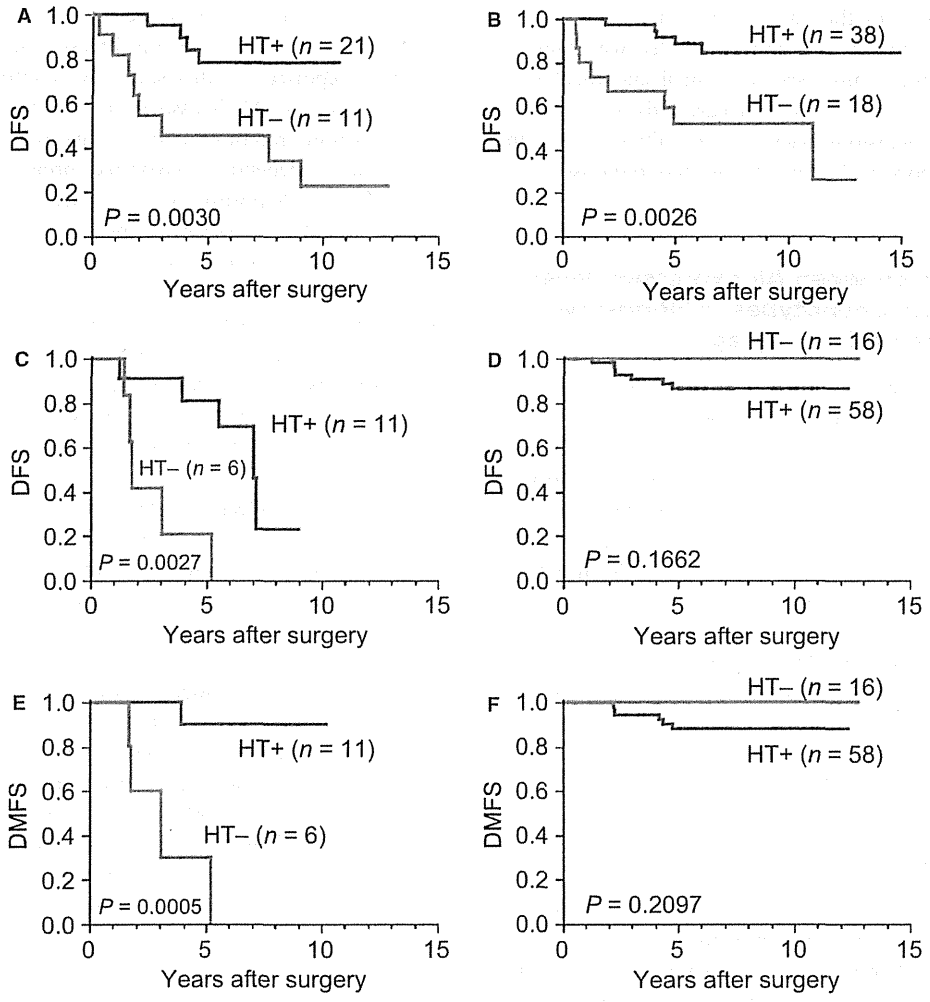

Figure 4. Association between administration of adjuvant hormone therapy and prognosis according to androgen receptor (AR) expression and age. (A and B) In the ≤50-year-old patients in both the AR-low (A) and AR-high (B) groups, disease-free survival (DFS) of the patients who received adjuvant hormone therapy was significantly better than that of the patients treated without adjuvant hormone therapy. (C and D) In patients who were 51 years old or older, the DFS of the patients treated with adjuvant hormone therapy was significantly better than that of the patients who did not receive adjuvant hormone therapy in the AR-low group (C), while there were no significant differences in the DFS of the patients with and without adjuvant hormone therapy in the AR-high group (D). (E and F) In the patients who were 51 years old or older, the distant metastasis-free survival (DMFS) of the patients treated with adjuvant hormone therapy was also significantly better than that of the patients who did not receive adjuvant hormone therapy in the AR-low group (E), while there were no significant differences in the DMFS of the patients with and without adjuvant hormone therapy in the AR-high group (F).

therapy was significantly better compared with the patients without adjuvant hormone therapy only in the AR-low group (P = 0.0027; Fig. 4C). On the other hand, in the AR-high group in these older female patients, there was no significant difference between the DFS of the patients with and without adjuvant hormone therapy (Fig. 4D). The DFS of the patients with low-AR expression was worse, in spite of the use of adjuvant hormone therapy, compared to the prognosis of patients with high-AR breast cancer (Fig. 4C). Notable events that affected survival were mainly local recurrence and contralateral breast cancer. In addition, in the older group, the DMFS of the patients treated with adjuvant hormone therapy was also significantly better compared with that in the patients without adjuvant hormone therapy, but only in the AR-low group (P = 0.0005; Fig. 4E), not in the AR-high group (Fig. 4F). In this older group, no significant difference was recognized in the tumor size, lymph node metastasis, nuclear grade, PR expression, HER2 status, or administration of adjuvant chemotherapy between the patients with and without adjuvant hormone therapy (data not shown). In terms of the kinds of hormone ther-

apy, the prognosis of the patients treated with AIs was a little better than that of the patients treated with tamoxifen. However, the sample size was small and there were heterogeneities in the patients' backgrounds, so it is difficult to draw conclusions regarding the differences in the relationships between AR expression and response to AI or tamoxifen from our data.

Associations between AR expression levels and biological phenotypes in ER-positive breast cancer patients by age

Because the association between AR expression and prognosis was different by age in the ER-positive cohort, the associations between AR expression levels and biological phenotypes were evaluated in the ER-positive cohort by age. In females who were 51 years old or older, high AR expression was associated with more nuclear grade 1 and less nuclear grade 3 disease ($P = 0.0632$), HER2 negativity ($P = 0.0445$), and a lower Ki67 index ($P = 0.0015$) (Table 3). However, there were no significant differences in the nuclear grade, PR, HER2, and Ki67 index between the AR-low and -high groups in patients ≤50 years old. These results suggest that, in females 51 years old or older, high AR expression was associated with less aggressive disease phenotypes (Table 3).

Discussion

Previous studies reported that AR expression is positively correlated with ERα and PR expression, low-grade disease, and advanced differentiation [2]. Several recent studies revealed that the AR is an independent prognostic factor for the outcome of ERα-positive breast cancer [5, 7–10]. However, the relationship between the role of the AR and the menopausal status or age in breast cancer patients has not been reported. In this study, we confirmed that the expression of the AR is associated with the expression of other hormone receptors and less aggressive features, and that is an independent favorable prognostic factor in patients with ER-positive breast cancer. In addition, we showed that the expression of the AR increased by age in patients with ER-positive tumors, and also demonstrated that the association between AR-high expression and a good prognosis is observed in females who are 51 or older, but not significant in females who are 50 or younger. To the best of our knowledge, this is the first report that describes the difference in the expression of the AR and its impact on the prognosis of ER-positive breast cancer by age.

Peters and colleagues demonstrated that the AR potently inhibited the transactivational activity of ERα and the 17β-estradiol–stimulated growth of breast cancer cells [1]. The AR is able to bind to estrogen-responsive elements in ERα and prevent its growth-stimulatory effects, which is considered to be one of the mechanisms by which the AR is associated with a good prognosis in ER-positive breast cancer. Thus, the AR is considered to be a potential tumor suppressor for ER-positive breast cancer. The AR-mediated antiproliferative effects in breast cancer cells are influenced by the relative levels of endogenous AR and ERα [2]. Therefore, the failure to upregulate AR signaling may result in insufficient androgenic antagonism, thereby providing a growth advantage that contributes to disease progression in ER-positive breast cancer [2].

The balance between the stimulatory effects of estrogens and the inhibitory effects of androgens is a critical

Table 3. Associations between androgen receptor (AR) expression and clinicopathological characteristics by age in the estrogen receptor (ER)-positive cohort.

	≤50 (n = 88)			>50 (n = 91)		
	AR			AR		
Factors	Low (n = 31)	High (n = 57)	P-value	Low (n = 17)	High (n = 74)	P-value
Nuclear grade						
1	17 (54.8)	30 (52.6)	0.8442	5 (29.4)	42 (56.8)	0.0632
2	6 (19.4)	14 (24.6)		6 (35.3)	22 (29.7)	
3	8 (25.8)	13 (22.8)		6 (35.3)	10 (13.5)	
Progesterone receptor						
Negative	6 (18.8)	9 (15.8)	0.7219	8 (47.1)	30 (40.5)	0.6244
Positive	26 (81.2)	48 (84.2)		9 (52.9)	44 (49.5)	
HER2						
Negative	31 (96.9)	53 (93.0)	0.424	12 (70.6)	67 (90.5)	0.0445
Positive	1 (3.1)	4 (7.0)		5 (29.4)	7 (9.5)	
Ki67 index (%)	16.8 ± 2.6	15.8 ± 2.10	0.7534	18.9 ± 2.1	11.3 ± 1.0	0.0015

factor that regulates mammary cell proliferation in both normal and cancer tissues [21]. The mechanism underlying estrogen production dramatically changes before and after menopause. In premenopausal females, estradiol, which is the dominant type of circulating estrogen, is secreted mostly by the ovaries. In postmenopausal females, adipose tissue is the primary source of endogenous estrogen production, instead of the ovary. Androgens become an important source of estrogen through their aromatization to estradiol and estrone in the breast and other tissues in postmenopausal subjects [22]. After menopause, the circulating androgens are derived mainly from the adrenal gland [12]. Circulating estradiol levels decrease by 10-fold; however, the testosterone levels decrease by only 1.5-fold [13] after menopause. Moreover, the plasma androgen levels are much higher than those of estrogens in postmenopausal females [12]. Therefore, it is possible that the role of androgens is larger in postmenopausal than in premenopausal females with breast cancer. The mean age at natural menopause in Japanese females is 50 years [20]. Therefore, we divided all of our present cases into two groups based on age: ≤50 and ≥51 years old.

We found that AR expression was different by age only in ER-positive cases. AR expression was significantly higher in the subjects in the ≥51-year-old group, most of whom were likely postmenopausal. In addition, AR expression increased with age in ER-positive cases. We speculate that this is because circulating hormone levels affect the growth and proliferation of ER-positive breast cancer, and the circulating estrogen/androgen ratio decreases with age after menopause. This possibility should be confirmed in future studies.

We also demonstrated that the association between AR-high expression and a good prognosis is observed in females who are 51 or older, but that there were no significant associations in females who were 50 years old or younger. In females who were 51 years old or older, the high AR expression was associated with lower grade tumors, HER2 negativity, and a lower Ki67 index, which are all associated with less aggressive phenotypes. We also showed that there were associations between the use of adjuvant hormone therapy and DFS according to AR expression and age in ER-positive patients. In the ≤50-year-old patients in both the AR-low and -high groups, the DFS of the patients treated with adjuvant hormone therapy was significantly better compared to that of the patients without adjuvant hormone therapy (Fig. 4A and B). These results suggest that hormone therapy is effective and important in ER-positive premenopausal breast cancer patients, regardless of AR expression. On the other hand, in the older (51 and over) females in the AR-low group, the DFS and DMFS of the patients treated with adjuvant hormone therapy was significantly better than that of the patients without adjuvant hormone therapy (Fig. 4C and E), while there was no significant difference between the DFS and DMFS of the patients with and without adjuvant hormone therapy in the AR-high patients in this age group (Fig. 4D and F). These results indicate that AR-high expression is associated with a good prognosis regardless of the administration of adjuvant hormone therapy, while in the AR-low group, hormone therapy can improve the prognosis.

Most studies have come to the same conclusion that AR expression is related to a favorable prognosis in ER-positive breast cancer. The problem is that there has been high variability in the patient population, assay methods, and the analysis of the results of these previous studies. In terms of the methods used for IHC, large studies analyzed AR expression by IHC using TMA [9, 10], but this may have caused some bias due to the heterogeneity in each sample. We employed a whole section analysis, which is better than a TMA analysis, to evaluate AR expression in our study, resulting in less heterogeneity. In addition, the cut-off values for evaluating the positivity of AR expression in breast cancer have varied widely among studies: 1% [9, 10], low, AR < 10%; intermediate 10 ≤ AR < 50%; high, AR ≥ 50% [8], 10%; [7, 11], 75% [1]. In this study, we set the cut-off value for AR positivity as 75%, because of the similarity in the immune reactivity for AR to a previous report [1]. We also evaluated the outcomes of our patients using the median value, 83.3%. The results were almost the same; however, the *P*-value was smaller when using the cut-off value of 75%. When the cut-off value was set at 10%, no statistically significant difference in the DFS was observed between the AR-high and AR-low groups. When we divided the patients into three groups based on AR expression, with values of 0–10%, 10–75%, and 75%+, the ER positivity was 25%, 55.4%, and 84.5% ($P < 0.0001$), the PR positivity was 25%, 44.6%, and 61.9% ($P = 0.0039$), 83.3%, 45.2%, and 21.9% of tumors were nuclear grade 3 ($P < 0.0001$), and the Ki67 index was 43.0%, 20.9%, and 14.2%, respectively ($P < 0.0001$). There were no significant differences in tumor size and lymph node metastasis among these groups. These results suggest that the higher expression of the AR is associated with low-grade tumors. Therefore, an AR cut-off of 75% is considered to be suitable for our study. It is important to establish standard methods for detecting and evaluating the positivity of AR expression in the future.

There are emerging data regarding AR expression in breast cancers and the efficacy of hormone therapy, tamoxifen, and AIs. A preclinical study using an ER-positive breast cancer cell line showed that overexpression of the AR may cause resistance to tamoxifen [23].

If the expression of the AR can interfere with the activity of tamoxifen [23], the use of tamoxifen should be confined to AR-negative cancers. On the other hand, preclinical findings have suggested that AIs may be more effective in the presence of AR activated by androgens [12]. This suggests that AIs are better for AR-positive postmenopausal breast cancer patients. However, based on our data, the prognosis of postmenopausal females with ER-positive breast cancer is very good, even without the administration of adjuvant hormone therapy, if the expression of the AR is high. Further studies are necessary to explore these possibilities and confirm our present findings.

In conclusion, AR expression is associated with a less aggressive phenotype and a good prognosis in patients with ERα-positive breast cancer. This is considered to be a specific phenomenon for postmenopausal breast cancer patients. The evaluation of AR expression may therefore be useful to provide more adequate adjuvant therapy for postmenopausal females with ER-positive breast cancer.

Acknowledgments

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Conflict of Interest

None declared.

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Totally Laparoscopic Distal Gastrectomy for Elderly Patients with Gastric Cancer

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Abstract Introduction : This study evaluated the feasibility of totally laparoscopic distal gastrectomy (TLDG) in elderly patients with gastric cancer.

Methods : We retrospectively analyzed the data from 138 patients who underwent TLDG from April 2005 to March 2009. Of these 138 patients, 20 were older than 75 years of age, and 118 were 75 years of age or younger.

Results : The preoperative respiratory function and American Society of Anesthesiologists (ASA) -physical status were significantly worse in the elderly patients than in the younger patients (P = 0.013). Hypertension and respiratory disease were more common in the elderly patients than in the younger patients (P = 0.032 / P = 0.005). The findings for the following parameters were similar in the two groups : intraoperative blood loss, operation time, severe postoperative complication rate, time required to start a solid diet, and duration of postoperative hospital stay. The rate of major complications was not different between the two groups, although minor complications were more commonly observed in the elderly patients.

Conclusion : TLDG was found to be a safe procedure for elderly patients. This method can be used as one of the standard treatments for gastric cancer in elderly patients.

Key words : Elderly · Gastric cancer · Laparoscopic gastrectomy

Introduction

Among malignant diseases, gastric cancer is the second most common cause of death in Japan. The number of elderly patients with gastric cancer is anticipated to increase with the increasing number of elderly patients[1)2)]. In Japan, gastric cancer is often detected early because of mass screening and endoscopic examination. Laparoscopy-assisted gastrectomy and lymph node dissection with curative intent have been recommended and practiced for the treatment of early gastric cancers in Japan since the first report of the use of laparoscopy-assisted distal gastrectomy (LADG) with a Billroth I anastomosis for a patient with gastric cancer in 1994[3)].

Age is an independent factor affecting the mortality and morbidity of patients undergoing

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gastrectomy[4)~7)]. Therefore, minimally invasive surgery, such as an LADG, may have a greater impact on the survival of the elderly population than of the younger population by reducing cardiorespiratory complications, shortening the duration of hospital stay, and permitting a more rapid return to physical activities. Totally laparoscopic distal gastrectomy (TLDG) is defined as a method used to perform both resection and anastomosis intracorporeally by using a laparoscopic technique. TLDG has several advantages over LADG, including smaller wounds, less invasiveness, and greater possibility of secure ablation[8)]. However, the introduction of TLDG for all patients remains controversial because it is generally believed that the operation time is longer and the surgical procedure is more difficult in TLDG than in LADG. To elucidate whether TLDG is a safe procedure for elderly patients, we compared the factors associated with TLDG in patients older than 75 years of age to those younger than or of 75 years of age.

Patients and Methods

Patients

Between April 2005 and March 2009, 138 patients underwent TLDG for the treatment of gastric cancer at the National Kyushu Cancer Center, Japan. Of these 138 patients, 118 were ≤ 75 years of age, and 20 patients were > 75 years of age. TLDG was performed in patients with cT1N0M0 or T2N0M0 gastric cancers regardless of their gender, age, body mass index, or comorbidities. The concurrent diseases, operation time, blood loss, duration of hospital stay, and postoperative morbidity were compared between the two groups. The rate of change of body weight and the hematological data were measured in the period from before the operation to 1 year after TLDG. The following information was collected from previous medical and anesthesia records : age, gender, operation time, estimated blood loss, findings of blood and lung function tests, pathological findings, and postoperative complications or parenteral nutritional support.

Operative procedures

Distal gastrectomy and lymph node dissection were performed according to the guidelines of the Japanese Gastric Cancer Association[9)]. The patient was placed under general anesthesia in the supine position. A 12-mm trocar was inserted in the umbilical region by using the cut-down method. A laparoscope was inserted through the trocar, and the liver was pulled up using a Penrose drain and a J-shaped retractor[10)]. The detailed surgical procedure has been reported previously[8)10)]. The distal stomach was removed and reconstructed using the Billroth I or Roux-en Y method. The Billroth I reconstruction was performed by using a delta-shaped anastomosis[11)], and the Roux-en Y reconstruction was performed using a linear stapler[12)]. Both anastomoses were completed intracorporeally.

Definitions of complications

Intraoperative complications were defined as conditions that required either an open conversion or procedures performed other than the planned surgery for whatever reason. Unexpected bleeding was defined as intraoperative bleeding of over 350 ml. Minor postoperative complications were defined as abdominal findings not requiring medication during the postoperative course, or systemic complications requiring pharmacological treatment. Major postoperative complications were defined as complications requiring surgical or radiological intervention.

Statistical analysis

Statistical analysis was performed by using the JMP 7 software package. All values are expressed as the mean ± standard deviation. The chi-square test and Fisher's exact test were used for statistical analysis.

Results

Clinicopathological findings

The characteristics of the 138 patients are summarized in Table 1. The mean ages of the patients in the elderly and younger age groups were 80.8 ± 3.2 years and 60.5 ± 9.1 years, respectively. The gender and body mass index (BMI), stage of gastric cancer, extent of lymph node dissections, and type of reconstructions were not significantly different in the two groups. However, the vital capacity and ratio of the forced expiratory volume in one s were significantly lower in the elderly group than in the younger group. In addition, the hemoglobin and albumin levels were significantly lower in the elderly group than in the younger group. Severe comorbidity (American Society of Anesthesiologists [ASA] class 3) was observed in 4 patients in the elderly group and in 8 patients in the younger group.

Concurrent disease

Table 2 shows the concurrent diseases in both groups. Of the 20 elderly patients, 8 (40.0%) had hypertension, 6 (30.0%) had a respiratory disease

Table 1 Clinicopathologic characteristics of patients who underwent totally laparoscopic distal gastrectomy

Characteristic		Age > 75 (n=20)	Age ≤ 75 (n=118)	p value
Mean age, years		80.8 ± 3.2	60.5 ± 9.1	< 0.001
Gender	M	10	65	0.67
	F	10	53	
BMI		22.5 ± 2.9	22.3 ± 3.1	0.34
VC		2678.5 ± 550.2	3403.9 ± 823.0	< 0.001
%FEV#		69.1 ± 10.5	77.1 ± 8.9	0.002
Hematological data	Hemoglobin (g/dl)	12.6 ± 2.0	13.7 ± 1.4	0.02
	Protein (g/dl)	6.90 ± 0.53	7.20 ± 0.49	0.03
	Albumin (g/dl)	4.00 ± 0.46	4.36 ± 0.31	< 0.001
ASA*	1	3	55	0.013
	2	13	55	
	3	4	8	
Cancer stage	Ia	17	93	0.57
	Ib	1	17	
	II	2	5	
	IIIa	0	3	
Extent of lymph node resection	D1 + α , β	33	85	0.91
	D2	6	33	
Type of operation	Billroth I	14	100	0.1
	Roux-en Y	6	18	

#%FEV : The ratio of the forced expiratory volume in 1 second.
*ASA : American Society of Anesthesiologists-physical status

Table 2 Concurrent diseases

Characteristic	Age > 75 (n = 20)	Age ≤ 75 (n = 118)	p value
Hypertension	8	22	0.032
Respiratory disease	6	10	0.005
Cardiovascular disease	3	9	0.279
Diabetes mellitus	5	12	0.516
Malignant disease	4	7	0.031
Liver disease	0	6	0.302
Operation history	0	7	0.264

such as emphysema, 3 (15.0%) had cardiovascular disease, 5 had diabetes mellitus, and 4 had malignant diseases. The most frequent concurrent disease in both groups was hypertension ; moreover, hypertension and respiratory disease were significantly more frequent in the elderly patients than in the younger patients. Concurrent malignant diseases were also more frequently detected in the elderly patients than in the younger patients.

Surgical and perioperative outcomes and postoperative complications

There was no difference in the operation time, estimated blood loss, and time required to start first solid diet (Table 3). The C-reactive protein level was slightly higher in the elderly patients than in the younger patients (Table 3). The

Table 3 Surgical outcomes of totally laparoscopic distal gastrectomy

Characteristic	Age > 75 (n = 20)	Age ≤ 75 (n = 118)	p value
Operation time (min)	342.6 ± 102.0	318.46 ± 66.3	0.53
Estimated blood loss (g)	104.8 ± 93.5	121.7 ± 146.09	0.86
Time to first diet (day)	3.55 ± 0.68	3.45 ± 1.00	0.26
CRP* (mg/dl)	4.54 ± 3.98	3.41 ± 4.09	0.06
Postoperative hospital stay (day)	25.5 ± 36.4	14.7 ± 6.5	0.01

* 7 days after operation

Table 4 Intraoperative complications

Characteristic	Age > 75 (n = 20)	Age ≤ 75 (n = 118)	p value
Open conversion	0	2	
Bleeding	0	8	
Re-anastomosis	0	1	
total	0	9*	0.201

*Duplicated cases were included

Table 5 Postoperative complications

Characteristic	Age > 75 (n = 20)	Age ≤ 75 (n = 118)	p value
Minor complication			
Wound infection	4	7	
Cholecystitis	0	1	
Lymphatic leakage	1	0	
Arrhythmia	1	0	
Delirium	0	1	
total	6	9	0.003
Major complication			
Leakage or intraabdominal fluid collection	1	2	
Leakage of pancreatic juice	0	3	
Liver infarction	0	1	
Colon injury	0	1	
Anastomosis bleeding	0	1	
Ileus	1	2	
total	2*	10*	0.5753

*Duplicate cases were included

Table 6 Changes in body weight and hematological data 1 year after totally laparoscipic distal gastrectomy

Characteristic		Age > 75 (n = 20)		Age ≤ 75 (n = 118)		p value
		Preoperation	1 year	Preoperation	1 year	
Body weight	(kg)	51.7 ± 7.9	44.5 ± 6.4	58.3 ± 10.9	51.4 ± 9.8	
	Rate of change (%)	12.7 ± 8.9		10.7 ± 6.7		0.328
Hemoglobin	(g/dl)	12.7 ± 2.0	11.5 ± 1.8	13.7 ± 1.5	12.7 ± 1.3	
	Rate of change (%)	8.0 ± 11.0		6.7 ± 6.1		0.768
Total protein	(g/dl)	6.90 ± 0.53	6.75 ± 0.41	7.21 ± 0.49	6.92 ± 0.46	
	Rate of change (%)	1.4 ± 7.7		3.7 ± 6.9		0.424
Albumin	(g/dl)	3.99 ± 0.46	3.91 ± 0.48	4.36 ± 0.31	4.21 ± 0.24	
	Rate of change (%)	0.8 ± 6.56		3.3 ± 6.5		0.120

duration of postoperative hospital stay was significantly longer in the elderly patients than in the younger patients (Table 3). Tables 4 and 5 summarize the perioperative complications. Two cases were converted from laparoscopic gastrectomy to open gastrectomy in the younger group. Unexpected bleeding (over 350ml) occurred in eight patients. One case in younger patient was converted open gastrectomy because of difficulty of anastomosis. Another case was converted open because of uncontrollable bleeding. Postoperative complications were categorized into minor or major complications. Minor complications were significantly more frequent in the elderly group because of the higher incidence of wound infection. However, no significant differences in the incidence of major complications such as anastomotic leakage, anastomotic bleeding, and colon injury were observed in the two groups. No surgical mortality occurred in either group.

Differences in clinical features 1 year after the gastrectomy

The preoperative body weight of the elderly group was lower than that of the younger group ; however, the decrease in body weight one year after TLDG was not different between the two groups. The levels of hemoglobin, total protein, and albumin were also not significantly different between the two groups (Table 6).

Discussion

Some previous studies have suggested that postoperative morbidity, mortality, or long-term survival were not associated with open gastrectomy for gastric cancer in the elderly or younger patients[5)13)]. However, other studies have shown high incidences of postoperative morbidity and mortality among elderly patients with gastric cancer who underwent open gastrectomies[14)15)]. Many surgeons believe that the laparoscopic approach for gastric surgery, rather than open surgery, would improve the morbidity and mortality of elderly patients. LADG is generally used for the treatment of gastric cancer because this type of surgery is beneficial[3)16)]. Recently, TLDG has been used for the treatment of gastric cancer[8)17)18)]. TLDG is a method in which both resection and anastomosis are performed intracorporeally using laparoscopic procedures. Compared to other surgical procedures, TLDGs are associated with much less surgical trauma, less pain, more rapid recovery of gastrointestinal function, and shorter duration of hospital stay and impaired respiratory function[8)19)]. Previous studies have shown favorable results with TLDGs and have shown that this approach along with lymph node dissection is a technically feasible and acceptable surgical modality for treating gastric cancers ; moreover, the morbidity rate of patients undergoing this procedure is not high, and this procedure has several advantages over LADG[8)]. Therefore, TLDG should be used for all patients, particularly elderly patients because of its surgical advantages. However, the introduction of TLDG has been controversial because TLDG requires more time, and the surgical procedures tend to be more difficult than those for LADG[20)]. In the current study, the operation time in the elderly group was 342.6 min, which was longer than that for a conventional open gastrectomy ; however, it was not longer than that for an LADG[8)].

This study confirms that TLDG is a safe and useful procedure even for elderly patients. The average age of the elderly patients was 20 years older than that of the younger patients. Therefore, the findings of the blood analysis and respiratory function tests were significantly different between the groups (Table 1). Despite the differences in the patients' background, the length of the operation, estimated blood loss, time interval before starting the first solid diet, and rate of severe complications were not significantly different between the groups. Being elderly did not affect the rate of postoperative complications. The duration of postoperative hospital stay was slightly longer in the elderly group than in the

younger group. A 76-year-old patient who had anastomosis leakage and intraabdominal abscess recovered and was discharged after 174 days ; the difference in postoperative hospital stay and levels of C-reactive protein after 7 postoperative days may be attributed to this particular case. Although previous reports have documented difficulties in performing laparoscopic surgeries in obese patients, we found that the body mass index (BMI) of the younger and elderly patients was not significantly different. Therefore, we evaluated the feasibility of performing TLDG in obese patients. On the basis of their BMI, the patients were divided into 2 groups : non-obese group (BMI < 25.0) and obese group (BMI ≥ 25.0). We found no differences in the duration of surgery, estimated blood loss, and rate of complications between the two groups (data not shown).

In this analysis, minor complications, such as wound infection, were more frequent in the elderly patients than in the younger patients. Most of the wound infections were in the umbilical port site. A 3-to 4-cm incision was made in the center of the umbilical port site, and the resected stomach was pulled out of the wound into a plastic bag. This method allows for the smallest and least noticeable wound for TLDG. However, the umbilical port site was sometimes infected possibly because of the indigenous bacteria, and complete sterilization may have been difficult. Umbilical port site infections were common in the early cases of TLDG. However, since the cleaning of the umbilical site 1 day before the operation was introduced in 2009, cases of umbilical port site infections have not been observed. This finding suggests that indigenous bacteria may have been responsible for the previously observed umbilical port site infections. The occurrence of umbilical port site infections is associated with all types of laparoscopic surgery. The rate of umbilical port site infection after laparoscopic cholecystectomy is 8-9%[21)-23)], and this finding was similar to that of our study. However, the infection rate associated with laparoscopic gastrectomy reported in previous studies is lower than that observed in our study[16)24)-26)]. The resected stomach is not removed from the umbilical port site in LADGs, instead it is removed via a small wound in the upper abdomen. The rate of wound infection after laparoscopic surgery may also be underreported[23)].

It is unclear why there were more umbilical port site infections in the elderly patients. The higher rate of infection might be caused by the greater amount of bacteria in the umbilicus of elderly patients than in younger patients ; however, umbilical flora is reported to be not responsible for wound infection after laparoscopic surgery[27)].

An earlier study in elderly patients showed a short-term advantage of the laparoscopic approach[2)6)28)29)]. However, the long-term effects remain controversial. The changes in body weight and levels of protein, albumin, and hemoglobin were examined 1 year after the operation. Although the level of hemoglobin, total protein, and albumin were lower in elderly patients than in the younger patients before the operation, the rate of change of the hematological data was not different in the two groups. The body weight of both the elderly and younger group apparently decreased after TLDG ; however, the rate of the change in body weight was not different between the two groups. The change in postoperative body weight is not associated with age in patients undergoing an open distal gastrectomy[30)].

In conclusion, TLDG is considered to be a safe and effective procedure for elderly patients, since there were no significant differences in the estimated blood loss or in the rate of complications, in spite of the differences in the patients' backgrounds. This method can therefore be recommended as one of the standard treatments for elderly patients.

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76歳以上高齢者に対する完全鏡視下幽門側胃切除術の検討

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【はじめに】高齢者に対する腹腔鏡下幽門側胃切除術(以下 TLDG)の安全性とその有用性は確立されていない. 本論文では, 76歳以上の高齢者に対する TLDG の安全性と有効性を 75歳以下の症例と比較検討した.
【症例】2005年4月～2009年3月までの間に行われた完全鏡視下幽門側胃切除 138 例のうち, 76歳以上 20 例と 75歳以下の 118 例について, 術中・術後合併症, 術後経過などについて比較した.
【結果】術前の ASA status は高齢者群で有意に悪く (P = 0.013), 高血圧と呼吸疾患の合併は高齢者で多かった (P = 0.032/P = 0.005). 術中の出血量や手術時間, 入院日数などに両者の違いはなかった. 術後合併症は, 重症なものは両者に違いはなかったが, 創感染など軽微なものが高齢者に多かった. 術後1年後の体重減少率や血液データなどに両者の違いは認められなかった.
【結語】背景因子には違いはあるが, 高齢者の TLDG は若年者と変わらず安全に施行可能であると考えられる.

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Phase II Trial of Alternating mFOLFOX6 and FOLFIRI Regimens in the First-Line Treatment for Unresectable or Metastatic Colorectal Cancer (KSCC0701)

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Key Words
Colorectal cancer · Oxaliplatin · Irinotecan · FOLFOX6 · FOLFIRI · FIREFOX · Neurotoxicity

Abstract
Objective: This phase II study examined the efficacy and safety of alternating regimens of mFOLFOX6 and FOLFIRI as a first-line treatment for unresectable or metastatic colorectal cancer. ***Patients and Methods:*** Forty-eight patients were enrolled in this study. Patients received an alternating regimen of 4 cycles of mFOLFOX6 followed by 4 cycles of FOLFIRI. ***Results:*** The characteristics of the study population were as follows: males/females 34/12, median age 66 years (range 43–75) and Eastern Cooperative Oncology Group performance status 0/1/2 in 37/9/0 patients. The overall response rate was 58.7% [95% confidence interval (CI) 43.9–73.5]. The median progression-free survival was 10.3 months (95% CI 7.5–11.9), and the median overall survival was 28.4 months (95% CI 22.5–35.7). Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), neurotoxicity (0%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), vomiting (2%), and hypersensitivity (0%). ***Conclusions:*** The results of this phase II study indicate that this alternating schedule is effective and well tolerated as a first-line treatment for unresectable or metastatic colorectal cancer. The low rate of grade 3 neurotoxicity is also promising.

Introduction

Colorectal cancer is the second most common form of cancer in Western countries. The development of metastatic disease is the leading cause of death from colon can-

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cer. Over the past decade, the results of clinical studies in patients with metastatic colorectal cancer have revealed substantial improvements in survival [1, 2]. 5-Fluorouracil (5-FU)-based chemotherapy is the mainstay of treatment for patients with metastatic colorectal cancer. Combinations of infusional 5-FU, leucovorin and oxaliplatin (FOLFOX) and infusional 5-FU, leucovorin and irinotecan (FOLFIRI), with or without molecular targeting agents, are considered standard treatments for metastatic colorectal cancer [1–5]. The order of combinations for first- and second-line treatment, for example FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX, does not affect patient survival [1]. However, 20–30% of patients do not proceed to second-line treatment [6]. Therefore, adequate and active first-line treatment is essential in the treatment of colorectal cancer. As exposure to active agents, i.e. 5-FU, oxaliplatin and irinotecan, rather than second-line therapy itself appears to predict improved survival [7], the 'up-front' administration of these 3 effective drugs may be the most effective means of improving outcomes. Consequently, several groups have investigated the triple-drug FOLFOXIRI regimen (5-FU, oxaliplatin and irinotecan) in patients with metastatic colorectal cancer to improve their prognosis [8, 9]. FOLFOXIRI resulted in significant increases in activity, efficacy and improvements in the long-term outcome. However, the triple-drug regimen causes further adverse effects [10, 11]. In particular, neurotoxicity is a common and frequent adverse event that diminishes the dose that can be administered [8, 12]. We hypothesized that alternating oxaliplatin and irinotecan would allow patients to benefit from concurrent treatment with all 3 drugs as soon as they were diagnosed with metastatic disease while allowing them to recover from the adverse events associated with each drug before its administration was repeated. The aim of this study was to explore the efficacy and safety of alternating regimens of 4 cycles of mFOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) in the first-line treatment of advanced colorectal cancer. Specifically, we wanted to evaluate the impact of this schedule on the dose-limiting neurotoxicity and diarrhea associated with oxaliplatin and irinotecan.

Methods

Eligibility Criteria

Patients with histologically proven, unresectable, advanced or metastatic colorectal cancer who had not received any previous treatment were eligible for the study if they met all of the following criteria: measurable disease, age ≥20 and ≤75 years, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥3 months and adequate bone marrow, hepatic and renal function. Written informed consent was obtained from all patients prior to enrollment in the study. The ethical, medical and scientific aspects of the study were reviewed and approved by the ethics committees of each participating institution in the University Hospital Medical Information Network clinical trials registry (UMIN000001340). The study was conducted in accordance with the Declaration of Helsinki of 1975, revised in 2000.

Treatment Schedule

Patients received an alternating regimen of 4 cycles of mFOLFOX-6 (85 mg/m^2 oxaliplatin, 200 mg/m^2 leucovorin on day 1 followed by 400 mg/m^2 bolus 5-FU and a 46-hour 2,400-mg/m^2 5-FU infusion every 2 weeks) followed by 4 cycles of FOLFIRI (oxaliplatin replaced with 150 mg/m^2 irinotecan on day 1). This schedule was repeated until unacceptable toxicity or progressive disease (PD) was observed. Treatment was administered until the observation of PD or unacceptable toxicity, withdrawal of consent, the physician's decision to terminate, or interruption of treatment for >14 days occurred. Dose modification was performed based on the hematological parameters and the degree of non-hematological toxicities. Chemotherapy was delayed until recovery if neutrophil counts decreased to <1,500/mm^3, platelet counts decreased to <75,000/mm^3, or significant persistent non-hematological toxicity occurred. The 5-FU dose was reduced to 300 (bolus) or 500 mg/m^2 (infusion) if grade 3/4 diarrhea, stomatitis, nausea/vomiting, anorexia, dermatitis, grade 4 neutropenia, or grade 3/4 thrombocytopenia occurred. Oxaliplatin was also reduced to 65 mg/m^2 for the same conditions, except for the occurrence of dermatitis; additionally, it was reduced in cases of persistent (15 days or longer) grade 2 neurotoxicity or temporary (8–14 days) grade 3 neurotoxicity. In cases of persistent (15 days or longer) grade 3 neurotoxicity or temporary grade 4 neurotoxicity, oxaliplatin was omitted from the regimen. The irinotecan dose was reduced to 130 mg/m^2 for the same reasons as described for oxaliplatin. The use of Ca/Mg treatment was not regulated as part of this protocol.

Endpoints

The primary endpoint of the study was the response rate (RR), and the secondary endpoints were progression-free survival (PFS), overall survival (OS) and adverse effects. During the 4 weeks before chemotherapy was initiated, all patients underwent the following: physical examination, complete blood cell count, hepatic and renal function tests, and chest and abdominal computed tomography or magnetic resonance imaging. A physical examination, hepatorenal function tests and blood counts were performed before each cycle. Patients were assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria version 3 [13]. Tumor evaluation was performed every month for the first 3 months and then every 2 months thereafter using the Response Evaluation Criteria in Solid Tumors version 1.0 [14]. A complete response (CR) was defined as the disappearance of all known lesions and the absence of new lesions. A partial response (PR) was defined as a reduction of 30% or more in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions. Stable disease (SD) was defined as a reduction of <30% or an increase of <20% in the sum of the maximum tumor lengths of up to 10 known lesions and the absence of new lesions.

PD was defined as an increase of ≥20% in the sum of the maximum tumor lengths of up to 10 known lesions or as the appearance of at least 1 new lesion.

Statistical Considerations

Using the binomial exact method (DSTPLAN) with a null RR of 40%, an expected RR of 60%, one-sided $\alpha = 0.05$ and power of 80%, 42 patients were needed for the study. Allowing that 10% of patients would be ineligible or drop out, the planned target number of patients was 47. The confidence interval (CI) for the RR was estimated by the exact method. The duration of survival was measured from the day of entry into the study, and the OS and PFS curves were calculated by the Kaplan-Meier method. A one-sided $p < 0.05$ was considered statistically significant at the statistical test of the primary endpoint. All statistical analyses were performed using Stata version 11 statistical analysis software (Stata, College Station, Tex., USA).

Results

Patient Characteristics

Between July 2007 and June 2008, 48 patients in 25 institutions in Japan were enrolled in this trial. Two of the patients did not meet the eligibility criteria: 1 did not undergo a prior imaging examination and the other had multiple active cancers. Forty-seven patients were treated with protocol therapy. Response, OS and PFS were assessed in 46 patients. The characteristics of 47 patients and those eligible for study inclusion are listed in table 1. The median number of administration cycles was 12 (range 1–47). Toxicity and tolerability were assessed with all 47 patients who received protocol therapy.

Efficacy

The overall RR as determined by the independent committee was 58.7% (95% CI 43.5–73.5), and it included 1 CR (2.1%) and 26 PRs (56.5%). The number of instances of SD and PD were 14 (30.4%) and 2 (4.3%), respectively; 3 (6.5%) patients were not evaluable (table 2). The tumor control rate (CR + PR + SD) was 89.1%. Irrespective of the order of treatment, the period from registration to the first evidence of progression on imaging analysis was defined as PFS. After a median follow-up of 27.5 months, the median PFS was 10.3 months in the 46 assessable patients (95% CI 7.5–11.9; fig. 1), and the median OS was 28.4 months in those patients (95% CI 22.5–35.7; fig. 2). The 1-, 2- and 3-year survival rates were 84.5% (95% CI 70.5–92.4), 60.2% (95% CI 44.4–72.7) and 32.9% (95% CI 17.8–48.8), respectively. Surgery was performed in 9 patients (19.6%) after treatment.

Table 1. Baseline patient characteristics

Characteristic	All cases (n = 47)
Age, years	
Median	66
Range	43–75
Gender	
Male	35 (74.5)
Female	12 (25.5)
Performance status	
0	38 (80.9)
1	9 (19.1)
Existence of a primary tumor	
Yes	19 (40.4)
No	28 (59.6)
Site of the primary tumor	
C	1 (5.3)
A	3 (15.8)
T	3 (15.8)
D	1 (5.3)
S	5 (26.3)
RS	1 (5.3)
Ra	2 (10.5)
Rb	3 (15.8)

Figures in parentheses are percentages. C = Cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon; RS = rectosigmoid colon; Ra = rectum above the peritoneal reflection; Rb = rectum below the peritoneal reflection.

Table 2. Antitumor efficacy

Response	Full analysis set (n = 46)
CR	1 (2.2)
PR	26 (56.5)
SD	14 (30.4)
PD	2 (4.3)
NE	3 (6.5)
Overall response rate (CR + PR)	27 (58.7)
95% CI	43.9–73.5*

Figures in parentheses are percentages. NE = Not evaluable.
* One-sided p = 0.0008 (exact method with the null RR = 40%).

Toxicity and Tolerability

The 4 cycles of FOLFOX6 and the 4 cycles of FOLFIRI could each be prescribed alternatively, although there were some treatment delays because of adverse reactions. In the shortest case, only 1 cycle was completed because

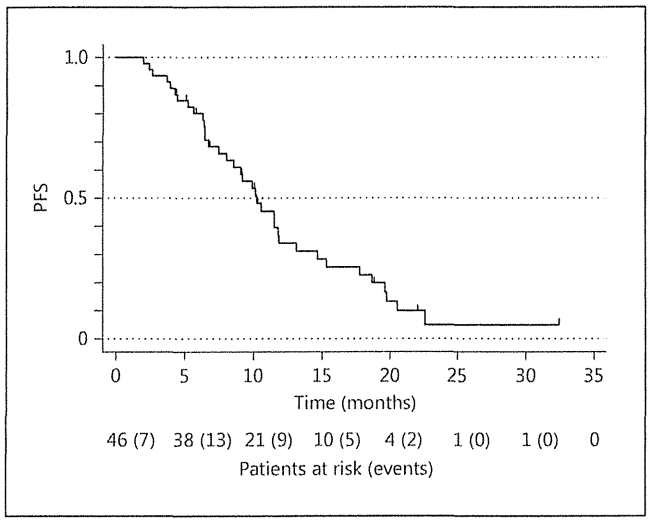

Fig. 1. Progression-free survival.

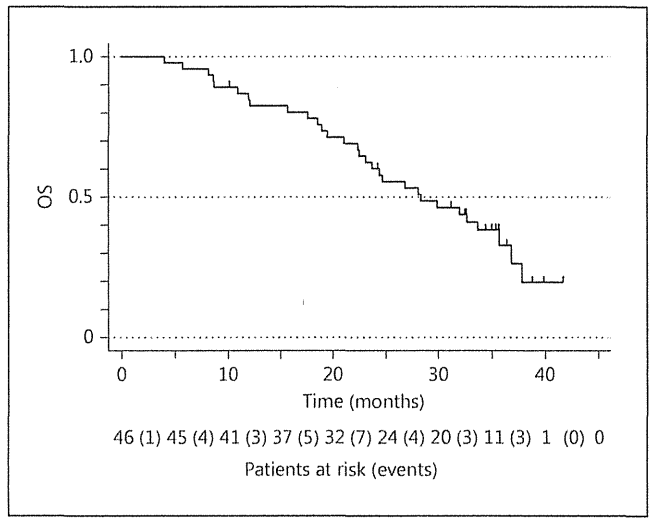

Fig. 2. Overall survival.

Table 3. Treatment-related adverse events

	All grades	G3	G4
Anorexia	32 (68.10)	4 (8.50)	0
Fatigue	27 (57.40)	2 (4.30)	0
Nausea	27 (57.40)	1 (2.10)	1 (2.10)
Mucositis	19 (40.40)	0	0
Constipation	17 (36.20)	0	0
Neurotoxicity (CTCAE)	17 (36.20)	0	0
Diarrhea	15 (31.90)	1 (2.10)	0
Alopecia	13 (27.70)	0	0
Vomiting	13 (27.70)	0	1 (2.10)
Fever	8 (17.00)	0	1 (2.10)
Hand-foot syndrome	6 (12.80)	0	0
Allergic reaction	4 (8.50)	0	0
Chromatosis	2 (4.30)	0	0
Febrile neutropenia	2 (4.30)	2 (4.30)	0
Insomnia	2 (4.30)	0	0
Pneumonia	2 (4.30)	1	0
Weight loss	2 (4.30)	0	0
Epistaxis	1 (2.10)	0	0
Gastrointestinal bleeding	1 (2.10)	0	0
Anemia	42 (89.40)	2 (4.30)	0
Neutropenia	41 (87.20)	17 (36.20)	9 (19.10)
AST elevated	39 (83.00)	3 (6.40)	0
Thrombocytopenia	35 (74.50)	2 (4.30)	0
ALT elevated	24 (51.10)	1 (2.10)	1 (2.10)
Total bilirubin elevated	9 (19.10)	0	0

Figures in parentheses are percentages.

of allergic reactions, whereas 47 cycles were completed in the longest case. The adverse events are shown in table 3. Among the 47 patients evaluated for toxicity, the most common grade 3–4 adverse events were leukopenia (26%), neutropenia (55%), anemia (4%), diarrhea (2%), febrile neutropenia (4%), nausea (4%), and vomiting (2%). No grade 3–4 neurotoxicity, which is a dose-limiting toxicity of oxaliplatin, was reported; only 1 case of grade 3–4 diarrhea was reported. Grade 3–4 hypersensitivity reactions were not reported. Figure 3 illustrates the occurrence of neurotoxicity for each patient in each cycle. Neurotoxicity occurred primarily during the FOLFOX cycles, although some of the neurotoxicity subsided during the FOLFIRI cycles.

Discussion

Among patients with unresectable colorectal cancers, the duration of survival has increased in the past decade. This improvement resulted primarily from the introduction of oxaliplatin or irinotecan into 5-FU-based regimens; additionally, molecular targeting agents have played a role in extending patient survival [1–5]. It is known that patient outcome is significantly improved with exposure to all active drugs in the course of disease treatment [1, 2]. Thus, the sequential administration of FOLFOX and FOLFIRI in any order with molecular targeting agents is the standard treatment for unresectable colorectal cancer [4, 5]. However, approximately 20–30%

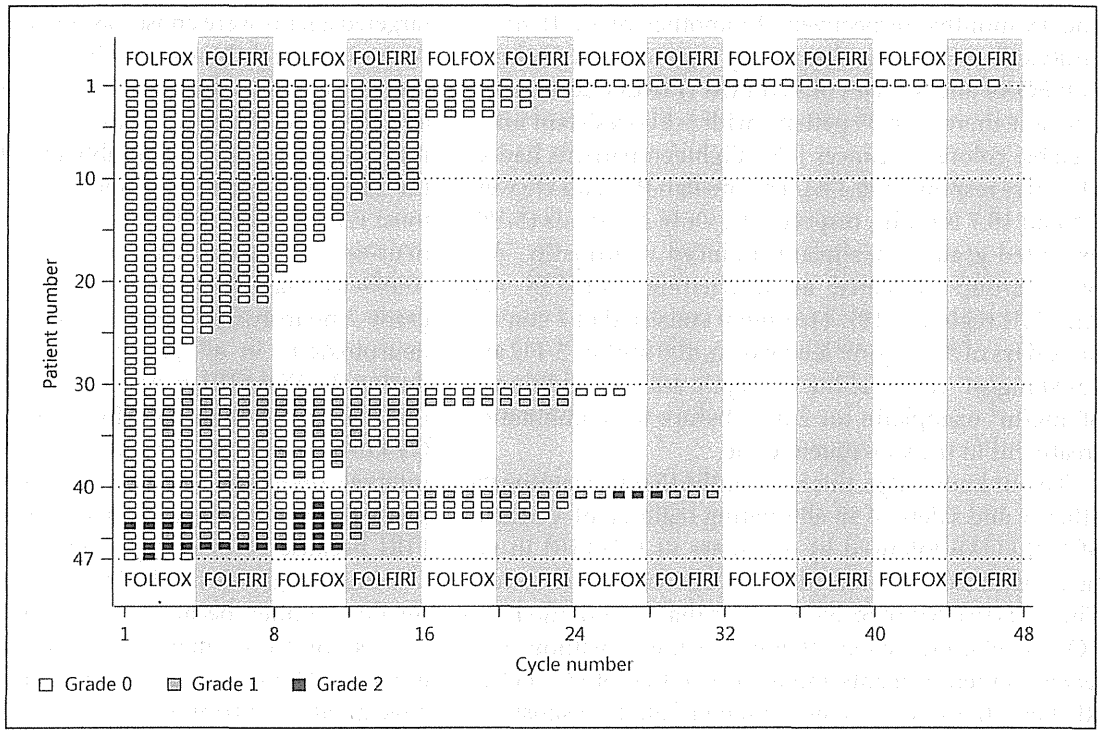

Fig. 3. Occurrence of neurotoxicity (CTCAE) in each cycle for all 47 patients. White squares indicate no toxicity; gray squares indicate grade 1 neurotoxicity; black squares indicate grade 2 neurotoxicity.

of patients exhibit PD after first-line therapy; hence, they do not receive further chemotherapy [6, 7]. Furthermore, an important limitation of this strategy is frequent grade 3 sensory neuropathy, which occurred in approximately one third of the patients initially treated using FOLFOX [15, 16]. This neuropathy forced many patients to stop oxaliplatin-containing treatment before tumor progression [1].

Three strategies have been proposed to avoid these toxicities and increase the rate of exposure to all active drugs. First, all 3 key drugs are administered during first-line therapy, as with the FOLFOXIRI regimen [8, 9, 12]. It is reported that combinations including irinotecan and oxaliplatin with 5-FU (FOLFOXIRI) are feasible. The principal benefit of the FOLFOXIRI regimen is its high RR; further, high liver resection rates have been reported. However, the toxicity of these drugs when given in combination results in dose reductions for each of the drugs [8, 10, 11].

The second strategy involves stop-and-go regimens such as the OPTIMOX series that include oxaliplatin-free intervals to reduce grade 3 sensory neuropathy [16]. This stop-and-go regimen avoided the problem of oxaliplatin-induced neurotoxicity by using a dose-intense FOLFOX7 regimen for a defined period, stopping the therapy before severe neurotoxicity developed, and later reintroducing the same regimen. This regimen was extremely useful for reducing the neurotoxicity of oxaliplatin; however, response and survival were not improved.

The third method involves alternating regimens such as 4 courses of FOLFOX and 4 courses of FOLFIRI, as investigated in this trial. To improve response and survival, other alternating regimens have been examined. Alternating oxaliplatin and irinotecan in association with the De Gramont regimen has been used in first- and second-line chemotherapy for metastatic colorectal cancer [17]. Seventy-nine patients with previously untreated, unresectable colorectal cancer were included in a study of this regimen as a first-line treatment. Treatment consisted of 5-FU/leucovorin plus oxaliplatin alternated biweekly with the same 5-FU/leucovorin regimen plus irinotecan. Treatment was maintained until tumor progression or unacceptable toxicity was noted. Grade 1 or 2 neurotoxicity was observed in 59% of cases, but no grade 3 and 4 neurotoxicity was observed. An objective RR of 54% was attained. The median time to progression and OS was 13

and 18 months, respectively. In another phase II study, GERCOR utilized an alternating regimen of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) as a second-line therapy in 39 patients with 5-FU-resistant unresectable colorectal cancer [18]. Eighteen patients had an objective response (46.1%). The median PFS and OS were 8.8 and 18.7 months, respectively. Only 2 patients (5.1%) exhibited grade 3 oxaliplatin-induced neuropathy. Another group evaluated an alternating XELFOX and XELFIRI regimen [19]. Treatment consisted of 2 consecutive days of 200 mg/m^2 leucovorin, 400 mg/m^2 5-FU and 2,000 mg/m^2 capecitabine in 1 cycle and the addition of 50 mg/m^2 oxaliplatin for 2 days before the combination treatment in the subsequent cycle.

To our knowledge, this study is the first to examine the efficacy and safety of an alternating regimen of 4 courses of FOLFOX6 followed by 4 courses of FOLFIRI in patients with non-pretreated metastatic colorectal cancer. The objective RR of 58.5% is better than that of the FOLFOX or FOLFIRI chemotherapy regimens without molecular targeting agents and is close to that of FOLFOXIRI chemotherapy [9]. This regimen might be a substitute for FOLFOXIRI which has a high rate of conversion to surgery. In our study, 9 (19.6%) patients were converted to surgery including liver resection. In addition, this strategy was implemented to increase the efficacy of treatment and extend survival. The median PFS and OS were 10.3 and 28.4 months, respectively. PFS for first-line FOLFOX6 or FOLFIRI treatment without molecular targeted agents was 8–10 months [1], and PFS increased to 10–14 months when second-line treatment was also administered. Therefore, PFS in this study was not long, although OS was extended. This survival may be partly influenced by the therapy that followed the treatment administered in the study. In this phase II study, because molecular targeted agents were not included in the protocol treatment, FOLFOX6 and FOLFIRI with molecular targeted agents were chosen as the second-line treatment. At present, oral fluoropyrimidine with molecular target agents were considered as a choice as a second therapy and the third therapy. Although survival was not a primary endpoint, the remarkably long OS associated with the FIREFOX regimen is noteworthy. Furthermore, the most remarkable result in this study was the low level of neurotoxicity. In particular, no grade 3–4 peripheral neurotoxicity was observed. Only 6 patients experienced grade 2 neurotoxicity. Figure 3 shows the occurrence of neurotoxicity in all patients. Neurotoxicity improved during the FOLFIRI cycles. This tendency was similar to that observed with the OPTIMOX regimen. However, the OPTIMOX regimen does not have a chemotherapy-free interval; therefore, PFS can be maintained well. In this phase II trial, only 6 (12.7%) patients did not receive FOLFIRI because of disease progression or patient refusal. The high usage rate for the 3 active drugs is advantageous for this regimen because 20–30% of patients cannot receive second-line chemotherapy because of disease progression. Therefore, this low level of neurotoxicity may have greatly contributed to the long PFS and OS in this study.

Our findings suggest that the alternating administration of 4 cycles of FOLFOX6 and 4 cycles of FOLFIRI (FIREFOX) is effective and well tolerated as a first-line treatment for metastatic colorectal cancer. A favorable toxicity profile and prolonged time to progression were observed. Based on this study, we recently conducted and finished another phase II study of 4 alternating cycles of FOLFOX6 and FOLFIRI with bevacizumab.

Disclosure Statement

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