデュリンとカルシトニン遺伝子関連ペプチドおよび受容体関連因子が動員され血流増加が起こることが推察された．

4. クローン病の治療

クローン病は炎症性腸疾患の代表であり原因は特定されていない．30年前には1000人にも満たなかったが，その後患者数は急増し，現在厚労省難病患者登録数から日本全体で13000人以上いると推定されている．欧米では100万人以上と報告されている．クローン病は漢方が確立した時代には存在しなかった疾病である．一時期，厚労省炎症性腸疾患班会議でクローン病に大建中湯を適用することが推奨されたことがあったが，臨床的効果はあるものの作用機序が不明のため，現在では一部の専門医師が使用しているに過ぎない．そのクローン病では腸管血流の減少が動物モデル，および臨床で報告されている(22, 23)．その原因は，繰り返す炎症で神経がダメージを受け，特に血管機能に関与するCGRPが顕著に減少することが考えられている．腸管血流低下のためクローン病の主病変である潰瘍治癒が遅延し，肉芽の過剰形成，それに伴う腸管狭窄に関連している．さらに潰瘍病変再発の原因にも考えられ，血流改善が重要な治療ターゲットであることが指摘されているが，具体的な治療法は確立していない(24-26)．

われわれは，大建中湯の適用が減少した腸管血流を改善させ，クローン病の病勢悪化を防ぐことができるのではないかと考えた(4)．また，ADMには抗炎症性サイトカイン作用が報告されており，クローン病の病因に関与している重要な炎症性サイトカインであるTNFαやINFγについても研究を進めた(3)．臨床上，TNFα抗体は特効薬的に使用され劇的な効果を生んでいる(27-29)．そこで，大建中湯のクローン病動物モデルにおける炎症性サイトカインへの作用を検討した結果，TNFαとINFγを抑制することが分かった．また，大建中湯投与後，粘膜障害が軽減し，クローン病変部の血流低下が正常レベルまで改善されることが観察された（投稿中）．クローン病において大建中湯を投与する臨床的意義は，繰り返す炎症でダメージを受け，神経組織が破壊され血流維持に必要なCGRPが減少した病態において，腸管粘膜上皮細胞のADMを刺激しCGRPを補い，血行を改善する可能性と，ADMによる抗炎症性サイトカイン，特にクローン病治療のターゲットであるTNFαやINFγを抑制し，炎症を制御する可能性の2つが考えられる（図4）．現在，日米でプラセボ使用二重盲検試験が計画されており，その結果が期待される．

まとめ

これまで明らかとなった大建中湯の薬理作用機序を概説した．大建中湯がカルシトニン遺伝子関連ペプチ

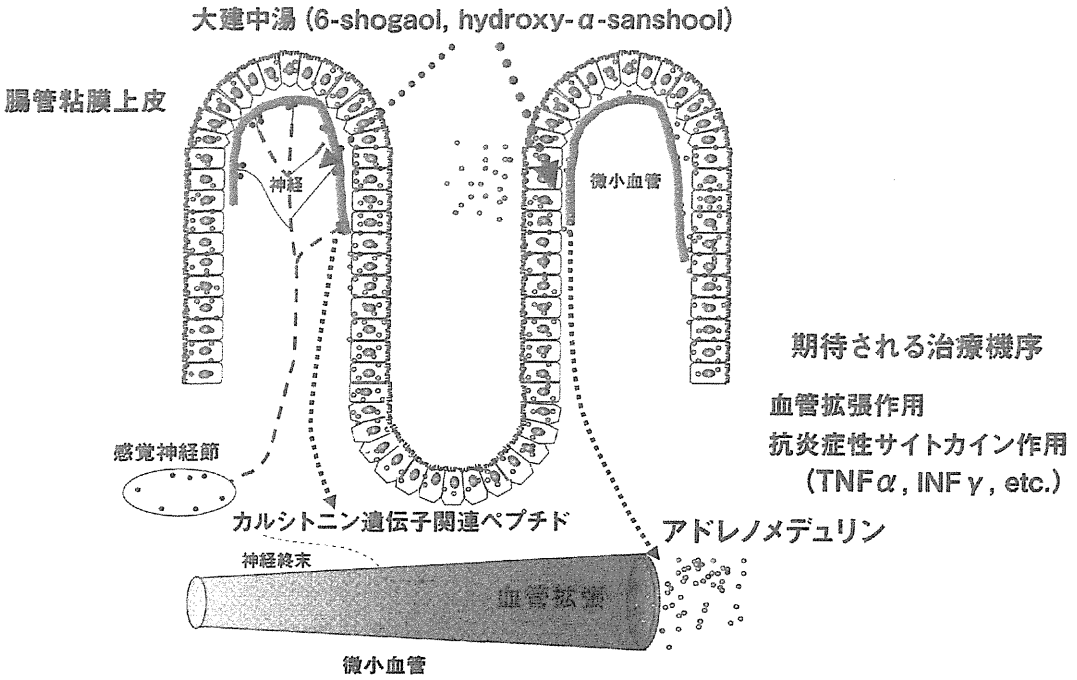

図4 大建中湯とクローン病
クローン病において繰り返す炎症でダメージを受けている神経組織から血流維持に必要なカルシトニン遺伝子関連ペプチドが減少し，血流低下が発生．大建中湯は腸管粘膜上皮細胞のアドレノメデュリンを刺激することで血流を改善する可能性とアドレノメデュリンによる抗炎症性サイトカイン，特にクローン病治療のターゲットであるTNFαやINFγを抑制し，炎症を制御できる可能性の2つが考えられる．

ドを介して腸管血流増加作用，抗炎症性サイトカイン作用を発現し，腸管血流不全や炎症性サイトカインによって病態形成が起こるとされるクローン病治療に有効である可能性を述べてきた．大建中湯の有効成分が山椒の hydroxy-α-sanshool と乾姜の 6-shogaol であることが判明した．最近の研究で，これらの成分の血中濃度の増加が明らかになった．今後，ますます機序解明が進むものと考えられる．臨床試験では米国メイヨークリニックで正常人の腸管運動促進作用に関して，プラセボ使用による二重盲検試験が行われ，有効性が証明されたことは特筆すべきことである(6)．漢方が代替補完医療から脱出し，西洋薬と同じように使用される時代はすぐそこにあると感じる(4)．

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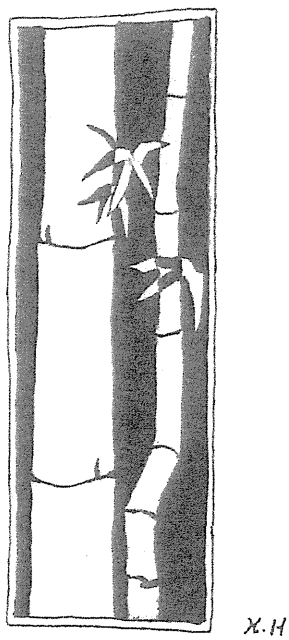

しなやかに

Impact of Operative Blood Loss on Survival in Invasive Ductal Adenocarcinoma of the Pancreas

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Objectives: The aim of this study was to determine the prognostic factors and assess the impact of excessive operative blood loss (OBL) on survival after pancreatectomy for invasive ductal adenocarcinoma.

Methods: From the retrospective analysis, 271 patients were eligible for evaluation. Overall survival was assessed to clarify the prognostic determinants, including patient characteristics, perioperative factors, and tumor characteristics.

Results: The overall survival was significantly affected by the amount of OBL. The median survival times were 26.0, 15.3, and 8.7 months for OBL less than 1000, 1000 to 2000, and greater than 2000 mL, respectively (<1000 vs 1000–2000 mL, $P = 0.019$; 1000–2000 vs >2000 mL, $P < 0.0001$). Operative blood loss greater than 2000 mL remained an independent prognostic factor in multivariate analysis ($P = 0.003$; hazards ratio, 2.55). Operative blood loss of 2010 mL was found to be an appropriate cutoff level to predict early mortality within 6 months after resection (sensitivity, 0.660; specificity, 0.739). Male sex, year of resection, and plexus invasion were independently associated with OBL greater than 2000 mL.

Conclusions: Excessive OBL was found to be a prognostic determinant of survival after surgery for pancreatic cancer. Operative blood loss can be used to stratify the risk for pancreatic cancer mortality. Successful curative resection with limited blood loss can contribute to improved survival.

Key Words: pancreatic cancer, operative blood loss, postoperative complication, blood transfusion, prognostic factor

Abbreviations: OBL - operative blood loss, DGE - delayed gastric emptying, ROC - receiver operating characteristic, MST - median survival time, HR - hazards ratio

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Pancreatic cancer is one of the most difficult malignancies to cure. Curative resection is considered to be the most important factor for determining the outcome in patients with pancreatic adenocarcinoma.[1,2] Notably, surgical resection is superior to chemoradiation for locally invasive pancreatic cancer without distant metastases or major arterial invasion and improves survival.[3]

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The following factors have been reported to be associated with overall survival in pancreatic cancer: patient demographics such as age and sex; histopathologic factors such as tumor size, differentiation, blood vessel or neural invasion, lymph node status, and resection margins; and perioperative factors such as type of resection, operative blood loss (OBL), red blood cell transfusion, operation time, era of resection, and chemotherapy.[4–15] Operative blood loss and red blood cell transfusion are also significant prognostic determinants for other cancer types, such as hepatocellular carcinoma and gastric cancer.[16,17] Pancreatectomy is one of the most difficult and challenging operations and sometimes leads to massive blood loss and prolonged operation time. Thus, it seems to be very important to better understand the effect of surgical stress on survival in pancreatic cancer. Although OBL has been proposed as a prognostic factor in several studies of pancreatic cancer,[5,7,11] no study has demonstrated a stratified risk for cancer mortality for OBL. Furthermore, to the best of our knowledge, no studies have determined whether the amount of OBL may be associated with early cancer mortality.

This was a retrospective study to identify prognostic factors after curative resection of pancreatic cancer. The experience of the large, single-center is favorable for this type of analysis, because experienced surgeons regularly perform pancreatectomies and the postoperative course is under a well-organized perioperative management protocol, which means that there should be little bias regarding treatments. The aim of this study was to detect prognostic factors through comprehensive evaluation, focusing on perioperative factors, particularly OBL. In addition, we wished to statistically clarify the negative impact of OBL on early cancer mortality and determine whether there is a threshold value for increasing the risk of early cancer mortality.

MATERIALS AND METHODS

Patient Selection

Between July 1981 and June 2009, there were 614 operative cases of invasive ductal adenocarcinoma of the pancreas at the Department of Surgery II, Nagoya University, and 416 patients underwent curative resection. The medical records of these patients were reviewed retrospectively. After resection, the patients were categorized based on the International Union Against Cancer classification system, sixth edition.[18] Patients at stages III and IV were considered inappropriate for this analysis because the influence of invasion to the celiac or superior mesenteric artery would likely mask other factors. Therefore, 104 patients at stage III or IV were excluded from this study, and the remaining 312 patients (204 males and 108 females) were evaluated. After analyzing the operational and anesthetic records, 41 patients were excluded because of insufficient data. Thus, 271 patients were finally included in this study.

Pancreatectomy and Perioperative Management

Pancreatic head resection, including pancreaticoduodenectomy and pylorus-preserved pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy was performed based on tumor location and the extent of invasion. Portal resection was performed in combination with standard pancreatectomy in patients with possible or definitive tumor invasion. Operative blood loss was calculated by adding the contents of suction containers to the weight of laparotomy sponges at the end of each surgical procedure. Unless contraindicated by the patient's condition, or for another reason, adjuvant chemotherapy was applied for all patients using a treatment regimen based on the protocols available at the time of treating each patient. Chemotherapeutics consisted of 5-fluorouracil or gemcitabine. Postoperative complications occurring during hospitalization were evaluated based on a modified Clavien grading system: grade 1, deviation from the normal postoperative course without the need for therapy; grade 2, complications requiring pharmacologic treatment; grade 3, complications requiring surgical, endoscopic, or radiologic intervention (3a/b: without/with general anesthesia); grade 4, life-threatening complications requiring intensive care; and grade 5, death.[19,20] To estimate pancreatic fistula, the classification of the International Study Group of Pancreatic Fistula was applied, and grade B (fistula requiring therapeutic intervention) or higher was regarded as significant.[21] The diagnosis of delayed gastric emptying (DGE) was based on the classification of the International Study Group of Pancreatic Surgery, and grade B or higher was regarded as significant.[22]

Potential Prognostic Factors

Potential prognostic factors included patient characteristics and perioperative factors. Perioperative factors included type of resection, operation time, OBL, and intraoperative red blood cell transfusion. The effects of intraoperative radiation therapy and adjuvant chemotherapy on survival were also evaluated. Because tumor characteristics may affect overall survival or perioperative morbidity, all resected tumors were analyzed histopathologically and evaluated as potential prognostic factors. Resection margin and invasion of the portal vein system, arterial system, and extrapancreatic nerve plexus were determined microscopically.

TABLE 1. Univariate Log-Rank Analysis of Patient Characteristics and Perioperative Factors

	No. Patients	1-Year, %	3-Year, %	MST, mo	*P*
Overall	271	59.9	22.3	14.6	
Age (mean ± SD, 63.3 ± 9.1), yr					
<70	196	63.7	24.6	15.7	
≥70	75	47.9	14.6	11.2	0.187
Sex					
Male	173	58.7	19.0	14.5	
Female	98	62.2	29.1	14.7	0.432
Type of resection*					
Pancreatic head resection	198	60.5	23.7	15.3	0.010
Distal pancreatectomy	48	70.2	19.0	16.5	0.024
Total pancreatectomy	25	34.0	17.0	8.6	
Operation time (mean, 7.7 ± 2.1), h					
≤8	149	66.9	30.8	21.1	
>8	122	53.1	13.9	12.8	0.014
OBL (mean, 1693 ± 1734), mL†					
<1000	102	82.0	35.6	26.0	
1000–2000	102	58.9	23.5	15.3	0.019
>2000	67	32.9	5.2	8.7	<0.0001
Red blood cell transfusion					
Yes	104	41.3	11.3	10.7	
No	167	74.3	31.1	23.7	<0.0001
Adjuvant chemotherapy					
Yes	158	71.1	22.7	19.2	
No	90	40.9	20.0	9.9	0.003
Intraoperative radiation therapy					
Yes	163	59.6	14.3	15.2	
No	108	61.1	36.6	14.6	0.068
Year of resection‡					
1981–1990	25	28.0	16.0	8.6	0.004
1991–2000	75	59.5	18.0	14.0	0.153
2001–2009	171	66.7	22.6	17.9	

*P values for pancreatic head resection versus total pancreatectomy and distal versus total pancreatectomy.

†P values for less than 1000 versus 1000 to 2000 mL and 1000 to 2000 versus Greater than 2000 mL.

‡P values for 1981–1990 versus 2001–2009 and 1991–2000 versus 2001–2009.

MST indicates median survival time.

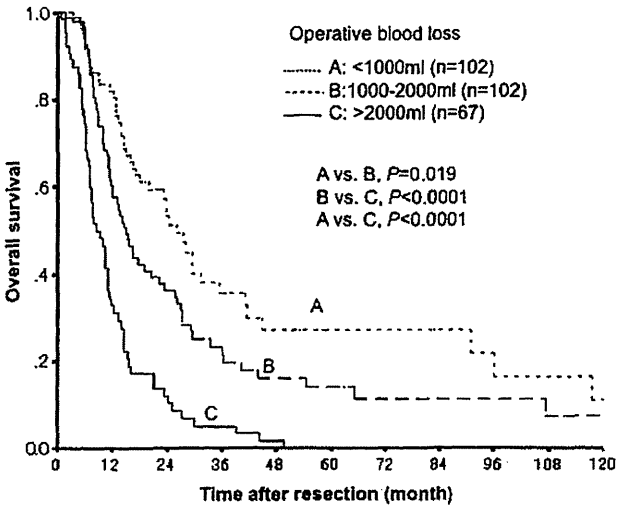

FIGURE 1. Overall survival of patients classified according to OBL. The patients were classified into 3 groups according to OBL of less than 1000 mL (n = 102; A), 1000 to 2000 mL (n = 102; B), and greater than 2000 mL (n = 67; C). The MSTs were 26.0, 15.3, and 8.7 months, respectively.

The impact of each factor on survival was evaluated to determine independent prognostic factors. In addition, the possible risk factors related to excessive blood loss were assessed. Any deaths occurring during hospitalization and deaths related to complications were excluded from the survival analysis because the purpose of this study was elucidating the negative effect of OBL on recurrence of cancer; only cancer-related deaths were included in the survival analysis.

Statistical Analysis

The overall survival rates were estimated using the Kaplan-Meier method, and the differences in the survival curves were analyzed using a log-rank test. Multivariate analysis was performed using the Cox regression model, which included variables with a log-rank test P value of less than 0.05 as covariates in the final model. The outcome was total mortality, excluding deaths attributed to complications. To analyze the risk factors related to excessive OBL, differences in the numerical data between the 2 groups were examined using a χ^2 test for univariate analysis and logistic regression analysis for multivariate analysis. Receiver operating characteristic (ROC) curve analysis was performed to estimate the cutoff level for early mortality after pancreatectomy. To detect the cutoff level, we analyzed the point of intersection of the ROC curve and the 45-degree line crossing from the right upper to the left lower corner and detected the intersection point closest to the left upper corner. Data are shown as means ± SD or medians with 95% confidence intervals. The software package SPSS (version 16.0; SPSS Japan Inc, Tokyo, Japan) was used for statistical analysis, and the level of significance was set at $P < 0.05$.

RESULTS

The patient characteristics are summarized in Table 1. The mean age was 63.3 ± 9.1 years, and 75 (27.7%) of 271 patients were older than 70 years. The mean operation time and OBL were 7.7 ± 2.1 hours and 1693 ± 1734 mL, respectively. The MST was 14.6 months (range, 12.8–16.5 months), with 1-, 3- and 5-year survival rates of 59.9%, 22.3%, and 13.5%, respectively. Adjuvant chemotherapy was indicated in 158 patients, and intraoperative radiation therapy was performed in 163 patients.

Evaluation of Prognostic Factors for Total Mortality

In univariate analyses, OBL, operation time, intraoperative red blood cell transfusion, adjuvant chemotherapy, and year of resection were significant prognostic factors (Table 1). Patients were classified into 3 groups according to OBL. Of the 271 patients, the OBL was less than 1000, 1000–2000, and greater than 2000 mL in 102, 102, and 67 patients, respectively. The overall survival rate decreased significantly with increasing blood loss (Fig. 1). The MSTs for OBL of less than 1000, 1000–2000, and greater than 2000 mL were 26.0, 15.3, and 8.7 months, respectively (<1000 vs 1000–2000 mL, $P = 0.019$; 1000–2000 vs >2000 mL, $P < 0.0001$; <1000 vs >2000 mL, $P < 0.0001$). When the patients were classified into 2 groups according to operation time of less than 8 hours (n = 149) and longer than 8 hours (n = 122), the MST was significantly shorter in the longer-than-8-hour group than in the less-than-8-hour group (12.9 vs 21.1 months, $P = 0.014$). The MST for patients with red blood cell transfusion versus those without was 10.7 versus 23.7 months ($P < 0.0001$).

We also evaluated the association between tumor characteristics and survival. Tumor size larger than 2 cm ($P = 0.0009$), not

TABLE 2. Univariate Log-Rank Analysis of Tumor Characteristics

	No. Patients	1-Year, %	3-Year, %	MST, mo	P
Tumor size, cm					
<2	44	82.3	41.0	27.1	
≥2	227	56.0	18.9	14.0	0.0009
Differentiation*					
Well	42	79.5	48.6	35.6	
Moderate or poor	229	55.8	15.5	14.0	0.0003
Invasion of the anterior pancreatic capsule*					
Positive	157	52.5	18.7	12.8	
Negative	114	68.1	26.2	16.4	0.032
Invasion of retroperitoneal tissue*					
Positive	192	55.6	20.8	14.0	
Negative	79	68.5	25.2	17.1	0.078
Portal invasion*					
Positive	121	47.0	12.7	11.7	
Negative	150	70.4	30.0	23.2	<0.0001
Arterial invasion*					
Positive	31	34.9	16.3	11.2	
Negative	240	63.1	23.3	15.6	0.033
Plexus invasion*					
Positive	67	34.2	11.5	10.6	
Negative	204	68.1	26.1	19.2	<0.0001
Lymph node metastasis*					
Positive	178	56.4	16.6	13.8	
Negative	93	65.6	31.4	17.9	0.012
Resection margin*					
Positive	76	39.1	12.8	9.9	
Negative	195	66.1	25.0	41.6	<0.0001

*Microscopic findings.

well-differentiated tumor (P = 0.0003), invasion of the anterior pancreatic capsule (P = 0.032), portal invasion (P < 0.0001), arterial invasion (P = 0.033), plexus invasion (P < 0.0001), lymph node metastasis (P = 0.012), and positive resection margin (P < 0.0001) were significantly associated with poor prognosis (Table 2).

Multivariate survival analysis was performed to determine which of the potential prognostic factors were independent predictors for survival (Table 3). Operative blood loss greater than 2000 mL (P = 0.003 vs <1000 mL), adjuvant chemotherapy (P < 0.0001), not well-differentiated tumor (P = 0.002), and plexus invasion (P = 0.014) remained independent factors, with HRs of 2.55, 0.43, 2.39, and 1.76, respectively. By contrast, operation time, intraoperative red blood cell transfusion, and year of resection were not independent factors. Similarly, after performing multivariate analysis with thresholds for OBL (500, 750, 1000, 1500, and 2000 mL), the P value was 0.005 for the threshold of 2000 mL, whereas the other thresholds were not significant. The P values for the thresholds of 500, 750, 1000, and 1500 mL were 0.818, 0.224, 0.095, and 0.330, respectively.

To assess the association between OBL and red blood cell transfusion, patients were classified into 4 groups (A, OBL ≤2000 mL and transfusion [−; n = 155]; B, OBL ≤2000 mL and transfusion [+; n = 49]; C, OBL >2000 mL and transfusion [−; n = 12]; and D, OBL >2000 mL and transfusion [+; n = 55]), and the overall survival was compared among these groups (Fig. 2). The effect of red blood cell transfusion was significant when OBL was 2000 mL or less (ie, A vs B, P = 0.011) but not significant when OBL was greater than 2000 mL (ie, C vs D, P = 0.596). Furthermore, OBL greater than 2000 mL was a significant factor, when excluding the influence of red blood cell transfusion (ie, A vs C, P = 0.003 and B vs D, P = 0.003). Finally, there was no significant difference in overall survival between patients with OBL greater than 2000 mL without transfusion and patients with OBL 2000 mL or less with transfusion (ie, B vs C, P = 0.256).

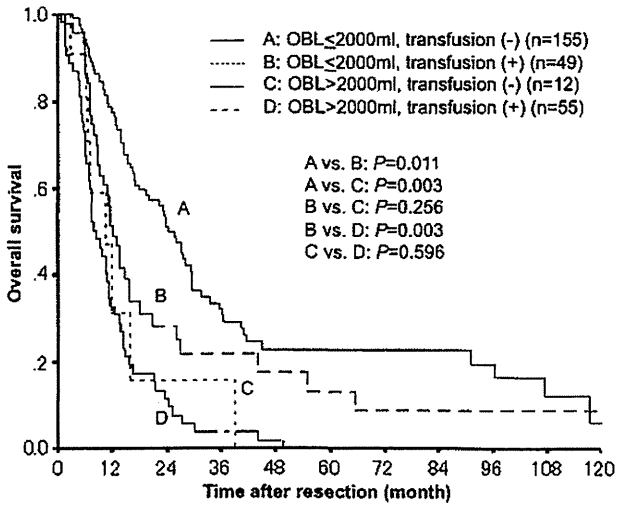

FIGURE 2. Overall survival of patients classified according to OBL and red blood cell transfusion. Patients classified into 4 groups based on blood loss of 2000 or less or of greater than 2000 mL and with versus without red blood cell transfusion (A, blood loss of 2000 mL or less and transfusion [−; n = 155]; B, blood loss 2000 mL or less and transfusion [+; n = 49]; C, blood loss greater than 2000 mL and transfusion [−; n = 12]; and D, blood loss greater than 2000 mL and transfusion [+; n = 55]). The MSTs were 24.4, 12.1, 10.7, and 8.7 months in groups A, B, C, and D, respectively.

Prediction of Early Mortality After Pancreatectomy

Early mortality was defined as death within 6 months after pancreatectomy. Receiver operating characteristic curve analysis was used to determine the relationship between OBL and early mortality (Fig. 3). The area under the curve was 0.751, and

TABLE 3. Multivariate Cox Regression Analysis

	HR	95% CI	P
Total pancreatectomy	1.42	0.87–2.32	0.159
Operation time >8 h	1.08	0.70–1.65	0.737
OBL, mL			
1000–2000*	1.69	0.87–2.22	0.173
>2000*	2.55	1.35–4.35	0.003
Red blood cell transfusion	1.17	0.74–1.84	0.499
Adjuvant chemotherapy	0.43	0.29–0.64	<0.0001
Year of resection, 1981–1990	1.48	0.85–2.59	0.166
Tumor size ≥2 cm	1.63	0.96–2.76	0.071
Not well differentiated	2.39	1.39–4.13	0.002
Invasion of the anterior pancreatic capsule†	1.08	0.75–1.55	0.672
Portal invasion†	1.33	0.92–1.93	0.133
Arterial invasion†	0.78	0.45–1.35	0.378
Plexus invasion†	1.76	1.12–2.77	0.014
Lymph node metastasis†	1.11	0.72–1.71	0.625
Resection margin†	1.37	0.97–1.95	0.078

*P values versus less than 1000 mL.
†Microscopic findings.
HR indicates hazards ratio.

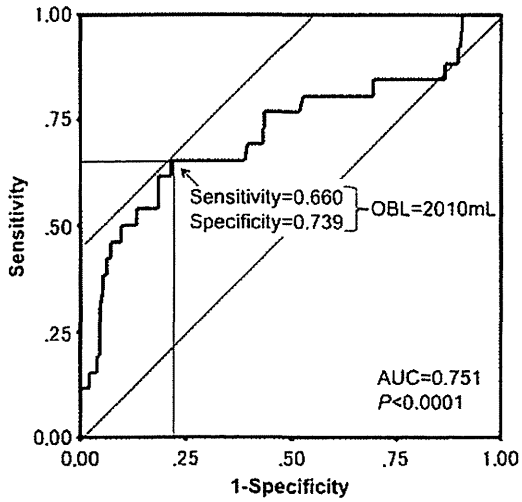

FIGURE 3. Receiver operating characteristic curve for blood loss as a predictor of early mortality (within 6 months after surgery). To detect the cutoff level for the prediction of early mortality, the point of intersection of the ROC curve and the 45-degree line crossing from the right upper to the left lower corner was determined. At the closest intersection point to the left upper corner, the sensitivity and the specificity were 0.660 and 0.739, respectively, at which the OBL was equivalent to 2010 mL. AUC indicates area under the curve.

$P < 0.0001$. Thus, OBL seems to be a good parameter to predict mortality within 6 months after resection. The closest intersection point to the left upper corner of the ROC curve and the 45-degree line crossing from the right upper to the left lower corner is shown in Figure 3. At the point of intersection, the sensitivity and the specificity were 0.660 and 0.739, respectively. The OBL at this point was equivalent to 2010 mL, which can be regarded as an appropriate cutoff level for the prediction of early mortality after a pancreatectomy for invasive ductal adenocarcinoma.

Risk Factors for Excessive Blood Loss

Our results previously described in this article show that excessive blood loss, particularly blood loss greater than 2000 mL, was associated with poor prognosis. Therefore, the possible risk factors related to OBL greater than 2000 mL were evaluated for patient and tumor characteristics. Table 4 shows the results of the univariate analyses. On multivariate analysis, all variables found to be significant in the univariate analyses, except for positive resection margin, were independently associated with OBL greater than 2000 mL (male: $P = 0.009$, HR = 2.76; year 1981–1990: $P < 0.0001$, HR = 13.69; year 1991–2000: $P < 0.0001$, HR = 4.08; plexus invasion: $P < 0.0001$, HR = 2.83; resection margin: $P = 0.284$, HR = 1.54). The correlation between operation time and blood loss was also analyzed and found to be significant ($P < 0.0001$; correlation coefficient, 0.528; data not shown).

TABLE 4. Possible Risk Factors for Blood Loss Greater than 2000 mL

	OBL >2000 mL		
	No. Patients (%)	P*	Odds Ratio (95% CI)
Tumor size, cm			
≥2	61/227 (26.9)	0.072	2.27 (0.91–5.64)
<2	6/44 (13.6)		
Differentiation			
Not well	58/229 (25.3)	0.703	1.17 (0.53–2.60)
Well	9/42 (21.4)		
Invasion of the anterior pancreatic capsule†			
Positive	35/157 (22.3)	0.276	0.74 (0.42–1.28)
Negative	32/114 (28.1)		
Invasion of retroperitoneal tissue†			
Positive	53/192 (27.6)	0.087	1.77 (0.92–3.42)
Negative	14/79 (17.7)		
Portal invasion†			
Positive	35/121 (28.9)	0.150	1.50 (0.86–2.61)
Negative	32/150 (21.3)		
Arterial invasion†			
Positive	10/31 (32.2)	0.301	1.53 (0.68–3.44)
Negative	57/240 (23.8)		
Plexus invasion†			
Positive	30/67 (47.8)	<0.0001	3.66 (2.01–6.66)
Negative	37/204 (18.1)		
Lymph node metastasis			
Positive	46/178 (25.8)	0.555	1.20 (0.66–2.16)
Negative	21/93 (22.6)		
Resection margin†			
Positive	26/76 (34.2)	0.025	1.96 (1.08–3.54)
Negative	41/195 (21.0)		
Age, yr			
≥70	17/75 (22.7)	0.627	0.86 (0.46–1.60)
<70	50/196 (25.5)		
Sex			
Male	54/173 (31.2)	0.001	2.97 (1.52–5.78)
Female	13/98 (13.3)		
Year of resection‡			
1981–1990	17/25 (68.0)	<0.0001	14.4 (5.5–37.3)
1991–2000	28/75 (37.3)	<0.0001	4.0 (2.1–7.7)
2001–2009	22/171 (12.9)		

*χ^2 analysis.

†Microscopic findings.

‡Univariate P values for 2001–2009 versus 1981–1990 and 2001–2009 versus 1991–2000.

Postoperative Complications

Postoperative complications of grade 3 or higher occurred in 29.5% of patients (3a, 71; 3b, 6; 4, 3). In patients with OBL of 2000 mL or less and greater than 2000 mL, the rates of complications of grade 3 or higher were 27.5% (56/204; 3a, 53; 3b, 2; 4, 1) and 35.8% (24/67; 3a, 18; 3b, 4; 4, 2), respectively ($P = 0.193$). There was no difference between these 2 groups regarding the rates of pancreatic fistula, bile leak, postoperative bleeding, severe infection, cardiopulmonary dysfunction, or liver dysfunction (data not shown). The development of DGE was significantly associated with greater blood loss ($P < 0.0001$; 18.5% [12/65] for ≤2000 mL vs 4.4% [9/203] for >2000 mL [data not available in 3 patients]).

DISCUSSION

The outcomes of pancreatic cancer are continuing to improve, but this cancer remains a devastating disease. There may be several reasons that contribute to the improved outcomes, including advances in surgical techniques, availability of novel antineoplastic agents, development of diagnostic tools, and patient education.[23–25] In this study, we evaluated potential prognostic factors by using comprehensive and specific analyses and found that excessive blood loss was significantly and negatively associated with the survival of patients with invasive ductal adenocarcinoma of the pancreas.

In other studies,[5,11] blood loss of 400 or 750 mL was proposed as a threshold for prognostic determinant. However, it is possible that these earlier studies ignored the stratified risk of blood loss because they only compared survival between 2 groups that were divided at these cutoff values. To date, no study has conducted a detailed statistical analysis by classifying patients into several groups based on the level of OBL in pancreatic cancer. When the thresholds were set at 1000 and 2000 mL, the overall survival was significantly affected based on the comparison among these 3 groups. Thus, these results propose a staging system to explain the stratified risk of OBL. This also clearly demonstrates the negative influence of OBL on survival after a pancreatectomy.

Moreover, OBL greater than 2010 mL was a sensitive and specific cutoff level to predict early mortality within 6 months after pancreatectomy for invasive ductal adenocarcinoma. Meanwhile, no studies have proposed a prediction level for early mortality. Surgical stress can deteriorate the patient's condition, which may increase susceptibility to complications or accelerate tumor progression. When considering the overall survival in patients with pancreatic cancer, it was unclear how much surgical stress can be significant. Our results suggest that OBL greater than 2010 mL significantly increases the possibility of early mortality, and this factor may be a surrogate parameter for fatal surgical stress. In recent years, the amount of blood loss has rarely exceeded 2000 mL because of improvements in surgical techniques. However, it is not uncommon to experience excessive blood loss in a resection of advanced pancreatic cancer, particularly when portal resection or plexus dissection is needed. In such situations, this cutoff level is valuable to realize the risk of serious sequelae.

There are several explanations for the negative effects of excessive blood loss. Excessive hemorrhage during operation may cause tumor manipulation, which may spread the tumor into the blood stream and may cause recurrence.[26,27] In addition, large amounts of blood loss are associated with elevated levels of interleukins 1 and 6 and tumor necrosis factor due to intraoperative hypotensive episodes, which could increase the risk for early postoperative mortality.[17,28,29] In our study, we excluded deaths during the first hospitalization and any related complications. It is assumed that excessive blood loss is associated with recurrence of pancreatic cancer. Of note, excessive OBL was not associated with the occurrence of postoperative complications, except for DGE. The lack of a significant relationship between the occurrence of major postoperative complications and OBL greater than 2000 mL means that the adverse effect of high-volume blood loss is latent and difficult to realize during the early postoperative period. Although these explanations are speculations, the possibility of a poor prognosis after excessive blood loss should be taken into consideration.

The mechanisms involved in the adverse effects of red blood cell transfusion may be related to impaired immunity or enhanced inflammation, which may lead to tumor growth or recurrence, although there is no definitive explanation for this.[30,31] Transfusion has been proposed as a prognostic factor in other malignancies.[11,16,32] On the other hand, in other studies of pancreatic cancer, OBL rather than red blood cell transfusion was an independent factor,[5,7,11] which is consistent with the results of this present study. When analyzing the prognostic factors overall, the influence of high blood loss possibly biased that of red blood cell transfusion, which explains why red blood cell transfusion was not an independent factor in multivariate analysis. However, red blood cell transfusion had a significant influence on survival when blood loss was 2000 mL or less. Although the effect of excessive blood loss on survival was more pronounced than that of red blood cell transfusion, the survival rate could be improved by avoiding red blood cell transfusion because, as shown in Figure 2, the survival rate was better in patients without transfusion than in patients with transfusion if the OBL was 2000 mL or less.

Established surgical techniques are essential for the resection of advanced pancreatic cancer.[33] Portal resection and plexus dissection are more performed in our institution than in other institutions to achieve curative resection.[2] According to our results, blood loss significantly increased when the tumor invaded the plexus, but invasion remained an independent prognostic factor. These results indicate that the negative effect of excessive blood loss and the aggressiveness of the tumor itself may independently affect prognosis. Thus, reducing blood loss in resectable advanced pancreatic cancer could provide further improvements in survival.

It is necessary to continue to improve and develop new surgical methods to reduce blood loss. More complicated procedures in a pancreatectomy involve dissection around the portal vein, the superior mesenteric artery, and the plexus. In our institution, the Anthron catheter (Toray Medical, Chiba, Japan), an antithrombogenic catheter made from a heparinized hydrophilic polymer, is implanted during resection of the portal vein.[34] This catheter helps to reduce the pressure of the superior mesenteric vein during portal clamping and facilitates dissection around the portal, splenic, and inferior mesenteric veins, thus decreasing blood loss. The mesenteric approach, which is routinely performed in our institution, also prompts the ligation of efferent vessels such as the gastroduodenal and inferior pancreatic duodenal arteries, thus allowing us to safely perform portal resection and to successfully complete radical lymph node dissection around the superior mesenteric artery and the portal vein.[2] It is hoped, despite the lack of hard evidence, that these sophisticated surgical procedures and novel ideas enable pancreatic resection with minimal blood loss, leading to improved survival. From this point of view, the year of resection should have been an important prognostic factor, whereas it was actually found not to be an independent prognostic factor in the multivariate analysis, suggesting that the year of resection is simply a proxy for operative techniques and, ultimately, OBL.

In conclusion, excessive blood loss was found to be a prognostic determinant for survival after surgery for pancreatic cancer based on this analysis of patients at a large surgical center. As a treatment strategy for pancreatic cancer, methods to reduce blood loss should be considered an important focus and might be accomplished with continued innovation in surgical methods. There is no doubt that curative resection should be sought in all cases. From the surgical point of view, it is very important to successfully perform a curative resection and also reduce blood loss. Because pancreatectomy is one of the most complicated and challenging operations, there is still ample opportunity for surgeons to play a role in improving outcomes by pursuing sophisticated surgical techniques.

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ORIGINAL ARTICLE

Modified FOLFOX6 with oxaliplatin stop-and-go strategy and oral S-1 maintenance therapy in advanced colorectal cancer: CCOG-0704 study

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Abstract
Background A combination of fluorouracil and leucovorin (5-FU/LV) with oxaliplatin (FOLFOX) is an established first-line therapy for metastatic colorectal cancer (mCRC). However, the cumulative neurotoxicity of oxaliplatin often requires therapy to be discontinued while the patient is still responding. A strategy to stop FOLFOX, deliver 5-FU/LV as a maintenance therapy and reintroduce FOLFOX was found to be equivalent in terms of efficacy while neurotoxicity was substantially reduced. The aim of this study was to evaluate feasibility of a stop-and-go strategy with S-1, an oral fluoropyrimidine derivative, as a maintenance therapy administered between modified FOLFOX6 (mFOLFOX6) as a first-line treatment of mCRC.
Methods Thirty patients with untreated mCRC were treated with six cycles of mFOLFOX6 followed by maintenance therapy with oral S-1. Reintroduction of mFOLFOX6 was scheduled after four cycles of S-1 or upon tumor progression. The primary endpoint was duration of disease control (DDC).
Results Twenty-one of the 30 patients who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in 15 patients. Median DDC and progression-free survival were 9.3 and 7.9 months, respectively. The response rates and disease control rates were 40.0 and 86.6% for the initial mFOLFOX6, 23.8 and 57.1% for S-1 maintenance therapy and 20.0 and 73.3% for mFOLFOX6 reintroduction, respectively. Twenty-eight patients (93.3%) had peripheral neuropathy, but grade 3 neurotoxicity was observed in only 1 patient (3.3%).
Conclusion The planned oxaliplatin stop-and-go strategy with oral S-1 maintenance therapy was feasible as a first-line treatment for Japanese mCRC patients. Further prospective randomized control study is warranted.

Keywords Metastatic colorectal cancer · First-line chemotherapy · Oxaliplatin · Neurotoxicity · S-1

Introduction

The combination of fluorouracil and folinic acid (5-FU/LV) with oxaliplatin (FOLFOX) has been established as one of the standard first-line treatments for metastatic colorectal cancer (mCRC) [1]. However, the sensory neurotoxicity, which is an adverse event typically correlated to the cumulative dose of oxaliplatin, often requires discontinuation of oxaliplatin in patients who are still responding. Oxaliplatin-induced cumulative neurotoxicity has been reported in the range of 18–21% in the majority of trials [1–3].

Among various attempts to manage and prevent this adverse reaction, the planned oxaliplatin stop-and-go strategy with maintenance therapy by 5-FU/LV has been considered an appropriate option. Tournigand and de Gramont [4] showed the efficacy of modified FOLFOX-7 with infusional 5-FU/LV as a maintenance therapy in the OPTIMOX1 trial, and proceeded to give no maintenance therapy in the OPTIMOX2 trial [5]. These studies suggested that

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oxaliplatin could be stopped after six cycles without compromising the efficacy on the condition that maintenance therapy with 5-FU/LV was given.

Recently, some new oral fluoropyrimidine derivatives that can be given on an outpatient basis and thus avoid catheter-related problems have been introduced and their non-inferiority when compared with infusional 5-FU has been proven in numerous clinical trials [6–9]. S-1 is another oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil, CDHP is a dihydropyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyl transferase, reducing gastrointestinal toxicities [10, 11]. In addition, DPD inhibition in tumor cells has been suggested to contribute to anti-tumor effects since S-1 has been effective against various solid tumours with high DPD expression [11]. The response rate (RR) of S-1 as a single agent was promising at around 35% for mCRC [11, 12]. These results suggested that the efficacy of S-1 as a maintenance therapy might be comparable to that of infusional 5-FU/LV and that S-1 might also be more convenient for both patients and medical facilities.

The aim of this study was to evaluate modified FOLFOX6 (mFOLFOX6) with maintenance therapy by oral S-1 in patients with mCRC in the first-line setting.

Patients and methods

Patient selection

The study enroled patients with histologically confirmed unresectable metastatic adenocarcinoma of the colon or rectum, who had not previously received chemotherapy for metastatic disease. Patients who had been treated with adjuvant 5-FU-based chemotherapy were eligible provided they had remained disease-free for at least 6 months after the completion of adjuvant therapy. The other eligibility criteria included age of 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, bidimensionally measurable disease, a life expectancy of at least 3 months, adequate organ function (white blood cell count 3,000–12,000 cells per μL, platelet ≥100,000 per μL, aspartate aminotransferase (AST) ≤100 IU/L, alanine aminotransferase (ALT) ≤100 IU/L, total bilirubin ≤25.7 μmol/L (≤15 mg/L), and creatinine ≤106.1 μmol/L (≤12 mg/L)). Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhea; clinically evident gastrointestinal hemorrhage; and ascites or pleural effusion needing treatment. The protocol of this study was approved by the institutional review board or ethics committee of the participating institutions. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients who were entered into the study.

Treatment plan

Patients received mFOLFOX6 (consisting of a 2-h infusion of oxaliplatin at 85 mg/m^2 and l-LV 200 mg/m^2 followed by intravenous bolus of 5-FU at 400 mg/m^2 followed by a 46-h infusion of 5-FU at 2,400 mg/m^2, every 2 weeks) for six cycles. Treatment was continued until disease progression, unmanageable toxicity, withdrawal of consent, or until six treatment cycles were completed. Oral S-1 maintenance therapy was initiated for patients who were in a state of persistent objective response or stable disease (SD) after the six cycles of mFOLFOX6. S-1 (80 mg for patients with body surface area (BSA) <1.25 m^2; 100 mg for patients with BSA 1.25 < 1.5 m^2; 120 mg for patients with BSA ≥1.5 m^2) was administered orally in two divided doses for 28 days, followed by a 14-day treatment-free interval. In the event of disease progression or after a maximum of four cycles of S-1 treatment, mFOLFOX6 could be reintroduced. The reintroduced mFOLFOX6 was continued until progression, unacceptable toxicity, or patient's wish to terminate the treatment. Surgical treatment of the metastatic lesions was allowed in patients with sufficient objective response that rendered the lesions resectable.

Patient evaluation

Physical examination and laboratory tests were performed at baseline and repeated at least biweekly during treatment. Tumor size was assessed at the baseline (within 1 month before enrolment), after every four cycles of mFOLFOX6 therapy, and after every two cycles of S-1 therapy. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.

National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used to assess toxicity. Treatment was delayed until recovery when the white blood cell count fell below 3,000 cells per μL, platelets fell below 100,000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25.7 μmol/L, creatinine was higher than 106.1 μmol/L, and when the patient experienced diarrhea of grade 1 or greater, or other non-hematologic toxicities greater than grade 2. If a patient experienced either a grade 4 hematologic or a grade 3 or higher non-hematologic toxicity, the dose was decreased by one level at the subsequent treatment course.

Statistical considerations

The primary endpoint was duration of disease control (DDC), which was defined as progression-free survival (PFS), or, if mFOLFOX6 was reintroduced, addition of the initial PFS and the PFS of the reintroduction, except in the case of progression at the first evaluation after mFOLFOX6 reintroduction.

The secondary endpoint was PFS, overall survival (OS), RR (complete response (CR) and partial response (PR)) of each therapy, disease control rate (DCR) (CR, PR and SD) of each and safety.

The Kaplan–Meier method was used to calculate the distribution of DDC, PFS, and OS, and the log-rank test was used to compare the curves.

Results

Patient characteristics

Thirty patients were enrolled from November 2007 to December 2009. Baseline characteristics of the patients are presented in Table 1. The median age was 66 years (range 47–74 years). All patients had a performance status of 0 or 1.

Treatment diagram

Thirty patients were treated by initial mFOLFOX6 therapy. The oral S-1 maintenance therapy was initiated in 21 patients and mFOLFOX6 was reintroduced in 15 patients. A treatment diagram is presented in Fig. 1.

DDC, PFS and OS

After a median follow-up time of 26.9 months, 25 patients (83.3%) had disease progression, and 5 patients (16.7%) died of various causes. Median DDC, the primary endpoint, was 9.3 months (Fig. 2), and median PFS was 7.9 months (Fig. 3). Median survival time was not reached.

Initial mFOLFOX6 therapy

Thirty patients were treated by initial mFOLFOX6 therapy. The median number of cycles administered was six (range 3–6) and the median relative dose intensity (RDI) of oxaliplatin in initial mFOLFOX6 was 78%. The objective response was CR in one patient, PR in 11 patients, SD in 14 patients, and PD in 4 patients. The RR and DCR were 40.0 and 86.6%, respectively (Table 2). Surgical removal of the residual metastases could be performed after six cycles of mFOLFOX6 in 2 patients (6.7%).

Table 1 Patient characteristics

Characteristic	No.	%
Age (years)		
Median	66	
Range	44–74	
Sex		
Male	20	66.7
Female	10	33.3
WHO PS		
0	21	70.0
1	9	30.0
Primary site		
Colon	10	33.3
Rectum	20	67.7
Metastases		
Metachronous	22	73.3
Synchronous	8	26.7
Metastatic sites		
Liver	11	36.7
Lung	10	33.3
Peritoneum	6	20.0
Lymph nodes	5	16.7
Adjuvant chemotherapy		
Yes	16	53.3
No	14	46.7
Oxaliplatin	0	0
S-1	0	0

WHO World Health Organization, *PS* performance status

S-1 maintenance therapy

The oral S-1 maintenance therapy was initiated in 21 patients (70.0%). The median number of cycles and treatment duration of S-1 maintenance therapy were 2 cycles (range 1–4 cycles) and 3.6 months (range 1.4–6.3 months). The median RDI of S-1 was 100% (range 77–100%). The objective response was CR in one patient, PR in 4 patients, SD in 7 patients, and PD in 9 patients. RR and DCR were 23.8 and 57.1%, respectively (Table 2).

mFOLFOX6 reintroduction

mFOLFOX6 was reintroduced in 15 patients (50.0%). The median cycles of reintroduced mFOLFOX6 was 6 (range 2–6) and the median RDI of oxaliplatin was 77.4%. Reasons for no reintroduction were early progression of disease (1 patient), brain metastasis (1 patient), debasement of PS (1 patient), patient's preference for other treatment options (2 patients), and surgical resection of residual metastasis (1 patient). One patient had CR, 2 patients had PR, and 8

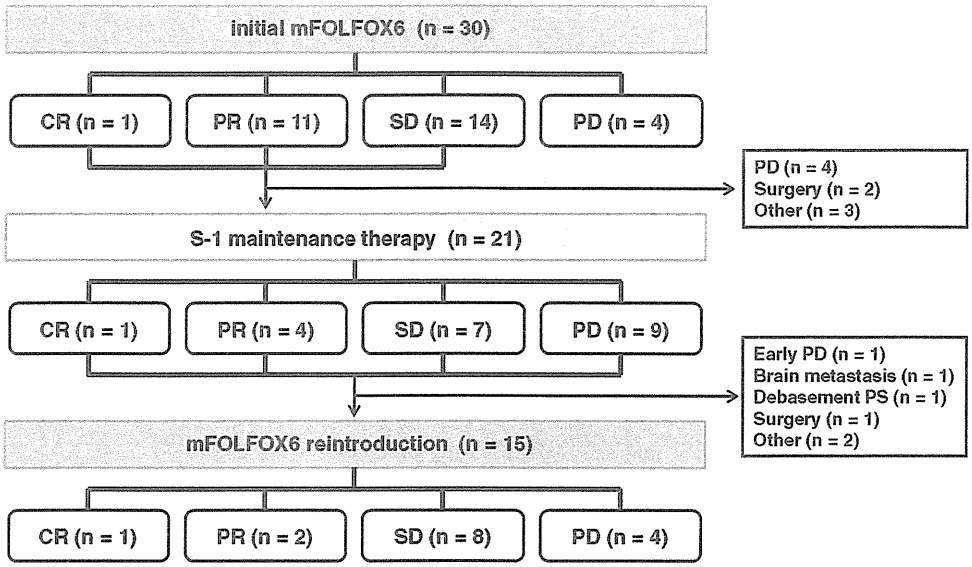

Fig. 1 Treatment diagram. Thirty patients were treated by initial mFOLFOX6 therapy. Twenty-one of the 30 patients (70.0%) who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in fifteen patients (50.0%)

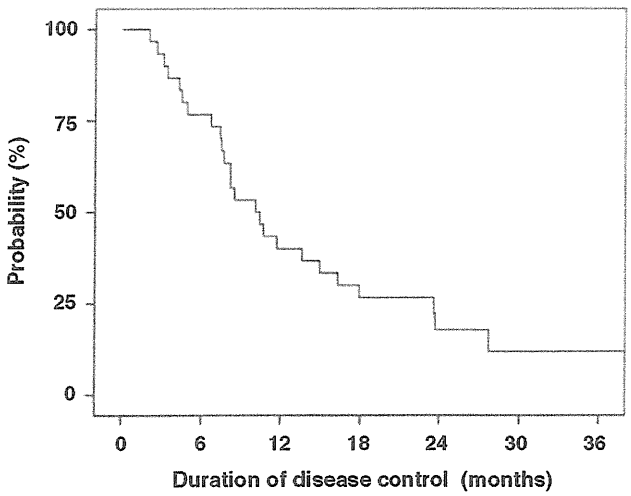

Fig. 2 Duration of disease control (DDC). After a median follow-up time of 26.9 months, 25 patients (83.3%) had disease progression. Median DDC, the primary endpoint, was 9.3 months

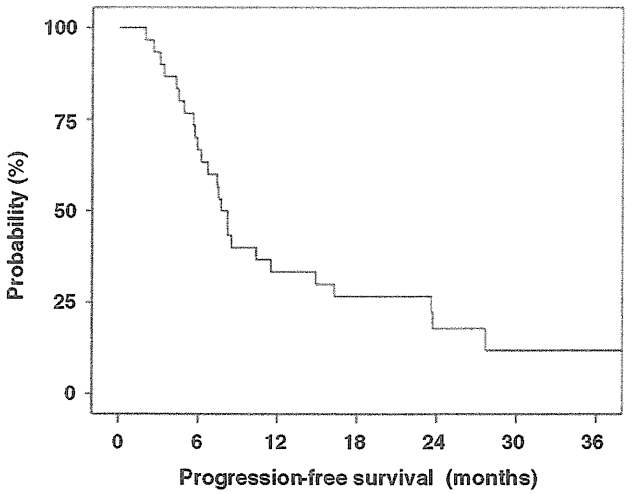

Fig. 3 Progression-free survival (PFS). Median PFS was 7.9 months

patients had SD. RR and DCR in reintroduced mFOLFOX6 were 20.0 and 73.3%, respectively (Table 2).

Second-line and subsequent therapy

After the study, 21 patients (70.0%) had received second-line chemotherapy; 16 patients (53.3%) had received an irinotecan-based second-line chemotherapy regimen. None of the patients had second-line therapy before progression; 6 patients (20.0%) received a second-line chemotherapy regimen with the addition of bevacizumab.

Adverse events

The most frequent toxicities during initial mFOLFOX6 chemotherapy were neutropenia (73.3%), thrombocytopenia (23.3%), anorexia (46.7%), nausea/vomiting (30.0%), diarrhea (16.7%) and mucositis (16.7%) (Table 3). The incidence of peripheral neuropathy during initial mFOLFOX6 chemotherapy was 86.7%; however, grade 3 neurotoxicity was observed in only one patient (3.3%).

The most frequent toxicities during S-1 maintenance therapy were neutropenia (42.9%), thrombocytopenia (38.1%), diarrhea (28.6%), anorexia (23.8%), hand–foot syndrome (19.0%) and mucositis (19.0%) (Table 3). The incidence of peripheral neuropathy decreased to 28.6%, with no patient suffering from grade 3 neurotoxicity after initiation of maintenance therapy (Fig. 4).

The most frequent toxicities during mFOLFOX6 reintroduction were neutropenia (53.3%), thrombocytopenia (15.0%), allergic reaction (33.3%), anorexia (20.0%), mucositis (13.3%) and nausea/vomiting (6.7%) (Table 3).

Table 2 Objective tumor response rates

Response	Initial mFOLFOX6 ($n = 30$)		S-1 maintenance ($n = 21$)		Reintroduced mFOLFOX6 ($n = 15$)	
	No.	%	No.	%	No.	%
CR	1	3.3	1	4.8	1	6.7
PR	11	36.7	4	19.0	2	13.3
SD	14	46.7	7	33.3	8	53.3
PD	4	13.3	9	30.0	4	26.7
RR	12	40.0	5	23.8	3	20.0
DCR	26	86.6	12	57.1	11	73.3

mFOLFOX6 modified FOLFOX6, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate (CR + PR), *DCR* disease control rate (CR + PR + SD)

Table 3 Frequency of common toxicities

Toxicity	Initial mFOLFOX6 ($n = 30$)		S-1 maintenance ($n = 21$)		Reintroduced mFOLFOX6 ($n = 15$)	
	All grade (%)	>Grade 3 (%)	All grade (%)	>Grade 3 (%)	All grade (%)	>Grade 3 (%)
Neutropenia	73.3	26.7	42.9	0	53.3	13.3
Thrombocytopenia	23.3	0	38.1	0	15.0	0
Anorexia	46.7	6.7	23.8	4.8	20.0	0
Nausea/vomiting	30.0	3.3	9.5	0	6.7	0
Diarrhea	16.7	3.3	28.6	9.5	0	0
Mucositis	22.3	0	19.0	0	13.3	0
Hand–foot syndrome	6.7	0	19.0	4.8	6.7	0
Allergy	3.3	0	0	0	33.3	20.0
Neurogenic	86.7	3.3	53.3	0	66.7	6.7

mFOLFOX6 modified FOLFOX6

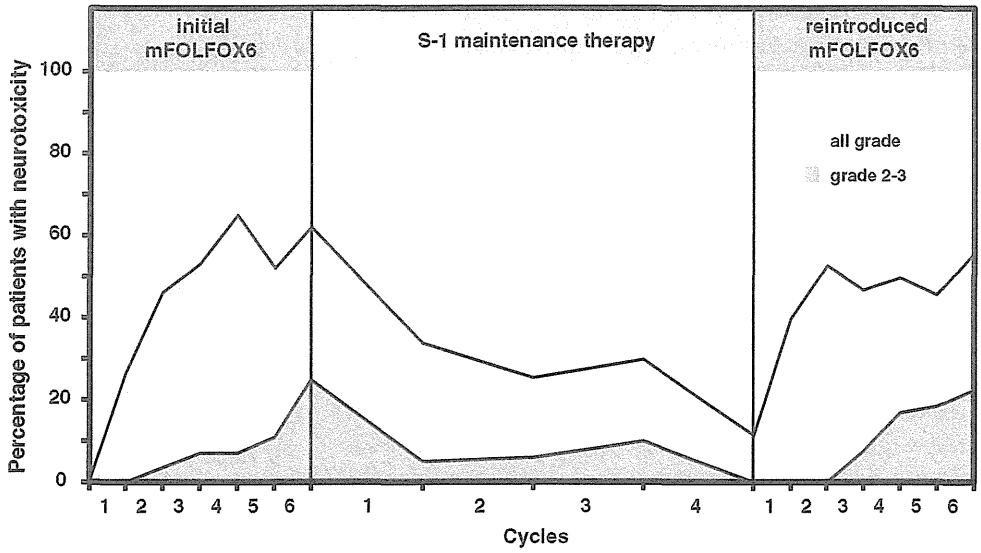

Fig. 4 Neurologic toxicity. The incidence of peripheral neuropathy during initial mFOLFOX6 chemotherapy was 86.7%; however, grade 3 neurotoxicity was observed in only one patient (3.3%). This incidence decreased to 28.6%, with no patients suffering from grade 3 neurotoxicity after initiation of S-1 maintenance therapy. After mFOLFOX6 reintroduction, peripheral neurotoxicity was observed in 66.7% of patients, but grade 3 neurotoxicity was observed in only one patient and did not require treatment discontinuation

Peripheral neurotoxicity was observed in 66.7% of patients after mFOLFOX6 reintroduction, but grade 3 neurotoxicity was observed in only one patient (6.7%) and did not require treatment discontinuation.

Discussion

In recent studies with the uninterrupted FOLFOX regimen, the median PFS was in the range of 8.2–9.0 months, and

severe neurotoxicity was observed in 18–21% of patients [1–4]. In the OPTIMOX1 trial, which evaluated the efficacy of oxaliplatin stop-and-go strategy, PFS and DDC were 8.7 and 10.9 months, respectively. Grade 3 sensory neuropathy was observed in 13.3% of patients. Oxaliplatin was reintroduced in 40.1% of patients and objective response or disease stabilization was observed in 69.4% of these patients [4]. With a median DDC of 9.3 months and a median PFS of 7.9 months, the current study showed that the stop-and-go strategy with mFOLFOX6, employing oral S-1 monotherapy as a maintenance therapy, achieved efficacy comparable to previous studies, while the incidence of severe neurotoxicity was greatly reduced. Grade 3 peripheral neurotoxicity was observed in only 3.3% during the initial mFOLFOX6 treatment. This incidence was reduced to 0% during S-1 maintenance therapy. After mFOLFOX6 reintroduction, 66.7% of patients had mild neurotoxicity, but grade 3 was observed in only one patient (6.7%) and did not require treatment discontinuation. The low incidence of severe neurotoxicity in this study was apparently due to the stop-and-go strategy.

In search of a convenient and well-tolerated treatment, S-1 was chosen to be tested as a maintenance therapy since this oral fluoropyrimidine is an effective alternative to intravenous 5-FU/LV for mCRC as well as being a promising alternative for use in the adjuvant setting in Japan. Median duration of S-1 maintenance therapy was 3.6 months (range 1.4–6.3 months) in the present study and adverse events were mild and typical of those observed with this agent. The RR (23.8%) and DCR (57.1%) were comparable to infusional 5-FU/LV regimens. Furthermore, S-1 maintenance therapy produced a 58.1% reduction in the incidence of peripheral neuropathy with no patient suffering from grade 3 toxicity. These results indicated that S-1 is useful in this setting.

mFOLFOX6 was reintroduced in 50% of patients and achieved disease control in 73.3% of the patients in our study. Only one patient developed grade 3 neurotoxicity after mFOLFOX6 reintroduction. In previous studies, the DCRs after reintroduction of oxaliplatin were similar and in the range of 45–73%. These findings suggest that the chemosensitivity to oxaliplatin is maintained despite an interruption by S-1, and adequate disease control can be expected after the reintroduction of FOLFOX.

Furthermore, the stop-and-go approach is not only a way to decrease oxaliplatin-induced neurotoxicity, but is also a new way to give chemotherapy with advantages in costs without deterioration in survival. In our strategy, S-1 maintenance therapy over 6 months costs approximately 3,700 US dollars, while mFOLFOX6 therapy for the same duration costs approximately 28,400 US dollars in Japan.

In summary, this study suggests that the oxaliplatin stop-and-go strategy with S-1 as a maintenance therapy is oncologically feasible and is associated with a very low incidence of grade 3 neurotoxicity. Although the number enroled was far too small for a definite conclusion, DDC and PFS were comparable to those usually reported in the treatment of mCRC patients. This study adds to a growing body of evidence showing the benefit of a 'stop-and-go' concept, and demonstrates the feasibility of S-1 as an alternative to be used as a maintenance therapy in this strategy.

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Conflict of interest No author has any conflict of interest.

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A Randomized Phase II Trial to Test the Efficacy of Intra-peritoneal Paclitaxel for Gastric Cancer with High Risk for the Peritoneal Metastasis (INPACT Trial)

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Owing to its peculiar pharmacological characteristics, paclitaxel attains substantial intra-peritoneal concentration for a prolonged period when delivered intra-peritoneally, and is active against peritoneal metastasis of ovarian cancer. It is also considered promising against disseminated gastric cancer. However, the fact that the intra-peritoneal paclitaxel has not been approved in Japan has rendered its evaluation by a formal clinical trial impossible. The authors designed a randomized phase II trial using the Kodo Iryo Hyoka system, a new system to legally test an yet unapproved mode of treatment. It is hoped that this trial will result in a breakthrough in the treatment of peritoneal carcinomatosis from gastric cancer.

Key words: paclitaxel – clinical trial – gastric cancer

TRIAL BACKGROUNDS AND RATIONALE

Curatively resected gastric cancer patients often suffer from recurrence as peritoneal carcinomatosis. This could be caused by cancer cells that had already been shed from the serosal surface at the time of surgery, sometimes detectable by examining the peritoneal washes, or those that were disseminated during surgical procedures. In addition to extensive irrigation of the peritoneal cavity (1), intra-peritoneal (IP) instillation of effective anticancer drugs could eliminate these cells to the extent that the recurrences could be prevented. Repeated IP administration of paclitaxel (PTX) has been shown to be safe and effective for disseminated ovarian cancer, another cancer type where peritoneal disease often turns out to be a major cause for disease failure (2). Since its efficacy when administered intravenously (DIV) against gastric cancer has been proved (3) and its potential advantage when given intra-peritoneally has been robustly shown pharmacologically (4,5), IP PTX has been considered promising also to eliminate peritoneal metastasis from gastric cancer.

Formal clinical trials to prove the efficacy of this approach have been hindered by the fact that the IP administration of PTX has not been approved by the Ministry of Health, Labour and Welfare in Japan. When using such drugs outside of the medical insurance system, all other expenses such as the cost of medical services at the outpatient clinic, including drugs such as steroids, H2 blockers and anti-emetics will have to be covered also by the individual researcher or the patient. The authors attempted to overcome this problem by making an official request to conduct a multi-institutional trial by using a system known as the 'Kodo Iryo Hyoka' system. Using this system, unapproved or experimental medical practice whose cost is covered by the individuals can be delivered simultaneously with general medical procedures that are covered by the insurance. To use this system, the study protocol will have to be scrutinized and approved by a committee appointed by the Ministry. Furthermore, a trial thus performed is expected to be designed so as to generate an evidence for future approval of

the treatment by the Ministry. A one-arm single-institutional phase II trial to confirm the efficacy of a regimen that includes IP PTX (6) has already been approved and is ongoing using the 'Kodo Iryo Hyoka' system. To add further evidence in support of the IP treatment and to ultimately establish a basis for the future approval by the Ministry, a head-to-head comparison of IP and DIV of the same drug under the same schedule was considered mandatory. Since the patients so allocated will then have to be treated by IP PTX alone for a fixed period of time, patients who are deemed eligible for the trial had to have a significant risk to develop peritoneal carcinomatosis, while harbouring no gross lesions that immediately call for systemic administration of the anticancer drugs.

The authors held a few meetings to finally compile a protocol for a clinical trial to evaluate IP PTX, as described in the following section. The study is called INPACT, in which INPACT is an abbreviation for 'IP administration of chemotherapeutic agent'.

PROTOCOL DIGEST OF THE STUDY

Purpose

The purpose of this study is to show a prognostic impact of repeated IP of PTX over the DIV on the identical treatment schedule, among patients who are considered to have a high risk of developing peritoneal carcinomatosis. In the event of detecting a survival advantage, this study should be one of valuable evidence based on which to request the Ministry of Health, Labour and Welfare for approval of the IP administration. The establishment of various combinations incorporating IP PTX to combat all types of metastatic gastric cancer and a subsequent randomized trial to prove their survival benefits would then be expected.

Resources

Data centre services and statistical supervision are funded by a non-profit organization, the Epidemiological and Clinical Research Information Network (ECRIN), Kyoto, Japan. All treatments with the exception of PTX-administered IP have been approved as a general practice within the scope of general medical insurance. IP administration of PTX has been approved by the Ministry of Health, Labour and Welfare as of July 2010, exclusively for the participants of this trial, using the Kodo Iryo Hyoka system. Bristol- Myers Squibb has kindly agreed to supply PTX to be given intra-peritoneally.

Endpoints

The primary endpoint is the 2-year overall survival (OS) rate. The secondary endpoints are the incidence of adverse events, progression-free survival time, and OS time.

Eligibility for Participating in the Trial

Approval of the protocol by the institutional review board is a prerequisite to participate in the trial. In addition, each participating institution is requested to fill in and send an application form to the Ministry of Health, Labour and Welfare via Nagoya University to obtain final approval by the government to join the Kodo Iryo Hyoka system.

Eligibility Criteria for the Enrollment

Inclusion criteria for primary registration:

(i) Histologically confirmed adenocarcinoma of the stomach.
(ii) Either macroscopically defined as Type 3 with a diameter >8 cm or Type 4 (linitis plastica), or defined as the other macroscopic type, but is considered highly suspicious for serosal invasion or peritoneal seeding.
(iii) Patients without the following findings on computerized tomography: cervical or mediastinal lymphadenopathy, bulky metastasis to suprapancreatic or retroperitoneal lymph nodes, distant organ metastasis, thoracic effusion, ascites spreading beyond the pelvic cavity.
(iv) No previous history of chemotherapy or radiation.
(v) Eastern Cooperative Oncology Group performance status of 0 or 1.
(vi) Age $\geq$20.
(vii) Adequate organ function is defined as follows: a white blood cell count of 3000–12 000/m^3, neutrophil count of >1500/m^3, platelet count of >100 000/m^3, AST and ALT $\leq$100 IU/l, total bilirubin $\leq$1.5, serum creatinin level $\leq$1.5 mg/dl, serum albumin level $\geq$3.0 g/dl.
(viii) Surgery planned within 1 month of registration.
(ix) Written informed consent.

Exclusion criteria for primary registration:

(i) Serious comorbidities include the following:
  (a) Ischemic heart disease and arrhythmia needing treatment.
  (b) Myocardial infarction within 6 months of onset.
  (c) Liver cirrhosis.
  (d) Interstitial pneumonitis.
  (e) Gastrointestinal bleeding in need of repeated blood transfusion.
  (f) Uncontrolled diabetes mellitus.
(ii) Bowel obstruction rendering treatment with oral drugs impractical.
(iii) Active synchronous cancer or disease-free metachronous cancer within 5 years of onset.
(iv) Signs of acute infection or inflammatory disease
(v) Systemic treatment with corticosteroids
(vi) Hypersensitivity to Cremophor EL.

(vii) Women who are pregnant, contemplating pregnancy or amid breast-feeding.
(viii) Mental disorders which may affect ability or willingness to provide informed consent.
(ix) History of severe hypersensitivity to any drugs.
(x) History of alcoholic anaphylaxis.
(xi) Peripheral neuropathy.
(xii) Patients otherwise considered inappropriate for inclusion in the study.

Inclusion criteria for secondary registration:

(i) Considered resectable either at laparotomy or laparoscopy.
(ii) If the macroscopic type was not Type 3 with a diameter >8 cm or Type 4 (linitis plastica), peritoneal seeding or positive cytology of the peritoneal washes need to be confirmed during surgery.
(iii) Placement of the IP reservoir is possible.

Registration

Participating investigators are instructed to send an eligibility criteria report to the data centre at the non-profit organization ECRIN for the primary registration within 1 month of the scheduled surgery. Investigators are then requested to proceed to the secondary registration by telephone upon laparotomy or laparoscopy, when the eligibility criteria such as resectability, peritoneal metastasis and peritoneal washing cytology findings were confirmed. Patients are randomized during surgery to one of the two treatment groups by a centralized dynamic method using the following factors as balancing variables: macroscopical Type (Types 3 and 4/others), curability of surgery (R0 and R1/R2), age (<75 years/≥75 years) and institution. Follow-up data including compliance to the treatment, adverse reactions and survival are to be reported to the data centre through clinical report forms.

The first 10 cases are to receive the IP PTX exclusively as a feasibility test, which will be evaluated only for toxicity and will be not included in the survival analysis. If more than four successful IP deliveries are conducted in less than 5 of the 10 patients, the study will either be terminated or modified appropriately.

The study has been registered in the University hospital Medical Information Network (UMIN) as No. 000002957.

Treatment Methods

Patients enrolled in this study are randomized to receive one of the following regimens of chemotherapy after gastrectomy.

Group A: IP administration group:

PTX: 60 mg/m2 IP on the day of surgery (day 1) and on days 15, 22, 29, 43, 50 and 57. The dose of IP PTX is based on a phase I trial performed in the USA for ovarian cancer patients, and its safety when given weekly has been confirmed by a phase II trial (2).

Group B: Intravenous administration group:

PTX: 80 mg/m^2 DIV on the day of surgery (day 1) and on days 15, 22, 29, 43, 50, and 57.

These regimens of treatment are to be followed after 2–3 weeks by a standard systemic chemotherapy for advanced gastric cancer which, at the time the trial started, would be either S-1 monotherapy or a combination of S-1 and cisplatin (CDDP) (7). S-1 is generally recommended after R0/R1 resection and S-1/CDDP after R2 resection, but the selection is left to the discretion of the physician in charge. When patients randomized into Group A failed to receive IP chemotherapy for reasons other than allergic reaction to PTX, they are expected to continue with intravenous PTX according to the predetermined schedule, so that the subsequent systemic chemotherapy will be started at the same time as in other patients.

Study Design and Statistical Methods

The current study is a randomized phase II trial applying selection design as proposed by Simon et al. with selection probability of around 80% (8). The primary analysis in this study is aimed to select an appropriate treatment arm for further evaluation, and the sample size was calculated on the hypothesis that the 2-year OS rate of the DIV arm, estimated to be 30–40%, could be improved by 10% in the IP arm. The selection probability is estimated to be 82–83% when a total sample size is 80 and 84–85% when a sample size is 100. Since the first 10 cases will be treated by IP therapy as a feasibility phase and will be excluded from the survival analysis, the total sample size will be 90–110 and 50–60 patients will receive IP therapy.

Interim Analysis and Monitoring

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding efficacy and safety data. The first interim analysis will be performed at 1 year after registration of the last patient and DSMC will decide whether or not to publish the results based on futility analysis and safety data.

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Conflict of interest statement

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