Table III. Influence of sex and coadministered drugs on AUC ratios and serum total bilirubin levels of patients with cancer who were administered irinotecan

	*AUC ratio (SN-38G/SN-38)**	*No.*	*Total bilirubin level (mg/dL)**	*No.*
Sex				
Male	4.45 (3.29-6.40)	64†	0.60 (0.50-0.80)	65
Female	4.06 (2.78-6.11)	20	0.65 (0.50-0.85)	20
Coadministered drug				
Irinotecan alone	5.22 (4.35-8.27)	23†	0.60 (0.50-0.90)	24
Platinum antineoplastics	4.00 (3.35-6.13)	43	0.60 (0.50-0.80)	43
5-Fluorouracil	2.88 (2.73-3.43)	7	0.70 (0.50-0.80)	7
Mitomycin C	3.41 (2.44-8.53)	9	0.50 (0.45-0.80)	9
Amrubicin	4.72	2	0.45	2

There were no significant differences in the AUC ratios and total bilirubin levels between sexes or among coadministered drugs.
AUC, Area under concentration-time curve.
*The values are expressed as the median with the interquartile range in parentheses.
†The analysis of AUC was not achieved for 1 patient.

dosage on these parameters and found no significant differences among them (Mann-Whitney and Kruskal-Wallis tests or Spearman correlation coefficient), except for a correlation of age with AUC ratio (r_s = 0.3690, P = .0006). However, we found no significant difference in the median values of age among the diplotypes in both blocks 1 and 2 (P = .5798 and P = .8593, respectively; Kruskal-Wallis test). Then we assessed the relationship between the genotype and the AUC ratio without normalization by age. We also confirmed that the diplotype configurations of both block 1 and block 2 were not significantly different with respect to the patient background factors (χ^2 test). On the basis of these findings, we assessed the correlation between the genotypes and phenotypes with all of the irinotecan-administered patients considered as a single group. The data for the effects of sex and coadministered drugs on the phenotypes are summarized in Table III.

As for block 1, the AUC ratios and total bilirubin levels were compared among all haplotype combinations (diplotypes) by use of the 4 haplotype groups, **1*, **60*, **6*, and **28*, and analyzed by the Kruskal-Wallis test (Fig 5). The observed P values were .0070 for the AUC ratio and .0503 for the total bilirubin level, respectively. A significant reduction in the AUC ratio was observed in the **6/*60* and **28/*6* haplotype groups (P = .049 and P = .0071, respectively; nonparametric Dunnett multiple comparison test) compared with the **1/*1* group. We separately evaluated the gene-dose effects of each haplotype by use of a nonparametric trend test (JT test) and summarized the results in Table IV. In the patients carrying the **60* haplotypes, although a **60*-dependent decreasing tendency in the AUC ratio was observed and the median AUC ratio for **60/*60* was reduced to 48% of that for the **1/*1* diplotypes, this trend was not statistically significant (P = .0724, JT test). As for the subjects with the **6* haplotypes, a moderate decrease was detected (P = .0372, JT test), and the **6/*6* diplotypes showed 67% of the median AUC ratio of **1/*1*. For the patients with the **28* haplotypes, a significant **28*-dependent decrease was observed among the **1/*1*, **28/*1*, and **28/*28* diplotypes (P = .0014, JT test). The median AUC ratio in **28/*28* was 56% of that of **1/*1*. In the **28/*1* patients, there was 1 heterozygote, with the **28c* haplotype having an additional nonsynonymous SNP, 686C>A (P229Q, **27*), and there were 2 heterozygotes of the **28d* haplotype lacking −3279T>G (**60*). The AUC ratios of these subjects fell within an interquartile range of the **28/*1* group. Thus the effects of these additional SNPs seemed not to be significant as compared with the effect of **28* alone. Regarding the effects of block 1 haplotype combinations, a further decreasing effect of the **6* haplotypes on the AUC ratios in the **60* or **28* group was evident when the **6/*60* diplotype was compared with **60/*1* or when the **6/*28* diplotype was compared with **28/*1* (P = .0149 and P = .0486, respectively; Mann-Whitney test). However, no apparent effect of the **60* haplotypes on the **28* heterozygotes was seen when **28/*1* and **28/*60* were compared (P = .2768, Mann-Whitney test) (Fig 5, *A*).

The effect of the *UGT1A1* block 1 haplotypes on the total bilirubin level was also evaluated. A significant increase in the bilirubin levels was observed in the patients with the **60* haplotypes (P = .0048, JT test), and a 1.2-fold increase in the median value of the **60/*60* diplotypes was observed compared with that of

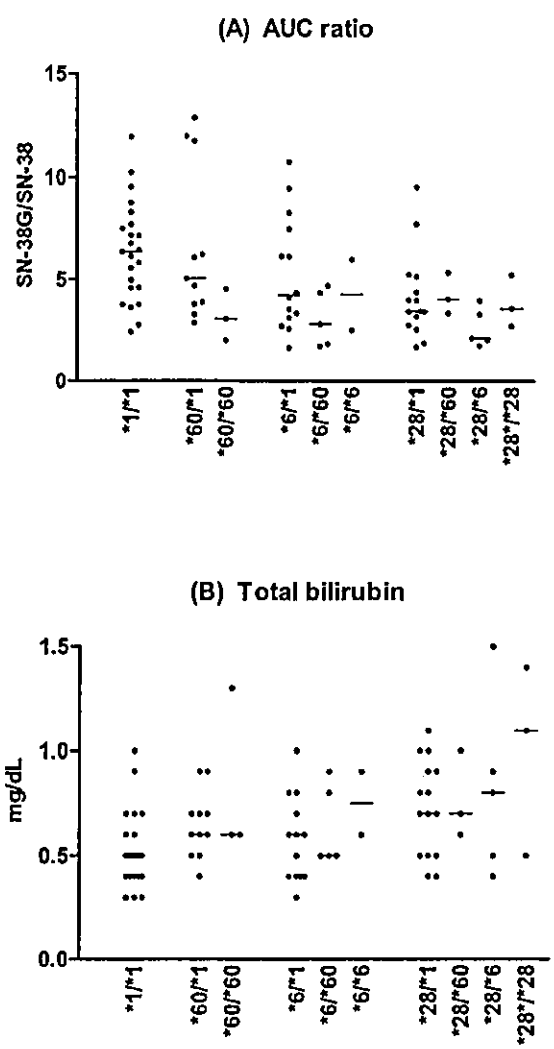


Fig 5. Association of the *UGT1A1* diplotypes in block 1 with the reduced area under the concentration-time curve (AUC) ratio (SN-38G/SN-38) (A) and with the increased serum total bilirubin levels (pretreatment) (B) in Japanese cancer patients who received irinotecan (84 patients for A and 85 for B). Each *point* represents an individual, and the median is indicated by a *bar*. The Kruskal-Wallis test for the full data sets (10 diplotypes) yielded *P* values of .0070 for A and .0503 for B. Significant reduction in the AUC ratio was detected in the **6/*60* and **28/*6* groups ($P = .049$ and $P = .0071$, respectively; nonparametric Dunnett multiple comparison test) compared with the **1/*1* group. Statistical analysis of gene-dose effect of each haplotype was separately conducted and is summarized in Table IV.

1/*1*. The bilirubin levels in the subjects with the **6* haplotypes were also elevated to 1.2- and 1.5-fold for the heterozygotes (6/*1*) and homozygotes (**6/*6*), respectively, although this trend was not statistically significant ($P = .0988$, JT test). For the **28* haplotypes, a significant genotype-dependent increase was evident when the **1/*1*, **28/*1*, and **28/*28* diplotypes were compared ($P = .0007$, JT test). The median values of the heterozygotes and homozygotes were elevated 1.4- and 2.2-fold, respectively, compared with the value for **1/*1* (Table IV). The additional effect (1.1-fold elevation) of the **6* haplotype on the increased levels of the **28* heterozygotes was also observed when **28/*1* and **28/*6* were compared, although it was not significant ($P = .4476$, Mann-Whitney test) (Fig 5, *B*). No apparent effect of **60* haplotypes on **28* was seen between **28/*1* and **28/*60* ($P = .4294$, Mann-Whitney test). Thus the effects of the haplotypes in block 1 on the bilirubin levels correlated well with those on the metabolic ratios.

As for block 2, we first overviewed the effect of each haplotype on the AUC ratios and the total bilirubin levels and found that these parameters for the subjects with **1b*, **1c*, **1j*, and **533P* (**1k* was not found in irinotecan-administered patients), which share the 3 SNPs 1813C>T, 1941C>G, and 2042C>G, were lower for the AUC ratios and higher for the bilirubin levels than those of **1a/*1a*. Moreover, significant differences among **1b*, **1c*, **1j*, and **533P* could not be detected. Therefore we joined these haplotypes into the **1B* haplotypes. Similarly, the non-**1B* haplotypes were combined as the **1A* haplotypes. Among the 21 patients who carried the **1B* haplotypes in block 2, only 2 were heterozygous for **28b* (their whole-gene diplotypes were **1a-*1c/*28b-*1a* and **1a-*1c/*28b-*1e*). Thus the majority of the subjects with **1B* had the non-**28* haplotypes in block 1; the effect of the **1B* haplotypes in block 2 was then analyzed among the non-**28* population. We further surveyed an additional effect of block 2 **1B* on the block 1 haplotypes and found that the **1B*-dependent reduction in the AUC ratios was remarkable in the **60*-bearing patients. Accordingly, we separately evaluated the **60*-positive subjects with **1B* in block 2. The AUC ratios and total bilirubin levels were compared among the diplotypes in block 2 and analyzed by the Kruskal-Wallis test, with *P* values of .3355 obtained for the AUC ratio and .0650 for the total bilirubin, respectively (Fig 6). We also evaluated the gene-dose effect of **1B* haplotypes, as summarized in Table IV. Although a **1B*-dependent decreasing tendency in the AUC ratios was observed and the median AUC ratio in **1B* homozygotes was

Table IV. Gene-dose effects of *UGT1A1* haplotypes on AUC ratio and serum total bilirubin levels

	Haplotype group	*No.*	*AUC ratio (SN-38G/SN-38)*	*Total bilirubin*
Block 1	**1/*1*	23	6.36 (4.59-8.00)	0.50 (0.40-0.65)
	**60/*1*	11	5.05 (3.84-11.87)	0.60 (0.55-0.80)
	**60/*60*	3	3.06	0.6
	P value		.0724 (NS)	.0048 ($P < .017$‡)
	**1/*1*	23	6.36 (4.59-8.00)	0.50 (0.40-0.65)
	**6/*1*	14 (15)†	4.23 (2.94-7.88)	0.60 (0.40-0.75)
	**6/*6*	2	4.27	0.75
	P value		.0372 (NS)	.0988 (NS)
	**1/*1*	23	6.36 (4.59-8.00)	0.50 (0.40-0.65)
	**28/*1*	15	3.45 (2.97-5.20)	0.7 (0.50-0.95)
	**28/*28*	3	3.57	1.1
	P value		.0014 ($P < .017$‡)	.0007 ($P < .017$‡)
Block 2	Non-**28*			
	**1A/*1A*	34 (35)†	6.04 (3.25-7.61)	0.50 (0.40-0.70)
	**1B/*1A*	22	4.65 (3.42-6.19)	0.60 (0.50-0.85)
	**1B/*1B*	2	3.37	0.90
	P value		.1551 (NS)	.0224 ($P < .025$§)
	60* in non-28*			
	**1A/*1A*	4	9.04	0.65
	**1B/*1A*	8	3.84 (3.18-5.64)	0.60 (0.55-0.80)
	**1B/*1B*	2	3.37	0.90
	P value		.0173 ($P < .025$§)	.4744 (NS)

Gene-dose effects of each haplotype were evaluated by the Jonckheere-Terpstra test. Values are expressed as the median with the interquartile range in parentheses.
NS, Not significant.
†The number in parentheses represents total bilirubin.
‡Significant level corrected by the number of comparisons in block 1 that corresponds to .05 of the type I risk.
§Significant level corrected by number of comparisons in block 2 that corresponds to .05 of the type I risk.

reduced to 56% of the **1A/*1A* group, it was not statistically significant ($P = .1551$, JT test). For the serum bilirubin level, a significant **1B*-dependent increase was observed ($P = .0224$, JT test); a 1.8-fold increase in **1B/*1B* was observed compared with **1A/*1A* (Fig 6, *B*, and Table IV).

Regarding the effect of the **1B* in the **60*-bearing subjects, a significant **1B*-dependent decrease in the AUC ratio was observed ($P = .0173$, JT test) (Table IV). The AUC ratios (median) of the **60*-bearing subjects in **1B/*1A* and **1B/*1B* were 42% and 37% of those of the non-**1B* subjects, respectively (Fig 6, *A*, and Table IV). We then attempted to evaluate the combined effects of **60* and **1B* on the same chromosome (**60-*1B*). Among the 10 **1B*-bearing subjects with **60/*1* or **60/*60*, however, only 4 were unambiguously assigned to have **60-*1B* as their whole-gene haplotypes. Therefore the effect of **60-*1B* could not be fully analyzed. Nonetheless, it must be noted that the values of the homozygote of **60-*1B* were the lowest with regard to the AUC ratio and the highest with regard to the bilirubin level among the **60/*60* group in block 1 (Fig 6).

To further assess the responsible factors for alteration of these phenotypes, we attempted a multiple regression analysis considering genetic polymorphisms. For the AUC ratio, there is a significant correlation with age ($P = .0094$) and with the polymorphisms of −40_−39insTA ($P = .0012$) and 211G>A ($P = .0065$), which are the markers for the **28* and **6* haplotypes, respectively (Table V). The positive correlation of age with AUC ratio may be a result of the decrease in renal function with age, which may cause a reduction in renal excretion of SN-38G and thereby its increase in the plasma. Regarding total bilirubin level, a significant relationship was detected in the polymorphisms of −40_−39insTA ($P < .0001$) and 1813C>T ($P = .0270$), which are the markers for the **28* and **1B* haplotypes, respectively (Table V). These findings confirmed the effects of **28*, **6*, and **1B*.

DISCUSSION

Our sequencing data revealed 25 polymorphisms, including 10 novel ones. On the basis of LD analysis of these polymorphisms, we divided the gene into 2

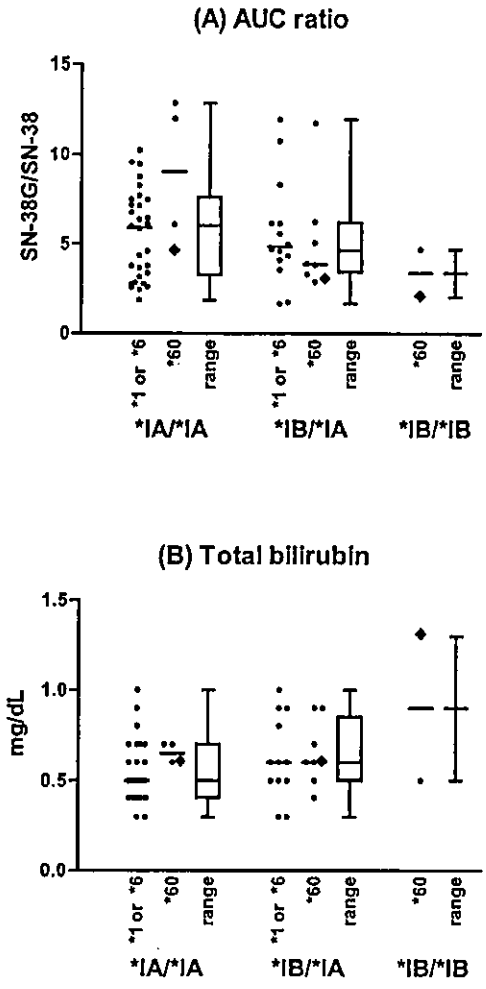


Fig 6. Association of the *UGT1A1* diplotypes in block 2 with the reduced AUC ratio (SN-38G/SN-38) (A) and with the increased serum total bilirubin levels (pretreatment) (B) in the non-**28* group of Japanese cancer patients administered irinotecan (58 patients for A and 59 for B). The distribution of the **1B* genotypes in block 2 was shown by a *box* representing the 25th to 75th percentiles with a *line* at the median and by *bars* representing the highest and lowest values. The patients having the **60* haplotype in block 1 are distinguished in each group, and the homozygotes of **60* are marked as *diamonds*. The Kruskal-Wallis test for the full data sets (5 diplotypes) yielded *P* values of .3355 for A and .0650 for B. Statistical analysis of gene-dose effect of **1B* was separately conducted and is summarized in Table IV.

blocks and designated haplotype groups (**6*, **27*, **28*, and **60*) in block 1 using the previously reported definitions. In block 2 (exons 2-5), we detected 3 perfectly linked SNPs in the 3'-UTR region (1813C>T, 1941C>G, and 2042C>G) and subsequently named the group having the 3 linked SNPs **1B*. In addition, we attempted to assign the haplotype combinations throughout both blocks (whole-gene haplotyping), but the assigned combinations were not complete; 17 subjects among 195 were not assigned to the block 1–block 2 combination. Interestingly, however, we found that block 2 **1B* exists with either block 1 **1a* or **60a* (or probably **6*) but not **28*.

Regarding the haplotypes in block 1, the impact of the **28* haplotype was the most significant in terms of the decreased AUC ratio (SN-38G/SN-38) and the increased total bilirubin level (Fig 5 and Table IV). Significant effects of −40_−39insTA (the marker of the **28* haplotype) on the AUC ratio and bilirubin level were also confirmed by multiple regression analysis (Table V). Our results were consistent with previous reports that showed correlations of **28* with hyperbilirubinemia in Gilbert syndrome or in cancer patients[11,12,19] and with decreased SN-38G formation in both in vitro and in vivo studies.[13,18,19]

The previous reports on **6* (G71R) showed a close linkage between hyperbilirubinemia and the genotype in Japanese infants[26] or decreased SN-38G formation in the *UGT1A1*6*-expressing cell line.[16,17] However, there were only limited pharmacokinetic data on irinotecan-administered subjects with the **6* haplotype. In this study it was shown that block 1 **6* was always linked to block 2 **1a* (or **1L*) and probably to block 2 **1c*. The patients bearing **6* alone showed trends for a decrease in the AUC ratios (SN-38G/SN-38) and an increase in total bilirubin levels, although the trends were not statistically significant (Table IV). It is noteworthy, however, that the AUC ratios in the patients bearing the **6* haplotype together with the **28* or **60* haplotype were significantly low compared with the **1/*1* group (Fig 5, *A*). The multiple regression analysis also indicated that 211G>A (**6* marker) had a significant effect on the AUC ratio (Table V). Ando et al[19] have also reported that the **6* allele alone is not a good predictor of severe toxicity of irinotecan but considered that it might enhance the **28*-associated irinotecan toxicity. Given that our haplotype analysis revealed that **28* and **6* were present on a mutually exclusive chromosome, **28* and **6* should exert an additive effect on irinotecan toxicity.

Regarding the **60* allele (−3279T>G), a decreasing tendency in the AUC ratio (SN-38G/SN-38) and a significant increase in total bilirubin levels were observed in the subjects bearing the **60* haplotypes (Fig 5 and Table IV), although multiple regression analysis

Table V. Multiple regression analysis of AUC ratio and total bilirubin level concerning *UGT1A1* polymorphisms

	Coefficient	*F value*	*P value*	R^2	*Intercept*
AUC ratio (SN-38G/SN-38)				0.2174	1.726
Variable					
Age	0.0722	7.08	.0094		
−40_−39insTA (**28*)†	−1.666	11.27	.0012		
211G>A (**6*)†	−1.461	7.80	.0065		
Total bilirubin				0.2029	0.539
Variable					
−40_−39insTA (**28*)†	0.213	20.10	<.0001		
1813C>T (**1B*)†	0.112	5.07	.0270		

The numbers of the cancer patients used for the analyses were 84 for AUC ratio and 85 for total bilirubin, respectively.
†The corresponding haplotype is described in parentheses.

revealed no significant relevance of the marker SNP of **60* (−3279T>G) to those phenotypic parameters. There is a possibility that the multiple regression analysis might miss the **60* marker, because this site is frequently associated with other marker sites of **28* or **1B*.

In this study we showed for the first time the effect of novel **1B* haplotypes on *UGT1A1*-related phenotypes. We found a **1B*-dependent decreasing trend in the AUC ratio (SN-38G/SN-38), although not significant, and a significant increase in serum total bilirubin levels (Fig 6 and Table IV). The multiple regression analysis also confirmed the significant relationship of the marker site of **1B* (1813C>T) to total bilirubin level (Table V). When the AUC ratios of **1a-*1A/*1a-*1A* and **1a-*1B/*1a-*1A* were compared, the difference (the effect of **1a-*1B*) was not clear (data not shown). However, the presence of **1B* together with **60* haplotypes in block 1 enhanced a trend for decreased AUC ratios (Fig 6, *A* and Table IV). Thus it is likely that the effects of **1B* could be more evidently manifested in the concurrent presence of **60*. One possible mechanism of the reduced UGT activity in the **1B* haplotypes might be an instability of messenger ribonucleic acid as a result of the nucleotide substitutions in the 3'-UTR. Because the 3'-UTR in *UGT1A1* is shared by other UGT1A isoforms, the **1B* haplotypes might also affect their activities.

We found that there were 2 types in the **60* haplotypes, **60-*1A* and **60-*1B* (data not shown). Because **60a* is known to partially reduce *UGT1A1* transcriptional levels,[14] the presence of **1B* on the same chromosome might cause a synergistic reduction in *UGT1A1* transcription, possibly through a **1B*-induced messenger ribonucleic acid instability. Thus we attempted to evaluate the combined effects of **60* and **1B* on the same chromosome (**60-*1B*). Among the 10 **1B*-bearing subjects with the **60* groups, the block 1−block 2 haplotype combinations for 6 patients could not be determined either to be on the same chromosome or not. Although this ambiguity hampered the precise evaluation of the effect of **60-*1B*, it is noteworthy that the diplotype of more than half of the **60*-bearing patients was estimated to have **60-*1B* and that values of the **60-*1B* homozygotes were the lowest with regard to the AUC ratio and the highest with regard to the bilirubin level among the **60/*60* group in block 1 (Fig 6).

On further studies of the association of the *UGT1A1* haplotypes with irinotecan-induced toxicity, such as neutropenia, we realized that the association should be evaluated among the patients who received irinotecan alone, because the coadministered drugs significantly potentiated the neutropenia. Because the number of patients administered irinotecan alone was still small, a precise evaluation was not available in this study. However, regarding the **1B* in block 2 (in which **1B/*1B* was not available), our preliminary observation revealed a significant decrease in the neutrophil count nadir in the **1B* heterozygotes ($P = 0.0044$, Mann-Whitney test); their median value was 1100 counts/μL ($n = 7$) versus 2500 counts/μL ($n = 10$) in the **1A* group. The elucidation of the clinical outcome of **1B*, as well as the other *UGT1A1* haplotypes, awaits further studies.

In this study we attempted to evaluate the functional significance of *UGT1A1* haplotypes by analyzing *UGT1A1*-related phenotypic parameters in irinotecan-administered patients and identified several *UGT1A1* haplotypes significantly associated with the reduced AUC ratio (**28* and **6*) and with the increased total bilirubin level (**28*, **60*, and **1B*). We also suggested that the novel haplotype **1B* might be functionally important, although this is still hypothetical. The clin-

ical significance of those haplotypes should be evaluated in a future study.

We thank Drs Tomoko Mogami and Shigeo Kojima for their generous support of this study, as well as Ms Chie Knudsen and Ms Hiromi Suzuki for their secretarial assistance.

None of the authors has any conflict of interest to declare with respect to the contents of this article.

References

1. Mathijssen RH, van Alphen RJ, Verweij J, Loos WJ, Nooter K, Stoter G, et al. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). Clin Cancer Res 2001;7:2182-94.
2. Garcia-Carbonero R, Supko JG. Current perspectives on the clinical experience, pharmacology, and continued development of the camptothecins. Clin Cancer Res 2002;8:641-61.
3. Slatter JG, Su P, Sams JP, Schaaf LJ, Wienkers LC. Bioactivation of the anticancer agent CPT-11 to SN-38 by human hepatic microsomal carboxylesterases and the in vitro assessment of potential drug interactions. Drug Metab Dispos 1997;25:1157-64.
4. Iyer L, King CD, Whitington PF, Green MD, Roy SK, Tephly TR, et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 1998;15:847-54.
5. de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, et al. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. Cancer Res 1994;54: 4347-54.
6. Kehrer DF, Sparreboom A, Verweij J, de Bruijn P, Nierop CA, van de Schraaf J, et al. Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. Clin Cancer Res 2001;7:1136-41.
7. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 1994;54:3723-5.
8. Sparreboom A, de Jonge MJ, de Bruijn P, Brouwer E, Nooter K, Loos WJ, et al. Irinotecan (CPT-11) metabolism and disposition in cancer patients. Clin Cancer Res 1998;4:2747-54.
9. Hanioka N, Ozawa S, Jinno H, Ando M, Saito Y, Sawada J. Human liver UDP-glucuronosyltransferase isoforms involved in the glucuronidation of 7-ethyl-10-hydroxycamptothecin. Xenobiotica 2001;31:687-99.
10. Fisher MB, Vandenbranden M, Findlay K, Burchell B, Thummel KE, Hall SD, et al. Tissue distribution and interindividual variation in human UDP-glucuronosyltransferase activity: relationship between UGT1A1 promoter genotype and variability in a liver bank. Pharmacogenetics 2000;10:727-39.
11. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995;333:1171-5.
12. Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 1996;347:578-81.
13. Iyer L, Hall D, Das S, Mortell MA, Ramirez J, Kim S, et al. Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. Clin Pharmacol Ther 1999;65:576-82.
14. Sugatani J, Yamakawa K, Yoshinari K, Machida T, Takagi H, Mori M, et al. Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. Biochem Biophys Res Commun 2002; 292:492-7.
15. Innocenti F, Grimsley C, Das S, Ramirez J, Cheng C, Kuttab-Boulos H, et al. Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. Pharmacogenetics 2002;12:725-33.
16. Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Mol Pharmacol 2002;62:608-17.
17. Jinno H, Tanaka-Kagawa T, Hanioka N, Saeki M, Ishida S, Nishimura T, et al. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan (CPT-11), by human UGT1A1 variants, G71R, P229Q, and Y486D. Drug Metab Dispos 2003; 31:108-13.
18. Iyer L, Das S, Janisch L, Wen M, Ramirez J, Karrison T, et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2:43-7.
19. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000;60:6921-6.
20. Judson R, Stephens JC, Windemuth A. The predictive power of haplotypes in clinical response. Pharmacogenomics 2000;1:15-26.
21. Saeki M, Saito Y, Jinno H, Tohkin M, Kurose K, Kaniwa N, et al. Comprehensive UGT1A1 genotyping in a Japanese population by pyrosequencing. Clin Chem 2003; 49:1182-5.
22. Saeki M, Ozawa S, Saito Y, Jinno H, Hamaguchi T, Nokihara H, et al. Three novel single nucleotide polymorphisms in UGT1A10. Drug Metab Pharmacokinet 2002;17:488-90.
23. Kitamura Y, Moriguchi M, Kaneko H, Morisaki H, Morisaki T, Toyama K, et al. Determination of probability distribution of diplotype configuration (diplotype distribution) for each subject from genotypic data using the EM algorithm. Ann Hum Genet 2002;66:183-93.

24. Otsuji S, Mizuno K, Ito S, Kawahara S, Kai M. A new enzymatic approach for estimating total and direct bilirubin. Clin Biochem 1988;21:33-8.
25. Sai K, Kaniwa N, Ozawa S, Sawada J. An analytical method for irinotecan (CPT-11) and its metabolites using a high-performance liquid chromatography: parallel detection with fluorescence and mass spectrometry. Biomed Chromatogr 2002;16:209-18.
26. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A 1998; 95:8170-4.
27. Akaba K, Kimura T, Sasaki A, Tanabe S, Ikegami T, Hashimoto M, et al. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. Biochem Mol Biol Int 1998;46:21-6.
28. Huang CS, Luo GA, Huang ML, Yu SC, Yang SS. Variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese. Pharmacogenetics 2000;10:539-44.

Phase II Study of Oral S-1 for Treatment of Metastatic Colorectal Carcinoma

Kuniaki Shirao, M.D., Ph.D.[1]
Atsushi Ohtsu, M.D., Ph.D.[2]
Hideho Takada, M.D., Ph.D.[3]
Yasushi Mitachi, M.D., Ph.D.[4]
Kosei Hirakawa, M.D.[5]
Noboru Horikoshi, M.D.[6]
Takeshi Okamura, M.D., Ph.D.[7]
Koichi Hirata, M.D., Ph.D.[8]
Soh Saitoh, M.D.[9]
Hiroharu Isomoto, M.D.[10]
Atsushi Satoh, M.D., Ph.D.[11]

[1] Department of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan.

[2] Department of Gastrointestinal Oncology/Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan.

[3] Department of Surgery, Kori Hospital, Kansai Medical University, Osaka, Japan.

[4] Department of Gastroenterology, Sendai Kosaikai Hospital, Sendai, Japan.

[5] Department of Surgical Oncology, Graduate School of Medicine, Osaka City University, Osaka, Japan.

[6] Department of Medical Oncology, Cancer Institute Hospital, Tokyo, Japan.

[7] Department of Gastroenterologic Surgery, National Kyushu Cancer Center, Fukuoka, Japan.

[8] Department of Surgery I, Sapporo Medical University, Sapporo, Japan.

[9] Department of Gastroenterology, Aomori Prefectural Central Hospital, Aomori, Japan.

[10] Department of Surgery, Kurume University Medical Center, Kurume, Japan.

[11] Department of Gastroenterology, Toyosu Hospital, Showa University, Tokyo, Japan.

Supported by Taiho Pharmaceutical Co. (Tokyo, Japan).

The authors thank Dr. Tetsuo Taguchi, Dr. Hisashi Furue, Dr. Shigeru Tsukagoshi, Dr. Kiyokazu Yoshida, and Dr. Yasuo Ohashi for their kind advice; Dr. Yuh Sakata, Dr. Wasaburo Koizumi, Dr. Yoshihiko Maehara, and Dr. Naoki Hirabayashi for performing extramural review; and all other participants in the S-1 Cooperative Colorectal Carcinoma Study Group. The authors also thank Takeshi Tahara and Koichiro Hoashi for their assistance with data management and Prof. J. Patrick Barron of the International Medical Communications Center at Tokyo Medical University (Tokyo, Japan) for his careful review of the current article.

BACKGROUND. The goal of the current study was to evaluate the objective response rate and toxicity associated with the oral fluoropyrimidine S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate) in patients with previously untreated metastatic colorectal carcinoma.

METHODS. Thirty-eight patients were enrolled in the study. S-1 was administered orally at a dose of 40 mg/m^2 twice daily for 28 days, followed by a 14-day rest period. Treatment was repeated every 6 weeks unless disease progression was observed.

RESULTS. A combined total of 173 courses of S-1 were administered to the 38 enrolled patients. The median number of courses administered to a given patient was 3.5 (range, 1–18). Although no patient exhibited a complete response to treatment, 15 had partial responses (response rate, 39.5%; 95% confidence interval, 24.0–56.6%). In addition, 5 patients had minor responses, and 14 had stable disease. Four patients were found to have progressive disease after two courses of treatment. The median survival time was 358 days (95% confidence interval, 305–490 days), and the 1-year survival rate was 47.4%. The most common adverse reactions included myelosuppression and gastrointestinal toxicity; most cases involved Grade 1 or 2 toxicity, but Grade 3 toxicities (anemia [7.9% of patients], neutropenia [5.3% of patients], diarrhea [2.6% of patients], and abnormal bilirubin levels [7.9% of patients]) also were noted. Neither Grade 4 toxicity nor treatment-related death was observed during the study.

CONCLUSIONS. Orally administered S-1 is active against metastatic colorectal carcinoma and has an acceptable toxicity profile. This promising agent has the potential to become a valuable chemotherapeutic option. *Cancer* **2004;100: 2355–61.** © *2004 American Cancer Society.*

KEYWORDS: colorectal carcinoma, S-1, 5-fluorouracil derivative, oral fluoropyrimidine, Phase II study.

Colorectal carcinoma is one of the most common causes of malignancy-related death in the United States, Japan, and most European countries. The median survival duration for patients with metastatic colorectal carcinoma treated with supportive care alone is approximately 4–6 months.[1] Systemic chemotherapy with 5-fluorouracil (5-FU) recently was shown to prolong survival, with a median

Address for reprints: Kuniaki Shirao, M.D., Ph.D., National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; Fax: (011) 81 3 3542 3815; E-mail: kshirao@ncc.go.jp

Received September 24, 2003; revision received February 27, 2004; accepted March 17, 2004.

DOI 10.1002/cncr.20277
Published online 28 April 2004 in Wiley InterScience (www.interscience.wiley.com).

survival time of 17–21 months associated with such treatment.[2,3] The administration of irinotecan together with 5-FU and leucovorin (LV) as first-line treatment for metastatic disease also has been shown to produce a survival benefit,[2,4] but recently, concern has been raised regarding the toxicity of the weekly bolus combination of these agents.[5]

A randomized cooperative group study has yielded preliminary data supporting the role of 5-FU and LV administered via continuous intravenous infusion (CVI) as the backbone of treatment strategies for metastatic colorectal carcinoma.[6] Nonetheless, CVI performed using a portable pump and an indwelling catheter is challenging and may induce phlebitis or infection originating at the injection site and requiring long-term hospitalization; thus, oral anticancer agents have been developed to address this problem.[7] The results of large Phase III studies of oral capecitabine and the combination of tegafur + uracil (UFT) with LV were reported recently and demonstrated survival benefits that were equivalent to those achieved using intravenous 5-FU + LV.[8–11] Oral chemotherapy has major advantages over intravenously administered treatment in terms of pharmacoeconomic considerations and patient preferences, because oral treatment can be administered on an outpatient basis, thereby reducing the length of patients' hospital stays.[12] Over time, the role of oral chemotherapy in the treatment of malignant disease is expected to become increasingly significant.

Gastrointestinal side effects represent the dose-limiting toxicity associated with 5-FU in a long-term administration schedule (i.e., a CVI schedule).[7] Therefore, to maximize the therapeutic effects of 5-FU, prevention of gastrointestinal toxicity is of primary importance. A new oral fluoropyrimidine, S-1, has been developed by Taiho Pharmaceutical Co. (Tokyo, Japan) and adapted for use in the treatment of advanced gastric[13–15] and head and neck malignancies[16]; at present, this agent is used widely throughout Japan. S-1 consists of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1.[17] Tegafur is a precursor of 5-FU and functions as an effector. As an enhancer of the antitumor activity of tegafur, CDHP is prescribed to potently and reversibly inhibit the 5-FU degradation enzyme dihydropyrimidine dehydrogenase (DPD); by inhibiting DPD, CDHP induced the long-term retention of an increased concentration of 5-FU in the blood.[18] Orally administered potassium oxonate is selectively distributed to the gastrointestinal tract with high concentration and inhibits orotate phosphoribosyltransferase, which phosphorylates 5-FU to yield the active metabolite form of 5-FU in humans.[19]

In rats bearing subcutaneous Yoshida sarcoma compared with UFT administered at an equally harmful dose to the rats, S-1 tended to maintain the concentration of 5-FU in plasma and tumor tissue for a longer duration and with less gastrointestinal toxicity.[20] Furthermore, compared with tegafur, UFT, and other fluoropyrimidines, S-1 exhibited greater therapeutic efficacy against various rat tumors and human xenografts.[21]

In a Phase I study involving Japanese patients, S-1 was administered orally for 28 days. The maximum allowed dose of S-1 was 150 mg once daily or 75 mg twice daily, and leukopenia was the resulting dose-limiting toxicity. The pharmacokinetic profile of S-1 revealed that twice-daily administration preserved therapeutic 5-FU levels without increasing the maximum 5-FU concentration in the blood.[22,23] Therefore, oral administration of S-1 at a dose of 75 mg twice daily for 28 consecutive days, with a subsequent 14-day rest period, was recommended. Two Phase II studies of twice-daily S-1 administered as a single agent for the treatment of metastatic gastric malignancy yielded response rates of approximately 50%, with minimal toxicity.[13–15]

Based on these results, two Phase II studies of S-1 in the treatment of metastatic colorectal carcinoma were initiated. Response rates of 17% and 35% were observed in these two trials.[13,24] To verify the reproducibility of these findings, we performed our own Phase II study of S-1 in the treatment of Japanese patients with metastatic colorectal carcinoma.

MATERIALS AND METHODS

Eligibility

Patients were entered into the study only if they fulfilled the following eligibility requirements: 1) histologically confirmed colorectal carcinoma; 2) inoperable metastatic disease or recurrent metastatic disease after surgery; 3) the presence of measurable or evaluable lesions; 4) age $\geq$ 20 years but $<$ 75 years; 5) Eastern Cooperative Oncology Group performance status (PS) $\leq$ 2; 6) no previous chemotherapy or radiotherapy for advanced disease (with any adjuvant chemotherapy for colorectal carcinoma required to have been completed $\geq$ 6 months before enrollment); 7) adequate bone marrow function (hemoglobin concentration $\geq$ 9.0 mg/dL, white blood cell count $\geq$ 4000/μL but $\leq$ 12,000/μL, and platelet count $\geq$ 100,000/μL); 8) adequate liver function (serum bilirubin levels $\leq$ 1.5 mg/dL, serum transaminase levels $\leq$ 100 international units per liter, and serum alkaline phosphatase levels $<$ 2 times the upper limit of normal); 9) adequate renal function (serum creatinine levels within normal limits); 10) no other severe med-

ical conditions; and 11) no other active malignancies. In addition, patients were required to provide written informed consent, and pregnant women were excluded from the study.

Treatment Schedule

S-1 was administered at a dose of 40 mg/m^2 twice daily for 28 consecutive days, with a subsequent 14-day rest period. Patients were assigned on the basis of body surface area (BSA) to receive one of the following doses twice daily: 40 mg (BSA < 1.25 m^2), 50 mg (BSA ≤ 125 to < 1.50 m^2), or 60 mg (BSA > 1.50 m^2). S-1 was supplied by Taiho Pharmaceutical Co. in the form of 20 and 25 mg capsules (i.e., 20 and 25 mg tegafur). A course of therapy was defined as 28 consecutive days of treatment followed by a 14-day rest period, and courses were repeated every 6 weeks until either disease progression or unacceptable toxicity was observed. Patients whose toxicities necessitated a rest period of more than 4 weeks were withdrawn from treatment. Prophylactic use of antiemetic agents was not allowed. For all patients, treatment compliance and receipt of treatment without hospitalization were verified by patient interviews conducted on a regular schedule.

Evaluation

Before entry into the study, patients were evaluated using appropriate investigational methods to determine the extent of disease. A complete blood cell count, liver function testing, renal function testing, and urinalysis were performed at least once every 2 weeks during treatment. Appropriate investigation was repeated as necessary to evaluate target lesion sites before every treatment course. Antitumor activity was evaluated in accordance with the general rules, based on the corresponding World Health Organization criteria, set forth by the Japanese Research Society for Colorectal Carcinoma.[25] Complete response (CR) was defined as the disappearance of all evidence of malignant disease for more than 4 weeks. Partial response (PR) was defined as a reduction (lasting longer than 4 weeks) of greater than 50% in the sum over all lesions of the product of the longest perpendicular tumor dimensions, with no evidence of new lesions or of the progression of any preexisting lesion. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum over all lesions of the product of the longest perpendicular tumor dimensions, with no evidence of new lesions. Progressive disease (PD) was defined by increases of greater than 25% in sum overall lesions of the product of the longest perpendicular tumor dimensions or the appearance of new lesions. The toxicity criteria of the Japan Society for Cancer Therapy, which were based (with some modification) on the World Health Organization criteria, were used to evaluate treatment-related toxicity.[26] The eligibility and suitability of patients for assessment and the responses of patients to treatment were reviewed extramurally.

TABLE 1
Patient Characteristics

Characteristic	No. of patients
No. of eligible patients	38
Median age in yrs (range)	58.5 (28–74)
Gender (%)	
Male	18 (47)
Female	20 (53)
ECOG PS (%)	
0	18 (47)
1	20 (53)
Primary lesion site (%)	
Colon	23 (61)
Rectum	15 (39)
Histology (%)	
Well/moderately differentiated	33 (87)
Poorly differentiated	5 (13)
Previous therapy (%)	
Surgery	23 (61)
Surgery + adjuvant chemotherapy	4 (11)
Surgery + radiotherapy	2 (5)
None	9 (24)
Mean body surface area in m^2 (range)	1.53 (1.26–1.85)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Statistical Methods

Previous Phase II studies have reported a 35.5% response rate for metastatic colorectal carcinoma treated with S-1. The current study was designed to have a target activity level of 35% and a minimum activity level of 15%, with an α error of 0.05 and a β error of 0.2; thus, a minimum of 38 patients were required. Survival was calculated from the date of treatment initiation using the Kaplan–Meier method.

Ethical Considerations

The current trial was approved by the institutional review boards of the clinical oncology programs at all participating hospitals. Approval was based on the 1975 revision of the Helsinki Declaration. Oral and written statements of informed consent were acquired from all patients.

RESULTS

Thirty-eight patients (18 men and 20 women) with advanced metastatic colorectal carcinoma were en-

TABLE 2
Body Surface Area and Corresponding S-1 Dose

BSA (m^2)	S-1 dose[a] (mg)	No. of patients (%)
< 1.25	40	0
≤1.25 to < 1.50	50	15 (39)
≥1.50	60	23 (61)

BSA: body surface area.
[a] Dose administered twice daily.

TABLE 3
Objective Response Data

Response type	No. of patients
Complete response	0
Partial response	15
Minor response	5
Stable disease	14
Progressive disease	4
Overall response rate[a]	39.5% (15/38)
95% confidence interval	24.0–56.6%

[a] Includes complete responses and partial responses.

tered into the trial between June 1999 and December 2000. Patient characteristics are summarized in Table 1. The median patient age was 58.5 years (range, 28–74 years). Eighteen patients had PS 0, and the remaining 20 had PS 1. The primary tumor was located in the colon in 23 patients (61%) and in the rectum in 15 patients (39%). Thirty-three patients (87%) had well or moderately differentiated adenocarcinoma, whereas 5 (13%) had poorly differentiated adenocarcinoma. Of the 38 patients in the current study, 29 (76%) had undergone surgery before entry, 4 (11%) had received 5-FU-based adjuvant chemotherapy, and 2 had received pelvic radiotherapy.

The mean BSA in the current study population was 1.53 m^2 (range, 1.26–1.85 m^2). Daily S-1 doses according to BSA are shown in Table 2. The median S-1 dose was 60 mg administered twice daily. A combined total of 173 treatment courses were administered to the 38 patients enrolled in the study. The median number of courses per patient was 3.5 (range, 1–18), and the median cumulative S-1 dose per patient was 10,080 mg (range, 2660–44,660 mg).

Response

All 38 patients had measurable metastatic lesions. Although no patient experienced a CR, 15 patients had PRs (response rate, 39.5%; 95% confidence interval, 24.0–56.6%) (Table 3). Among these 15 patients, the median time required for a 50% reduction in tumor

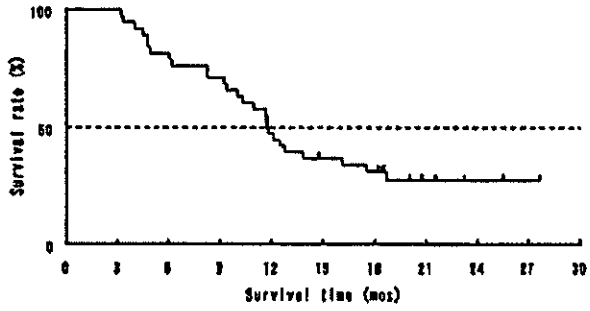


FIGURE 1. Overall survival of 38 patients treated with S-1 for previously untreated metastatic colorectal carcinoma. Median survival time, 358 days (95% confidence interval, 305–490 days).

size was 68 days (range, 29–130 days), and the median duration of response was 232 days (range, 96–679 days). Five patients had minor responses, and 14 had SD. The remaining four patients were found to have PD after two courses of treatment. Response rates according to metastatic site were as follows: liver, 38% (9 of 24 patients); lung, 27% (4 of 15 patients); and lymph nodes, 30% (3 of 10 patients). The response rate among patients with colon carcinoma was 44% (10 of 23 patients), and the response rate among patients with rectal carcinoma was 33% (5 of 15 patients). The response rate at the primary site as evaluated using the roentgenographic evaluation criteria proposed by the Japanese Society for Cancer of the Colon and Rectum was 43% (3 of 7 patients). One of the four patients who had a history of adjuvant chemotherapy achieved a PR.

At the close of the trial, the median time to evidence of disease progression was 162 days (range, 118–254 days). The median survival time from the beginning of treatment was 358 days (median follow-up, 666 days; 95% confidence interval, 305–490 days) for the overall study cohort, and the 1-year survival rate was 47.4% (Fig. 1).

Toxicity

For each toxicity, the patient distribution with respect to highest observed grade is summarized in Table 4. The most common adverse reactions included myelosuppression and gastrointestinal toxicity, although these events generally were mild, and no cumulative toxicity was noted. Neither Grade 4 toxicity nor treatment-related death was observed during the study. Toxicity incidence rates were as follows: anemia, 45% (17 of 38 patients); leukopenia, 45% (17 of 38 patients); neutropenia, 42% (16 of 38 patients); and thrombocytopenia, 13% (5 of 38 patients). Nonetheless, Grade ≥ 3 toxicities were noted in less than 8% of patients.

TABLE 4
Toxicity Data

Toxicity	Grade 1	2	3	4	Grade ≥3 (%)
Anemia	7	7	3	0	7.9
Leukopenia	7	10	0	0	0
Neutropenia	4	10	2	0	5.3
Thrombocytopenia	4	1	0	0	0
Diarrhea	5	8	1	0	2.6
Nausea/vomiting	8	7	0	0	0
Anorexia	15	4	0	0	0
Stomatitis	11	3	0	0	0
Hand-foot syndrome	2	0	0	0	0
Pigmentation	15	0	0	0	0
Malaise	17	2	0	0	0
Bilirubinemia	—[a]	14	3	0	7.9

[a] Grade 1 bilirubinemia is not defined in the toxicity criteria of the Japan Society for Cancer Therapy. (See: Japan Society for Cancer Therapy. Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. *J Jpn Soc Cancer Ther.* 1993;28:101–130.[20])

The overall incidence rate for diarrhea was 37% (14 of 38 patients), with Grade 3 diarrhea noted in 3% of the study cohort (1 of 38 patients). The overall stomatitis incidence rate was 37% (14 of 38 patients); however, Grade ≥ 3 stomatitis was not observed. The incidence rate for hand-foot syndrome (palmar-plantar erythrodysesthesia) was 5% (2 of 38 patients); Grade 1 erythrodysesthesia was noted in both cases. Overall, abnormal bilirubin levels were noted in 45% of the study cohort (17 of 38 patients), with an incidence rate of 8% (3 of 38 patients) for Grade 3 bilirubin abnormalities. Nonetheless, no Grade ≥ 3 elevation of aspartate aminotransferase or alanine aminotransferase levels was observed in the current study.

Toxicity caused two patients to discontinue S-1 treatment. One of these two was hospitalized for abdominal pain (Grade 2), nausea with vomiting (Grade 2), and anorexia (Grade 2) during the third treatment course, and S-1 treatment subsequently was discontinued. The other patient withdrew from the study during the second treatment course due to diarrhea (Grade 3) and neutropenia (Grade 2). Discontinuation of treatment was not considered necessary for any of the other patients who experienced Grade 2 or Grade 3 toxicities; instead, these patients were able to continue receiving treatment after a brief interruption or after dose reduction. Thirty-five of 38 patients (92%) were treated as outpatients, a finding that indicates extremely good compliance. Of the 173 courses that were administered overall, 163 (94%) were administered at ≥ 75% of the protocol-defined dose.

DISCUSSION

The current study was conducted to evaluate the objective response rate and toxicity associated with an oral regimen of S-1 for patients with previously untreated metastatic colorectal carcinoma. We observed a response rate of 39.5%, which was equal to or greater than the corresponding response rates associated with 5-FU alone and with 5-FU + LV. In an earlier Phase II study of S-1, an overall response rate of 35% was reported for patients who had not previously received chemotherapy.[24] That earlier study and the current one were similar in terms of dosing and scheduling of S-1, eligibility criteria, and response criteria, and both studies also reported similar response rates and survival times; these similarities suggest that the activity of oral S-1 against metastatic colorectal carcinoma represents a reproducible finding.

In a previous Phase I study involving Japanese patients, S-1 was administered orally for 28 consecutive days.[22] The maximum allowable S-1 dose was 150 mg once daily or 75 mg twice daily, and myelosuppression (primarily leukopenia) was found to be the dose-limiting toxicity. This daily dose of 150 mg per day is equivalent to 100 mg/m^2 per day for the average Japanese patient, who has a BSA of 1.5 m^2. For the current study, we selected an S-1 dose of 80 mg/m^2 per day (40 mg/m^2 twice daily), which was slightly less than the maximum allowable dose identified by Phase I trials.[22] The most commonly observed adverse reactions in the current study were myelosuppression and gastrointestinal toxicity; these events generally were mild, with no Grade 4 toxicity noted. Although a small number of cases of Grade 4 myelosuppression have been reported in other Phase II studies in which a total daily dose of 80 mg/m^2 S-1 was used to treat malignant disease (gastric,[14,15] colorectal,[24] head and neck,[16] lung,[27] or breast[28]), the incidence and degree of toxicity observed in those studies did not differ substantially from what was documented in the current study.

The toxicity profile of 5-FU is schedule dependent. Myelosuppression is the primary toxic effect observed in patients receiving bolus 5-FU schedules, whereas hand-foot syndrome, stomatitis, neurotoxicity, and cardiotoxicity are associated with continuous infusion of 5-FU.[7] Hand-foot syndrome, in addition to being a typical side effect of prolonged 5-FU administration via CVI,[29] is commonly associated with the oral administration of other fluoropyrimidines, such as capecitabine.[10,11] The mechanism involved in the development of hand-foot syndrome has not been completely elucidated; however, some 5-FU catabolites are believed to be inducers of this condition.[30]

Thus, the low incidence of hand-foot syndrome associated with UFT use is consistent with the observation of low plasma levels of 5-FU catabolites in patients receiving UFT.[31] In the current trial, hand-foot syndrome was observed in only 5% of the study cohort (2 of 38 patients); furthermore, both of these cases involved reversible, Grade 1 hand-foot syndrome. In other trials, only mild S-1-induced hand-foot syndrome, which was not suggestive of dose-limiting toxicity, has been reported. These findings may reflect the inhibitory effect of CDHP on DPD.

The pharmacokinetic characteristics of prolonged S-1 administration were believed to be consistent with the use of CVI; however, the dose-limiting toxicity induced by S-1 was myelosuppression, which is associated with the bolus dose protocol. In a previous Phase I study, the maximum plasma 5-FU concentration was estimated to be approximately 230 ng/mL for Japanese patients who received S-1 at a dose of 75 mg per day.[22] This relatively high peak plasma 5-FU concentration may result in myelotoxicity, rather than gastrointestinal toxicity, in spite of the prolonged S-1 administration protocol. The low severity of gastrointestinal toxicity, even in the face of a relatively high peak plasma 5-FU concentration[22,23] and area under the plasma concentration–time curve, suggests the usefulness (previously noted in rats[19]) of potassium oxonate in humans. The toxicity observed in the current trial, in which S-1 was administered at a dose of 80 mg/m^2 per day (40 mg/m^2 twice daily), was mild and reversible, and yet the observed activity was remarkable, being equal to or greater than the activity of 5-FU alone.

Oral chemotherapy, for which only limited hospitalization is necessary, has major advantages over intravenously administered treatment in terms of pharmacoeconomic considerations and patient preference, as well as compliance.[12] In one study, it was reported that more than 90% of patients with advanced solid malignancies preferred oral agents over infusional agents when both types of treatment provided comparable efficacy.[32] Furthermore, a randomized crossover trial involving patients with advanced colorectal carcinoma found that oral UFT + LV compared favorably with intravenous 5-FU + LV in terms of toxicity and patient preference.[31]

In the current study, the S-1 regimen was administered successfully, with good treatment compliance, on an outpatient basis. Due to the absence of severe toxicity, especially with regard to symptoms such as nausea, vomiting, and diarrhea, almost all patients received ≥ 75% of the full protocol-defined S-1 dose; it is clear that good compliance increases the likelihood of favorable therapeutic responses. Thus, the findings of the current study indicate that S-1 is a promising agent that has the potential to become a valuable oral treatment option, along with capecitabine and UFT + LV, for patients with colorectal carcinoma. Clinical studies of S-1 in the treatment of metastatic colorectal and gastric malignancies[33,34] also suggest that S-1 possesses superior therapeutic activity compared with other regimens.

The combination of irinotecan or oxaliplatin with 5-FU + LV recently has been identified as a candidate regimen for the standard treatment of metastatic colorectal carcinoma. To determine which of these chemotherapeutic agents are most suitable for use in combination with S-1, clinical trials are essential. Three Phase I/II trials of S-1 with LV irinotecan or oxaliplatin for the treatment of metastatic colorectal carcinoma have been scheduled. In addition, a Phase III study of adjuvant chemotherapy (surgery alone vs. surgery followed by S-1) in the treatment of gastric tumors and a Phase III study comparing the use of S-1 alone with the use of S-1 + cisplatin in the treatment of metastatic gastric malignancies are ongoing. In another ongoing Phase III trial involving patients with gastric malignancies, the Japan Clinical Oncology Group is comparing 5-FU, which currently is the standard treatment agent, with single-agent S-1 and with cisplatin + irinotecan.

REFERENCES

1. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomized comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ.* 1993;306:752–755.
2. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. *Lancet.* 2000;355:1041–1047.
3. Douillard JY, Sobrero A, Carnaghi C, et al. Metastatic colorectal cancer: integrating irinotecan into combination and sequential chemotherapy. *Ann Oncol.* 2003;14 Suppl 2:II7–II12.
4. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2000;343:905–914.
5. Sargent D, Niedzwiecki D, O'Connell MJ, Schilsky RL. Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med.* 2001;345:144–145.
6. Goldberg RM, Morton RF, Sargent DJ, et al. N9741: oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Initial toxicity and response data from a GI Intergroup study [abstract]. *Proc Am Soc Clin Oncol.* 2002;21:128a.
7. Malet-Martino M, Martino R. Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review. *Oncologist.* 2002;7:288–323.

8. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter Phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2002;20: 3605–3616.
9. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2002;20:3617–3627.
10. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous 5-fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer. Results of a randomized Phase III study. *J Clin Oncol.* 2001;19:2282–2292.
11. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large Phase III study. *J Clin Oncol.* 2001;19:4097–4106.
12. DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. *J Clin Oncol.* 1998;16:2557–2567.
13. Sugimachi K, Maehara Y, Horikoshi N, et al. An early Phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. *Oncology.* 1999;57:202–210.
14. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late Phase II study of novel oral fluoropyrimidine anticancer drugs S-I (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer.* 1998;34:1715–1720.
15. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. *Oncology.* 2000;58:191–197.
16. Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B. [Late Phase II study of S-1 in patients with advanced head and neck cancer. S-1 Cooperative Study Group (Head and Neck Cancer Working Group)]. *Gan To Kagaku Ryoho.* 2001;28: 1381–1390.
17. Shirasaka T, Nakano K, Takechi T, et al. Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res.* 1993;56: 2602–2606.
18. Tatsumi K, Fukushima M, Shirasaka T, Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res.* 1987;78:748–755.
19. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res.* 1993;53:4004–4009.
20. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rat. *Cancer Chemother Pharmacol.* 1997;39:205–211.
21. Fukushima M, Satake H, Uchida J, et al. Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. *Int J Oncol.* 1998;13:693–698.
22. Taguchi T, Inuyama Y, Kanamaru R, et al. [Phase I study of S-1. S-1 Study Group]. *Gan To Kagaku Ryoho.* 1997;24:2253–2264.
23. Hirata K, Horikoshi N, Aiba K, et al. Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res.* 1999;5:2000–2005.
24. Ohtsu A, Baba H, Sakata Y, et al. Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. *Br J Cancer.* 2000;83:141–145.
25. Japanese Society for Cancer of Colon and Rectum. Japanese classification of colorectal carcinoma (1st English edition). Tokyo: Kanehara Syuppan, 1997:77–80.
26. Japan Society for Cancer Therapy. Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. *J Jpn Soc Cancer Ther.* 1993;28:101–130.
27. Kawahara M, Furuse K, Segawa Y, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer.* 2001;85:939–943.
28. Saeki T, Takashima S, Sano M, et al. [A late Phase II clinical study of S-1 in patients with progressed, refractory breast cancer]. *Gan To Kagaku Ryoho.* In press.
29. Meta-Analysis Group in Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol.* 1998; 16:3537–3541.
30. Diasio RB. Can eniluracil improve 5-fluorouracil therapy? *Clin Colorectal Cancer.* 2002;2:53.
31. Borner MM, Schoffski P, de Wit R, et al. Patients preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer.* 2002;38: 349–358.
32. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol.* 1997;15:110–115.
33. Chollet P, Schoffski P, Weigang-Kohler K, et al. Phase II trial with S-1 in chemotherapy-naive patients with gastric cancer. A trial performed by the EORTC Early Clinical Studies Group (ECSG). *Eur J Cancer.* 2003;39:1264–1270.
34. Van den Brande J, Schoffski P, Schellens JH, et al. EORTC Early Clinical Studies Group early Phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer.* 2003;88:648–653.

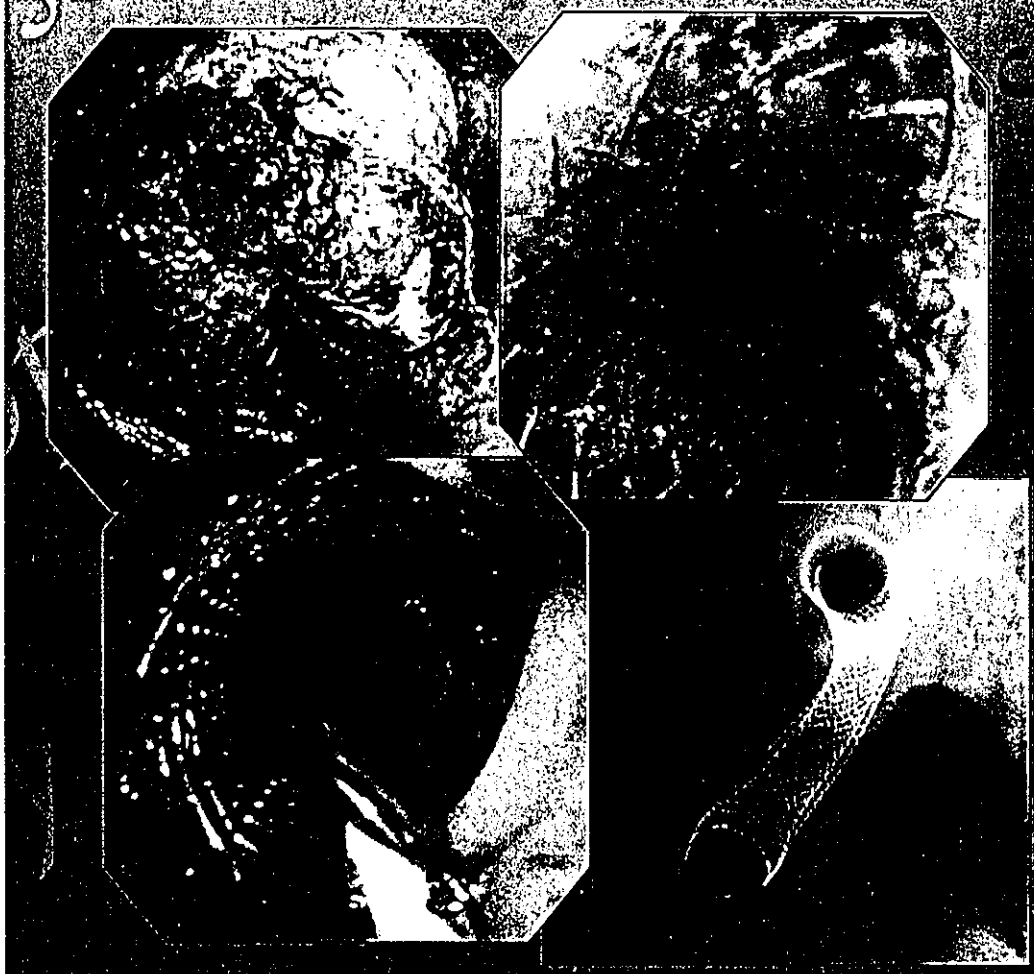
Volume 16

Supplement

2004

ISSN 0915-5635

Digestive Endoscopy



Blackwell Publishing

Official Journal of the Japan Gastroenterological Endoscopy Society and Asian Pacific Society for Digestive Endoscopy

Digestive Endoscopy

Production Editor
Lisa Schmidt (email: lisa.schmidt@blackwellpublishingasia.com)

This journal is also published online at www.blackwellsynergy.com

Aims and Scope: *Digestive Endoscopy* is published four times per year by Blackwell Publishing Asia on behalf of the Japan Gastroenterological Endoscopy Society and the Asian Pacific Society for Digestive Endoscopy. *Digestive Endoscopy* serves as a medium for presenting original articles that offer significant contributions to knowledge in the broad field of endoscopy. The Journal also includes case reports, informal editorial opinions, abstracts, and news items that may be of interest to endoscopists. All articles are peer-reviewed by at least two experts (except for Invited Articles) in the field of the submitted paper.

Publication Frequency: Four issues per year.

Address for Editorial Correspondence: Dr Tatsuo Yamakawa, c/- Japan Gastroenterological Endoscopy Society, Taimei Building, 3-22, Kanda Ogawa-machi, Chiyoda-ku, Tokyo 101-0052, Japan.

Cover images: Double colonic TTS stent. Colonoscopic findings shows a ulcerative infiltrating lesion at the hepatic flexure, causing complete luminal obstruction. The picture down left shows the expanded uncovered Niti-S colon stent *in situ* right after deployment. The picture up right shows fully expanded covered Niti-S colonic stent, which had been deployed inside the uncovered Niti-S stent. The radiological view shows the double placement of colonic stents across the hepatic flexure.

ISSN 0915-5635 (Print)
ISSN 1443-1661 (Online)

This journal is printed on acid-free paper.

For submission instructions, subscription and all other information visit www.blackwellpublishing.com/den

DEN.JEB.Jul04

Digestive Endoscopy (2004) 16 (Suppl.), S5–S8

UPPER DIGESTIVE TRACT STRICTURE

TREATMENT STRATEGIES FOR ESOPHAGEAL STRICTURE BEFORE OR AFTER CHEMORADIOTHERAPY FOR ADVANCED ESOPHAGEAL CANCER

MANABU MUTO, ATSUSHI OHTSU AND SHIGEAKI YOSHIDA

Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

ABSTRACT

Esophageal stricture due to advanced cancer is one of the serious complications of esophageal cancer as it causes dysphagia. A self-expandable metallic stent is easily inserted in such patients and provides immediate symptomatic relief of dysphagia. Alternatively, definitive chemoradiotherapy has demonstrated a significant improvement in local control and overall survival, and is now commonly used for not only unresectable esophageal cancer patients but also in resectable cases. However, little is known about its role in relief of dysphagia. Therefore, we reviewed our experience of patients with esophageal stricture who were treated with chemoradiotherapy. We expect that the findings in this article might be useful in future clinical practice.

Key words: esophageal stricture, chemoradiotherapy, self-expandable metallic stent, percutaneous endoscopic gastrostomy.

INTRODUCTION

Patients with locally advanced esophageal cancer sometimes develop an esophageal stricture, which is one of the serious complications of esophageal cancer as it causes dysphagia. Self-expandable metallic stents (EMS) have been used for palliation and provide immediate symptomatic relief of dysphagia.[1,2] Alternatively, definitive chemoradiotherapy (CRT) has demonstrated a significant improvement in local control and overall survival[3–6] and is now accepted as one of the standard treatments for esophageal cancer;[7,8] however, little is known about its role in relief of dysphagia.

Selection of treatment for patients with stricture due to untreated esophageal cancer

First, we should consider patients with newly diagnosed esophageal cancer with severe stricture at presentation. If they have unresectable T4 (TNM classification) tumors, how are those patients best managed? We know that EMS is easily deployed for such patients and resolves dysphagia promptly. However, it is only palliative therapy and does not provide a survival benefit. To evaluate the role of relief of dysphagia by CRT, we reviewed our experience of 51 patients with unresectable T4 esophageal cancer who were treated with definitive CRT. The CRT consisted of 60 Gy of external beam irradiation in 30 fractions concurrent with chemotherapy (5-fluorouracil (5FU) + cisplatin or nedaplatin). The ability to swallow was evaluated before and after completion of CRT and expressed as a dysphagia score: a score of 0 denoted complete dysphagia; (1) the ability to swallow only liquid; (2) the ability to eat semi-solids only; and (3) the ability to eat solid food. The results are shown in Figures 1 and 2. The dysphagia score improved in most patients. The median dysphagia score was 2 before CRT, and 3 after completion of CRT (Fig. 1). In addition, the complete response rate was 35% (18/51), and definitive CRT achieved a three-year survival rate of 26% (Fig. 2). These results indicate that definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival.

Correspondence: Manabu Muto, Division of Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. Email: mmuto@east.ncc.go.jp

CRT for patients with malignant fistulae due to esophageal cancer

How are esophageal cancer patients with malignant fistulae best managed? Most physicians and surgeons believe that radiotherapy or CRT for the patients with malignant fistula is contraindicated, because it may worsen the fistula. We previously reported that malignant fistulae closed in 92% (11/12) of patients after the completion of CRT, and most of them had improved the dysphagia scores[6] (Fig. 3). While the median survival time (MST) of patients with fistulae has been reported to be one to six weeks, the MST of those treated by definitive CRT was 7 months in our previous study (Fig. 4). This indicates that definitive CRT provides a chance of closure of fistulae and improves the survival.

Risks of EMS combined with CRT

Data regarding the combination treatment of EMS placement with subsequent CRT for patients with esophageal stricture due to advanced cancer is quite limited. Recently, Nishimura *et al.* reported an important investigation on the placement of stents before or during radiotherapy to the patients with advanced esophageal cancer.[9] They gathered

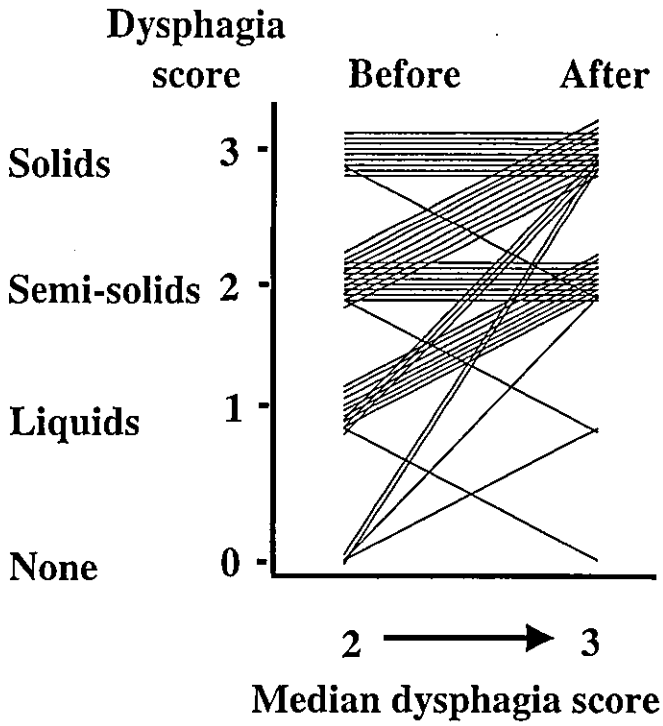


Fig. 1. Improvement of dysphasia score in the patients with esophageal stricture after completion of definitive chemoradiotherapy.

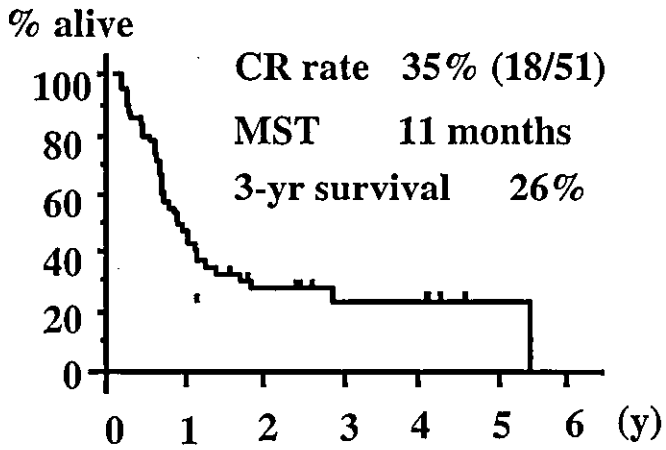


Fig. 2. Overall survival of the patients with T4 esophageal cancer treated with definitive chemoradiotherapy.

clinical data of 47 patients from 17 institutions in Japan. Covered metallic stents were used for 30 patients, uncovered metallic stents for 13 patients, plastic or silicon prosthesis for three patients, and an unknown type for one patient. Esophageal intubation was performed before the start of radiation for 23 patients and during the course of radiation for remaining 24 patients. The median total external beam radiotherapy dose was 60 Gy (6–70) and two-thirds of the patients received more then 50 Gy. Formation of or a worsening esophageal fistula occurred in 28% of such patients. Furthermore, possible treatment-related deaths were 21%. They concluded that patients with an esophageal stent introduced before or during radiotherapy have a high risk of life-threatening compli-

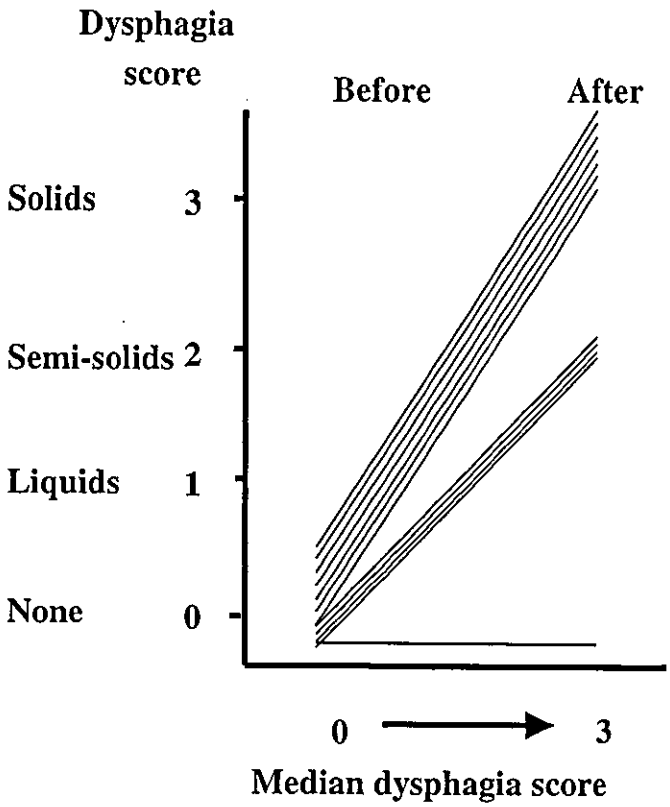


Fig. 3. Improvement of dysphasia scores in esophageal cancer patients with malignant fistula after completion of definitive chemoradiotherapy.

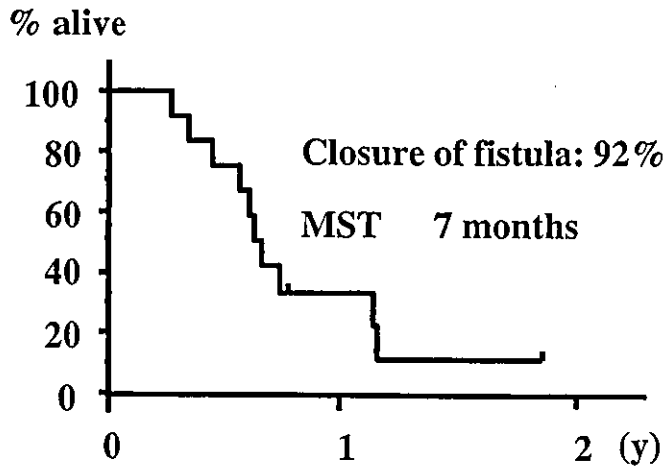


Fig. 4. Overall survival of esophageal cancer patients with malignant fistula treated with definitive chemoradiotherapy.

cations. Palliative stent placement should be delayed until radiotherapy or CRT appears to have failed, because a longer survival time is expected for patients with locally advanced esophageal cancer after CRT.

Risk of EMS placement for recurrent stricture after failure of CRT

Dysphagia due to recurrent stricture after failure of CRT means that the patient will suffer similarly to those with non-

Table 1. Self-expandable metallic stent placement for recurrent esophageal stricture after failure of radiotherapy and/or chemotherapy

Authors	Year	*n*	Rate of life-threatening complications	Does it increase the risk?
Kinsman K *et al.*[11]	1996	22	36%	Yes
Bethge N *et al.*[12]	1996	13	23%	Yes
Siersema PD *et al.*[13]	1998	20	43%	Yes
Raijman I *et al.*[14]	1997	39	8%	No
Muto M *et al.*[10]	2001	13	54%	Yes
Kaneko K *et al.*[15]	2002	12	17%	Yes
Sumiyoshi T *et al.*[16]	2003	22	High	Yes

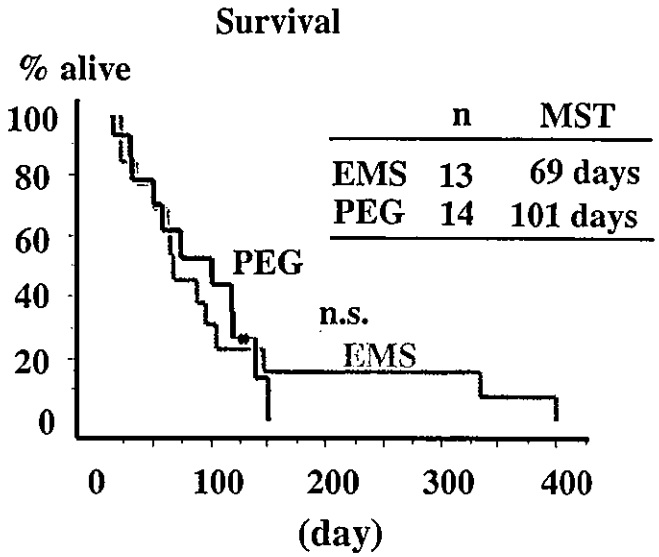


Fig. 5. Comparison of the overall survival between the patients inserted with a self-expandable metallic stent and those treated by percutaneous endoscopic gastrostomy.

treated esophageal cancer at presentation. Therefore, the main goal of palliative treatment is to relieve dysphagia even in such patients. However, it has been suggested that prior radiotherapy to the EMS placement may be associated with an increased rate of complications. We have also reported that although EMS after failure of definitive CRT improved the dysphagia score, it increased the risk of life-threatening pulmonary complications.[10] To date, many investigators have also reported the results of EMS placement for recurrent esophageal stricture after failure of radiotherapy or CRT.[11–16] We have summarized the rates of life-threatening complication in their reports (Table 1) and most concluded that EMS after failure of radiotherapy or CRT increased the rate of complications.

How should patients with recurrent dysphagia be managed after failure of CRT?

We compared the efficacy and safety between EMS and percutaneous endoscopic gastrostomy (PEG) after failure of CRT. The types of EMS deployed are summarized in Table 2. A covered stent was used for eight patients and a non-covered type was used for five. A 'one step button' was used for all PEG procedure. As for clinical events, the incidence of high fever, severe chest pain that required analgesics, and inflammation were significantly higher in the EMS group (Table 3). Survival was not different between the two groups (Fig. 5). Therefore, to improve the patients' quality of life (QOL), it seems that PEG is more feasible and safer than EMS placement.[17]

Table 2. Self-expandable metallic stent (EMS) devices and percutaneous endoscopic gastrostomy used for recurrent dysphagia after failure of definitive chemoradiotherapy

		n	Total
EMS			
Ultraflex (covered)		7	
Ultraflex (non-covered)		2	
Wall (covered)		1	
Wall (non-covered)		1	
Z-stent		2	13
PEG			
One step button	18Fr	4	
	24Fr	10	14

Table 3. Comparison between self-expandable metallic stent (EMS) and percutaneous endoscopic gastrostomy (PEG) after failure of definitive chemoradiotherapy

	EMS ($n = 13$)	PEG ($n = 14$)
High fever*	11 (85)	3 (21)
Severe pain*	8 (73)	2 (14)
CRP ↑	11 (85)	8 (57)
Pneumonia/Mediastinitis*	7 (54)	0 (0)
Peritonitis	0 (0)	1 (7)
Hospital stay (Median day, range)	28 (10–106)	13 (6–36)

(%); * $p < 0.005$.

CONCLUSION

Although SEM placement provides effective palliation for patients with esophageal stricture due to advanced cancer, long-term survival is not expected by this modality. In contrast, definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival. Therefore, we should

carefully select the treatment for such patients in consideration of the advantages for their QOL and survival.

REFERENCES

1. Knyrim K, Wagner HJ, Bethge N *et al.* A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N. Engl. J. Med.* 1993; **329**: 1302–7.
2. Vakil N, Bethge N. Metal stents for malignant esophageal obstruction. *Am. J. Gastroenterol.* 1996; **91**: 2471–6.
3. Minsky BD. Nonsurgical treatment approaches for esophageal cancer. *Proc. Am. Soc. Clin. Oncol.* 1997; **14**: 164–75.
4. Al-Sarraf M, Martz K, Herskovic A *et al.* Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J. Clin. Oncol.* 1997; **15**: 277–84.
5. Ohtsu A, Boku N, Muro K *et al.* Definitive chemoradiotherapy for T4 and/or M1 LYM squamous cell carcinoma of the esophagus. *J. Clin. Oncol.* 1999; **17**: 2915–21.
6. Muto M, Ohtsu A, Miyamoto S *et al.* Concurrent chemoradiotherapy for esophageal carcinoma patients with malignant fistula. *Cancer* 1999; **86**: 1406–13.
7. Geh JI. The use of chemoradiotherapy in oesophageal cancer. *Eur. J. Cancer* 2002; **38**: 300–13.
8. Enginger PC, Mayer RJ. Esophageal cancer. *N. Eng. J. Med.* 2003; **349**: 2241–52.
9. Nishimura Y, Nagata K, Katano S *et al.* Severe complications in advanced esophageal cancer treated with radiotherapy after intubation of esophageal stents: a questionnaire survey of the Japanese Society for Esophageal Diseases. *Int. J. Radiat. Oncol. Biol. Phys* 2003; **56**: 1327–32.
10. Muto M, Ohtsu A, Miyata Y *et al.* Self-expandable metallic stent for patients with recurrent esophageal carcinoma after failure of primary chemoradiotherapy. *Jpn. J. Clin. Oncol.* 2001; **31**: 270–4.
11. Kinsman KJ, DeGregrio BT, Katon RM *et al.* Prior radiation and chemotherapy increase the risk of life-threatening complications after insertion of metallic stents for esophagogastric malignancy. *Gastrointest. Endosc* 1996; **43**: 196–203.
12. Bethge N, Sommer A, Kleist D *et al.* A prospective trial of self-expanding metal stents in the palliation of malignant esophageal obstruction after failure of primary curative therapy. *Gastrointest. Endosc* 1996; **44**: 283–6.
13. Siersema PD, Hop WC, Dees J *et al.* Coated self-expanding metal stents versus latex prostheses for esophagogastric cancer with special reference to prior radiation and chemotherapy: a controlled, prospective study. *Gastrointest. Endosc* 1998; **47**: 113–20.
14. Raijman I, Siddique I, Ajani J *et al.* Palliation of malignant dysphagia and fistulae with coated expandable metal stents: experience with 101 patients. *Gastrointest. Endosc* 1998; **48**: 172–9.
15. Kaneko K, Ito H, Konishi K *et al.* Implantation of self-expandable metallic stent for patients with malignant stricture after failure of definitive chemoradiotherapy for T3 or T4 esophageal squamous cell carcinomas. *Hepatogastroenterology* 2002; **49**: 699–705.
16. Sumiyoshi T, Gotoda T, Muro K *et al.* Morbidity and mortality after self-expandable metallic stent placement in patients with progressive or recurrent esophageal cancer after chemotherapy. *Gastrointest. Endosc* 2003; **57**: 882–5.
17. Muto M, Manabe T, Katada C *et al.* Treatment strategy for esophageal cancer on consideration for patients' QOL. *Shokakika* 2001; **33**: 252–60. (In Japanese.)