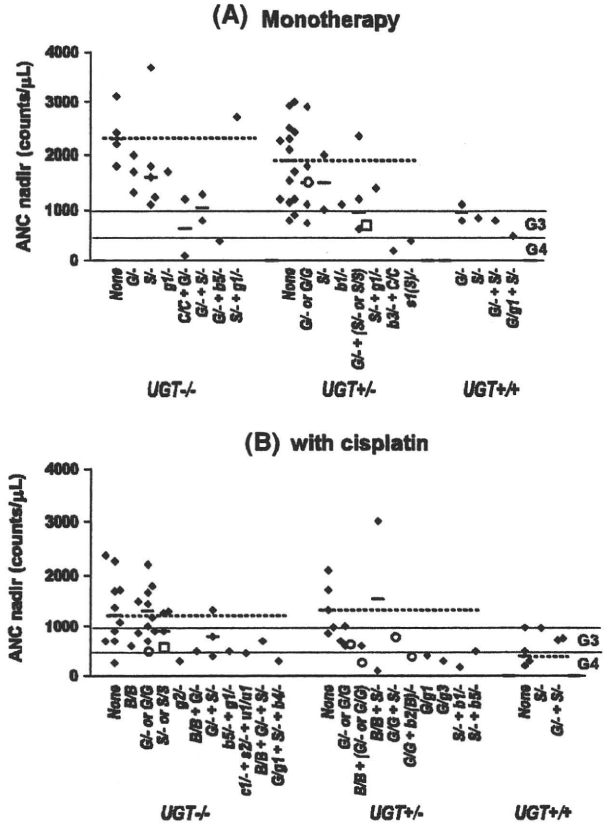


Fig. 2 Additive effects of transporter haplotypes/variations on ANC nadirs in irinotecan monotherapy (a) and combination therapy with cisplatin (b). *UGT+ = UGT1A1*6* or **28*; *B = ABCB1*2*; *C = ABCC2*1A*; *G = ABCG2#IIB* (*open circle*, *#IIB/#IIB*); *S = SLCO1B1*15 · 17* (*open square*, **15 · 17/*15 · 17*); *b1–u1* = minor variations listed in Table 3. a *None = non-*(*C*, *G*, *S* or *minors*), b *None = non-*(*B*, *G*, *S* or *minors*). The *bar* in each genotype represents the median. The *dotted lines* in each *UGT* genotype show the median values of patients without any selected transporter polymorphisms/variations (*None*). The *lines* (G3 and G4) represent the border of grade 3 and 4 neutropenia

In the irinotecan monotherapy, the increasing effect of *ABCB1*2/*2* (block 2) on SN-38 AUC/dose was evident while contributions of *ABCB1 BJL* (block 1), *ABCB1*1b* (block 3), *ABCG2#IIB* and *SLCO1B1*15 · 17* were not significant in the multivariate analysis. For neutropenia, additive effects were suggested for *ABCC2*1A/*1A*, *ABCG2#IIB*, *SLCO1B1*15 · 17*, and possibly some minor genetic variations in addition to *UGT1A1*6* or **28* (Fig. 2a). The association of *ABCB1*2* (block 2) with grade 3 diarrhea was also observed.

In the combination therapy with cisplatin, an increase in the SN-38 AUC/dose by *ABCB1*2* and for a decrease by *ABCB1*1b* were observed, but the multivariate analysis did not show their significant contributions. Regarding neutropenia, additive effects of *ABCB1*2/*2*, *ABCG2#IIB/#IIB*, and possibly, *SLCO1B1*15 · 17/*15 · 17* and some minor variations were suggested (Fig. 2b).

Thus, in both regimens, the associations of *ABCB1*2* (block 2) with higher SN-38 AUC/dose levels and toxicities (diarrhea or neutropenia), and additive effects of *ABCG2#IIB* and *SLCO1B1*15 · 17* with *UGT1A1*6* or **28* on neutropenia were observed. The current study also suggests that combination genotypes with two or more genes could have a greater effect on neutrophil count reduction than a single gene, indicating a quantitative property of multiple genetic factors affecting phenotype. These findings could partly explain a large interindividual variation in irinotecan toxicities within each *UGT* genotype.

In this study, influences of the transporter genotypes on SN-38 AUC/dose did not always correlate to an influence on neutropenia as observed in the combination therapy with cisplatin and in the case of *ABCB1*2* (block 2) in the monotherapy. Although weak negative correlations were observed between the SN-38 AUC level and ANC nadir, the SN-38 AUC values of patients who exhibited grade 3/4 neutropenia (ANC nadir < 1,000 counts/μL) were fairly diverse, especially in the combination therapy with cisplatin (Fig. 3). It is likely that the extent of toxicities depends not only on systemic exposure levels of the active metabolite for which hepatic UGT activity is a large contributor, but also on the elimination from the target cells (neutrophil progenitor cells or enterocytes) where transporter function might be more critical.

Our previous study showed the association of *ABCB1* block 2 **2* [1236C>T, 2677G>T (A893S) and 3435C>T] with lower renal clearance of irinotecan and its metabolites [16]. The current data obtained in the irinotecan monotherapy also suggest higher AUC/dose for irinotecan, SN-38G, and SN-38 with *ABCB1*2/*2*. Since a high affinity of P-gp for irinotecan is known, lower elimination rate of irinotecan could also result in higher plasma levels of its metabolites. Other studies have also suggested associations of the haplotype 1236T–2677T (corresponding to our **2* group in this study) with a reduced excretion rate of P-gp substrates [37] and SN-38 [25], and associations of the haplotype 2677T–3435T (corresponding to our **2* group in this study) with paclitaxel-induced neutropenia [38].

For *ABCC2*, *ABCC2* −1774delG, a tagging SNP of **1A*, was reported to be associated with low promoter activity and cholestatic or mixed-type hepatitis [32]. Patients with *ABCC2*1A/*1A* together with *ABCB1*2/*2* or *ABCG2#IIB* showed higher values of SN-38 AUC (Fig. 1) and neutropenia in the monotherapy (Fig. 2a), but these trends were not evident in the *UGT−/−* patients treated with cisplatin-combination therapy (data not shown). Thus, the effects of *ABCC2* might be dependent on combinations with other genetic and non-genetic factors. Conflicting clinical outcomes of *ABCC2* 3972C>T, a marker of **1C/G*, were reported to cause higher AUC of irinotecan and its

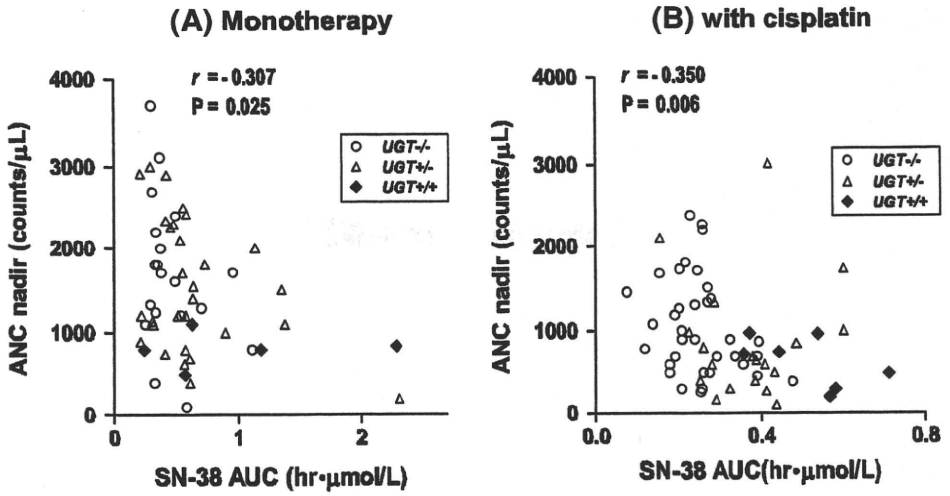


Fig. 3 Correlations between SN-38 AUC and ANC nadir in patients in irinotecan monotherapy (a) and combination therapy with cisplatin (b). *r* Spearman's rank correlation coefficient

metabolites in Caucasians treated with irinotecan monotherapy [18] and to lower the incidence of grade 3 diarrhea in Koreans treated with a combination therapy of irinotecan and cisplatin [24]. In the current study, no significant association of *ABCC2*1C/G* on PK/PD was observed in the monotherapy. Although a high incidence of grand 3/4 neutropenia was observed in patients with *ABCC2*1C/G* in the combination therapy with cisplatin, most patients also had *ABCG2#IIB* (data not shown); thus, the effect of *ABCC2*1C/G* remains obscure.

For *ABCG2*, the current study examined the association with the combinatorial haplotypes consisting of the three previously defined block haplotypes [28]. *ABCG2#IIB* contains the non-synonymous SNP 421C>A (Q141K), which was detected at higher frequencies in Asians and was reported to cause reduced expression of BCRP in vitro [36, 39–41]. In clinical studies, the association of 421C>A (Q141K) with higher plasma levels of diflomotecan was shown in Caucasians [42]. However, an association of this SNP with irinotecan PK/PD had not been shown [19, 24]. An association of 421C>A (Q141K) alone with irinotecan PK/PD was not significant in our hands (data not shown), but *#IIB* containing both 421C>A (Q141K) and IVS12 + 49G>T showed a moderate association with neutropenia. It is unclear whether the additional SNP IVS12 + 49G>T itself or another unknown linked SNP is causative for the reduced function. *ABCG2#IIIC* contains a non-synonymous SNP 34G>A (V12M) which has no influence on BCRP expression or activity in vitro [36, 39–41]. Our study showed no influence of *ABCG2#IIIC* on the SN-38 AUC/dose levels and neutropenia in the irinotecan monotherapy (data not shown), but did show a decreasing trend in grade 3/4 neutropenia in the combination therapy with cisplatin. In contrast, a report on Korean patients suggested the association of *ABCG2* 34G>A (V12M) with a higher incidence of grade 3 diarrhea in a combination therapy of irinotecan and cisplatin [24].

Among *SLCO1B1* polymorphisms, 521T>C (V174A), a tagging SNP of **15 · 17*, was demonstrated to reduce in vitro SN-38 influx [7], and clinical studies in Asians also showed its relevance to a higher SN-38 AUC and severe neutropenia in combination therapy of irinotecan with cisplatin [22–24]. Our results support these previous findings. Note that our **15 · 17* mainly consists of **17* [containing −11187G>A, 521T>C (V174A) and 388A>G (N130D)].

Taken together, the clinical data on transporter genotypes show variability among the studies. The reasons for these conflicting findings might be partly attributed to the ethnic differences in transporter genotypes and the regimens used. In addition, non-genetic factors, such as disease status and inflammation [43, 44], hepatic or renal function [45], and co-administered or pre-administered drugs, may also influence the clinical outcome.

The current study suggests combined effects of multiple haplotypes/variations on neutropenia. From clinical aspects of irinotecan therapy, the benefit of additional genotyping of transporters to predict severe toxicities should be clarified. Regarding grade 3 and 4 neutropenia, positive prediction values for two or more candidate genotypes including *UGT* (+) (Fig. 2) were 46 and 89% in the monotherapy and the cisplatin-combination therapy, respectively, which are low compared with *UGT+/+* (80 and 100%, respectively). Regarding grade 4 neutropenia, positive predictive values for these candidate genotypes were 15 and 41% in the monotherapy and the cisplatin-combination therapy, respectively, while for *UGT+/+*, they were 0 and 43%, respectively. Further studies using a

larger population size are needed to further elucidate the roles of these candidate markers.

In conclusion, the current study suggests there are additive effects for several transporter genotypes on the SN-38 AUC level and the reduction of neutrophil counts in irinotecan therapy. The clinical benefits of additional genotyping of these candidate markers should be further delineated.

Acknowledgments This study was supported in part by the Program for the Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation, and by the Program for the Promotion of Studies in Health Sciences of the Ministry of Health, Labor and Welfare of Japan. We thank Yakult Honsha Co., Ltd (Tokyo, Japan) for providing analytical standards of irinotecan and its metabolites. We also thank Ms. Chie Sudo for her administrative assistance.

References

1. Slatter JG, Su P, Sams JP, Schaaf LJ, Wienkers LC (1997) 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 25:1157–1164
2. Iyer L, King CD, Whitington PF, Green MD, Roy SK, Tephly TR, Coffman BL, Ratain MJ (1998) 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 15:847–854
3. Ciotti M, Basu N, Brangi M, Owens IS (1999) Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38) by the human UDP-glucuronosyltransferases encoded at the UGT1 locus. Biochem Biophys Res Commun 260:199–202
4. Gagne JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C (2002) Common human UGT1A polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Mol Pharmacol 62:608–617
5. Haaz MC, Rivory L, Riché C, Vernillet L, Robert J (1998) Metabolism of irinotecan (CPT-11) by human hepatic microsomes: participation of cytochrome P-450 3A and drug interactions. Cancer Res 58:468–472
6. Sparreboom A, Danesi R, Ando Y, Chan J, Figg WD (2003) Pharmacogenomics of ABC transporters and its role in cancer chemotherapy. Drug Resist Updat 6:71–84
7. Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I (2005) Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: in vitro evidence and effect of single nucleotide polymorphisms. Drug Metab Dispos 33:434–439
8. Ando Y, Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y (2000) Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60:6921–6926
9. Iyer L, Das S, Janisch L, Wen M, Ramirez J, Karrison T, Fleming GF, Vokes EE, Schilsky RL, Ratain MJ (2002) UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2:43–47
10. Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramírez J, Rudin CM, Vokes EE, Ratain MJ (2004) Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22:1382–1388
11. Han JY, Lim HS, Shin ES, Yoo YK, Park YH, Lee JE, Jang IJ, Lee DH, Lee JS (2006) Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. J Clin Oncol 24:2237–2244
12. Minami H, Sai K, Saeki M, Saito Y, Ozawa S, Suzuki K, Kaniwa N, Sawada J, Hamaguchi T, Yamamoto N, Shirao K, Yamada Y, Ohmatsu H, Kubota K, Yoshida T, Ohtsu A, Saijo N (2007) Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: Roles of UGT1A1*6 and *28. Pharmacogenet Genomics 17:497–504
13. Jada SR, Lim R, Wong CI, Shu X, Lee SC, Zhou Q, Goh BC, Chowbay B (2007) Role of UGT1A1*6, UGT1A1*28 and ABCG2 c.421C>A polymorphisms in irinotecan-induced neutropenia in Asian cancer patients. Cancer Sci 98:1461–1467
14. Sai K, Saito Y, Sakamoto H, Shirao K, Kurose K, Saeki M, Ozawa S, Kaniwa N, Hirohashi S, Saijo N, Sawada J, Yoshida T (2008) Importance of UDP-glucuronosyltransferase 1A1*6 for irinotecan toxicities in Japanese cancer patients. Cancer Lett 261:165–171
15. Mathijssen RH, Marsh S, Karlsson MO, Xie R, Baker SD, Verweij J, Sparreboom A, McLeod HL (2003) Irinotecan pathway genotype analysis to predict pharmacokinetics. Clin Cancer Res 9:3246–3253
16. Sai K, Kaniwa N, Itoda M, Saito Y, Hasegawa R, Komamura K, Ueno K, Kamakura S, Kitakaze M, Shirao K, Minami H, Ohtsu A, Yoshida T, Saijo N, Kitamura Y, Kamatani N, Ozawa S, Sawada J (2003) Haplotype analysis of ABCB1/MDR1 blocks in a Japanese population reveals genotype-dependent renal clearance of irinotecan. Pharmacogenetics 13:741–757
17. Zhou Q, Sparreboom A, Tan EH, Cheung YB, Lee A, Poon D, Lee EJ, Chowbay B (2005) Pharmacogenetic profiling across the irinotecan pathway in Asian patients with cancer. Br J Clin Pharmacol 59:415–424
18. Innocenti F, Undevia SD, Chen PX, Das S, Ramirez J, Dolan ME, Relling MV, Kroetz DL, Ratain MJ (2004) Pharmacogenetic analysis of interindividual irinotecan (CPT-11) pharmacokinetic (PK) variability: evidence for a functional variant of ABCC2. In: 2004 ASCO annual meeting proceedings (post-meeting edition), vol 22, No 14S, abstract no: 2010
19. de Jong FA, Marsh S, Mathijssen RH, King C, Verweij J, Sparreboom A, McLeod HL (2004) ABCG2 pharmacogenetics: ethnic differences in allele frequency and assessment of influence on irinotecan disposition. Clin Cancer Res 10:5889–5894
20. de Jong FA, Scott-Horton TJ, Kroetz DL, McLeod H, Friberg LE, Mathijssen RH, Verweij J, Marsh S, Sparreboom A (2007) Irinotecan-induced diarrhea: functional significance of the polymorphic ABCC2 transporter protein. Clin Pharmacol Ther 81:42–49
21. Xiang X, Jada SR, Li HH, Fan L, Tham LS, Wong CI, Lee SC, Lim R, Zhou QY, Goh BC, Tan EH, Chowbay B (2006) Pharmacogenetics of SLCO1B1 gene and the impact of *1b and *15 haplotypes on irinotecan disposition in Asian cancer patients. Pharmacogenet Genomics 16:683–691
22. Takane H, Miyata M, Burioka N, Kurai J, Fukuoka Y, Suyama H, Shigeoka Y, Otsubo K, Ieiri I, Shimizu E (2007) Severe toxicities after irinotecan-based chemotherapy in a patient with lung cancer: a homozygote for the SLCO1B1*15 allele. Ther Drug Monit 29:666–668
23. Han JY, Lim HS, Shin ES, Yoo YK, Park YH, Lee JE, Kim HT, Lee JS (2008) Influence of the organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer. Lung Cancer 59:69–75

24. Han JY, Lim HS, Park YH, Lee SY, Lee JS (2009) Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and toxicity in patients with advanced non-small cell lung cancer. Lung Cancer 63:115–120
25. Michael M, Thompson M, Hicks RJ, Mitchell PL, Ellis A, Milner AD, Di Iulio J, Scott AM, Gurtler V, Hoskins JM, Clarke SJ, Tebbut NC, Foo K, Jefford M, Zalcberg JR (2006) Relationship of hepatic functional imaging to irinotecan pharmacokinetics and genetic parameters of drug elimination. J Clin Oncol 24:4228–4235
26. Sai K, Itoda M, Saito Y, Kurose K, Katori N, Kaniwa N, Komamura K, Kotake T, Morishita H, Tomoike H, Kamakura S, Kitakaze M, Tamura T, Yamamoto N, Kunitoh H, Yamada Y, Ohe Y, Shimada Y, Shirao K, Minami H, Ohtsu A, Yoshida T, Saijo N, Kamatani N, Ozawa S, Sawada J (2006) Genetic variations and haplotype structures of the ABCB1 gene in a Japanese population: an expanded haplotype block covering the distal promoter region, and associated ethnic differences. Ann Hum Genet 70:605–622
27. Sai K, Saito Y, Itoda M, Fukushima-Uesaka H, Nishimaki-Mogami T, Ozawa S, Maekawa K, Kurose K, Kaniwa N, Kawamoto M, Kamatani N, Shirao K, Hamaguchi T, Yamamoto N, Kunitoh H, Ohe Y, Yamada Y, Tamura T, Yoshida T, Minami H, Matsumura Y, Ohtsu A, Saijo N, Sawada J (2008) Genetic variations and haplotypes of ABCC2 encoding MRP2 in a Japanese population. Drug Metab Pharmacokinet 23:139–147
28. Maekawa K, Itoda M, Sai K, Saito Y, Kaniwa N, Shirao K, Hamaguchi T, Kunitoh H, Yamamoto N, Tamura T, Minami H, Kubota K, Ohtsu A, Yoshida T, Saijo N, Kamatani N, Ozawa S, Sawada J (2006) Genetic variation and haplotype structure of the ABC transporter gene ABCG2 in a Japanese population. Drug Metab Pharmacokinet 21:109–121
29. Kim SR, Saito Y, Sai K, Kurose K, Maekawa K, Kaniwa N, Ozawa S, Kamatani N, Shirao K, Yamamoto N, Hamaguchi T, Kunitoh H, Ohe Y, Yamada Y, Tamura T, Yoshida T, Minami H, Ohtsu A, Saijo N, Sawada J (2007) Genetic variations and frequencies of major haplotypes in SLCO1B1 encoding the transporter OATP1B1 in Japanese subjects: SLCO1B1*17 is more prevalent than *15. Drug Metab Pharmacokinet 22:456–461
30. Takane H, Kobayashi D, Hirota T, Kigawa J, Terakawa N, Otsubo K, Ieiri I (2004) Haplotype-oriented genetic analysis and functional assessment of promoter variants in the MDR1 (ABCB1) gene. J Pharmacol Exp Ther 311:1179–1187
31. Kim RB, Leake BF, Choo EF, Dresser GK, Kubba SV, Schwarz UI, Taylor A, Xie HG, McKinsey J, Zhou S, Lan LB, Schuetz JD, Schuetz EG, Wilkinson GR (2001) Identification of functionally variant MDR1 alleles among European Americans and African Americans. Clin Pharmacol Ther 70:189–199
32. Choi JH, Ahn BM, Yi J, Lee JH, Lee JH, Nam SW, Chon CY, Han KH, Ahn SH, Jang IJ, Cho JY, Suh Y, Cho MO, Lee JE, Kim KH, Lee MG (2007) MRP2 haplotypes confer differential susceptibility to toxic liver injury. Pharmacogenet Genomics 17:403–415
33. Tirona RG, Leake BF, Merino G, Kim RB (2001) Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. J Biol Chem 276:35669–35675
34. Niemi M, Schaeffeler E, Lang T, Fromm MF, Neuvonen M, Kyrklund C, Backman JT, Kerb R, Schwab M, Neuvonen PJ, Eichelbaum M, Kivistö KT (2004) High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenetics 14:429–440
35. Saeki M, Saito Y, Sai K, Maekawa K, Kaniwa N, Sawada J, Kawamoto M, Saito A, Kamatani N (2007) A combinatorial haplotype of the UDP-glucuronosyltransferase 1A1 gene (#60-#IB) increases total bilirubin concentrations in Japanese volunteers. Clin Chem 53:356–358
36. Tamura A, Wakabayashi K, Onishi Y, Takeda M, Ikegami Y, Sawada S, Tsuji M, Matsuda Y, Ishikawa T (2007) Re-evaluation and functional classification of non-synonymous single nucleotide polymorphisms of the human ATP-binding cassette transporter ABCG2. Cancer Sci 98:231–239
37. Wong M, Evans S, Rivory LP, Hoskins JM, Mann GJ, Farlow D, Clarke CL, Balleine RL, Gurney H (2005) Hepatic technetium Tc 99m-labeled sestamibi elimination rate and ABCB1 (MDR1) genotype as indicators of ABCB1 (P-glycoprotein) activity in patients with cancer. Clin Pharmacol Ther 77:33–42
38. Sissung TM, Mross K, Steinberg SM, Behringer D, Figg WD, Sparreboom A, Mielke S (2006) Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. Eur J Cancer 42:2893–2896
39. Imai Y, Nakane M, Kage K, Tsukahara S, Ishikawa E, Tsuruo T, Miki Y, Sugimoto Y (2002) C421A polymorphism in the human breast cancer resistance protein gene is associated with low expression of Q141K protein and low-level drug resistance. Mol Cancer Ther 1:611–616
40. Kondo C, Suzuki H, Itoda M, Ozawa S, Sawada J, Kobayashi D, Ieiri I, Mine K, Ohtsubo K, Sugiyama Y (2004) Functional analysis of SNPs variants of BCRP/ABCG2. Pharm Res 21: 1895–1903
41. Mizuarai S, Aozasa N, Kotani H (2004) Single nucleotide polymorphisms result in impaired membrane localization and reduced ATPase activity in multidrug transporter ABCG2. Int J Cancer 109:238–246
42. Sparreboom A, Gelderblom H, Marsh S, Ahluwalia R, Obach R, Principe P, Twelves C, Verweij J, McLeod HL (2004) Diflomotecan pharmacokinetics in relation to ABCG2 421C>A genotype. Clin Pharmacol Ther 76:38–44
43. Teng S, Piquette-Miller M (2008) Regulation of transporters by nuclear hormone receptors: implications during inflammation. Mol Pharm 5:67–76
44. Englund G, Jacobson A, Rorsman F, Artursson P, Kindmark A, Rönnblom A (2007) Efflux transporters in ulcerative colitis: decreased expression of BCRP (ABCG2) and Pgp (ABCB1). Inflamm Bowel Dis 13:291–297
45. de Jong F, van der Bol J, Mathijssen R, van Gelder T, Wiemer E, Sparreboom A, Verweij J (2008) Renal function as a predictor of irinotecan-induced neutropenia. Clin Pharmacol Ther 84:254–262

日本病院薬剤師会雑誌　別刷

日本病院薬剤師会雑誌

JOURNAL OF JAPANESE SOCIETY OF HOSPITAL PHARMACISTS

Vol.46.　No.3.　2010

社　団　法　人
日　本　病　院　薬　剤　師　会

論文　日病薬誌　第46巻3号　2010年

がん化学療法におけるレジメン登録制の構築とレジメンオーダシステム導入の評価

佐藤雄己*†1，安部智英[1]，鈴木陽介[1]，西村文宏[1]，半田有希子[1]
河島史絵[1]，伊東弘樹[1]，大津　智[2]，白尾國昭[2]，武山正治[1]

大分大学医学部附属病院薬剤部†1，腫瘍内科[2]

Establishment of a System for Registering Cancer Chemotherapy Regimens and Evaluation of Introduction of a Regimen Ordering System

Yuhki Satoh*†1, Tomohide Abe[1], Yohsuke Suzuki[1], Fumihiro Nishimura[1], Yukiko Handa[1], Fumie Kawashima[1], Hiroki Itoh[1], Satoshi Ohtsu[2], Kuniaki Shirao[2], Masaharu Takeyama[1]

Department of Pharmacy†1, Department of Medical Oncology[2], Oita University Hospital

〔受付：2009年10月19日　受理：2010年1月12日（特別掲載）〕

近年，がん化学療法において，薬剤師が組織的にレジメン管理に携わる機会が多くなってきた。大分大学医学部附属病院では，入院・外来がん化学療法においてレジメンオーダシステムの運用を全面的に開始するため，レジメン登録制を開始した。今回，レジメンの登録内容を調査するとともに，レジメンオーダシステムについて疑義照会内容を基に導入の評価を行った。その結果，レジメン総登録件数222件に対して，臨床エビデンスレベルII以上のレジメンは74.3%を占めていた。一方，本システム導入前後では，制吐剤や補液など前投薬に関することが多かった開始前と比較し，開始後では疑義照会の内容に変化がみられた。以上より，レジメン登録制の導入により院内のがん化学療法が標準化され，また，投与計画に即した処方の点検が可能となり，加えて，レジメンがセット化されたことでより安全性の向上が図れたと考えられる。

キーワード—レジメン登録制，レジメンオーダシステム，レジメン管理，がん化学療法

緒　言

近年，新規抗がん剤の開発や支持療法の進歩により，がん化学療法は外来で実施されるようになってきた。平成20年４月の診療報酬改定では，外来化学療法加算Ｉを算定する施設基準の１つとして，がん化学療法レジメン（以下，レジメン）の妥当性を院内で承認する必要性が規定され，これを契機として各施設においてレジメン登録システムの整備が進められるようになった。レジメン管理において薬剤師は，レジメン審査委員会などでレジメンの妥当性を評価するとともに，リスクマネジメント，経済性の面からもレジメンを適切に管理し，がん化学療法における有効性と安全性の確保に寄与することが必要である[1]。

近年，レジメンは電子カルテやレジメンオーダシステム（以下，レジメンオーダ）により管理される傾向にある。ごく最近では，レジメンオーダを利用して，薬剤師がレジメン管理を実践するようになった[2]。その一方で，大学病院等の施設においては，同じがん種に使用される同じレジメンであっても，投与量や投与スケジュールなどが診療科ごとに異なることが知られている。そのため，リスクマネジメントの観点から，院内でのレジメンの統一が重要な課題とされている。

大分大学医学部附属病院（以下，当院）では，2006年の外来化学療法室の開設と同時に，外来がん化学療法を対象としてレジメン登録制を導入し，薬剤部における抗がん剤調製並びにレジメンに基づいた注射処方せんの処方監査を開始した。2008年９月より入院のがん化学療法についてもレジメン登録制を導入し，2009年４月よりレジメンオーダの運用を全面的に開始した。今回，当院に

†大分県由布市挾間町医大ヶ丘1-1；1-1, Idaigaoka, Hazama-machi, Yufu-shi, Oita, 879-5593 Japan

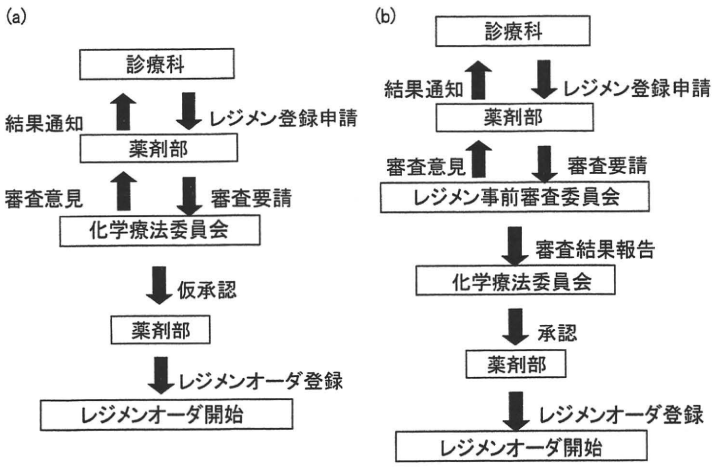


図1　レジメン登録手順
(a) 2008年９月～2009年３月まで，(b) 2009年４月以降

おける登録レジメンの内容調査と，レジメンオーダ導入前後における薬剤部からの疑義照会内容を比較し，導入の評価を行った。

表1　レジメン申請書記載内容

1．レジメン分類
　がん種，レジメン名，使用分類（日常診療，臨床試験など）適応分類（術前，術後化学療法など）
2．投与スケジュール
　１コース期間，目標コース数，１日のスケジュールなど
3．投与基準
　適格基準，開始基準，投与量変更基準
4．エビデンスレベル
　Ⅰ：PhaseⅢのランダム化比較試験の結果，優越得性もしくは非劣性を示したもの
　Ⅱ：PhaseⅡのprospective studyの結果により，標準治療になり得ることが学会などで広くコンセンサスを得ているもの
　Ⅲ：Retrospective study（case control study）
　Ⅳ：Case reports
　Ⅴ：専門家の意見
5．申請理由
6．臨床試験の場合
　試験名，試験期間，phase，IRB承認の有無（予定），プロトコルの概要
7．レジメンオーダ登録用紙
　注射剤の商品名，投与量，投与ルート，投与速度など

方　法

1．レジメン登録制の概要

2008年９月～2009年３月までに申請されたレジメンについては，レジメンオーダ全稼働までの時間的な制約や制度変更に伴う日常臨床への影響を考慮し，「仮承認」という形で登録した。「仮承認」レジメンについては１年を期限として，以後，妥当性の検証を行うよう規定した。2009年４月以降は，がん化学療法の運営にかかわる化学療法委員会の下部組織として，がん化学療法を実施する各診療科からの代表医師，腫瘍内科医師，薬剤師，看護師並びに事務担当者で構成されるレジメン事前審査委員会を設置した。レジメンの登録手順として，事務局である薬剤部に申請されたレジメンを月１回，レジメン事前審査委員会でその妥当性を審議し，申請内容に修正や回答が必要な場合には各申請科へ結果通知した。修正・回答を確認後に化学療法委員会で「承認」とし，薬剤部にてレジメンオーダに登録するようにした（**図1**）。

2．レジメン登録申請書

レジメン登録申請書の様式として，７つの記載項目を設けた（**表1**）。また，レジメンのエビデンスレベルはAgency for Health Care Policy and Researchによるエビデンス分類を参考に，レベルⅠ～Ⅴで申請科が記入できるようにした。

3．レジメンオーダの概要

オーダリングシステム（PC-ORDERING/ADR，NEC）および電子カルテ（MegaOak NEMR，NEC）にてレジメンオーダを導入した。ホルモン剤やインターフェロンを除く「抗がん剤」区分で登録された注射剤については，すべてレジメンオーダにおいてのみ処方が可能となるよう設定し，抗がん剤を溶解する輸液や補液，制吐剤などの前投薬などもセット化した。また，抗がん剤については体表面積や体重，腎機能に応じて自動計算されるよう設定したが，小数点の端数が生じないよう，処方医が計算量の１～105%で変更できるようにした。複数規格を採用している薬剤については，投与量の計算量に応じて薬剤費を考慮した最適な規格を自動選択して処方に反映する機能を付加した（**図2**）。

4．登録レジメンの集計

2008年９月～2009年７月に登録されたレジメンについて，がん種別にエビデンスレベルと登録数を集計した。また，レジメン事前審査委員による審査後の申請科への照会内容を調査した。

5．疑義照会内容調査

抗がん剤を含む処方に関して，レジメンオーダ導入前（2009年１～３月）と導入後（2009年４～６月）における，レジメンオーダ総処方件数に対する疑義照会件数および処方変更件数と疑義照会内容を比較した。

結　果

1．レジメンの登録状況

2008年９月～2009年３月までの「仮承認」レジメンは205件であり，2009年７月までの登録レジメン数と合わせると全222件，23がん種であった。がん種別では，皮膚がんが30件，肺がんが28件，リンパ増殖性疾患が25件，

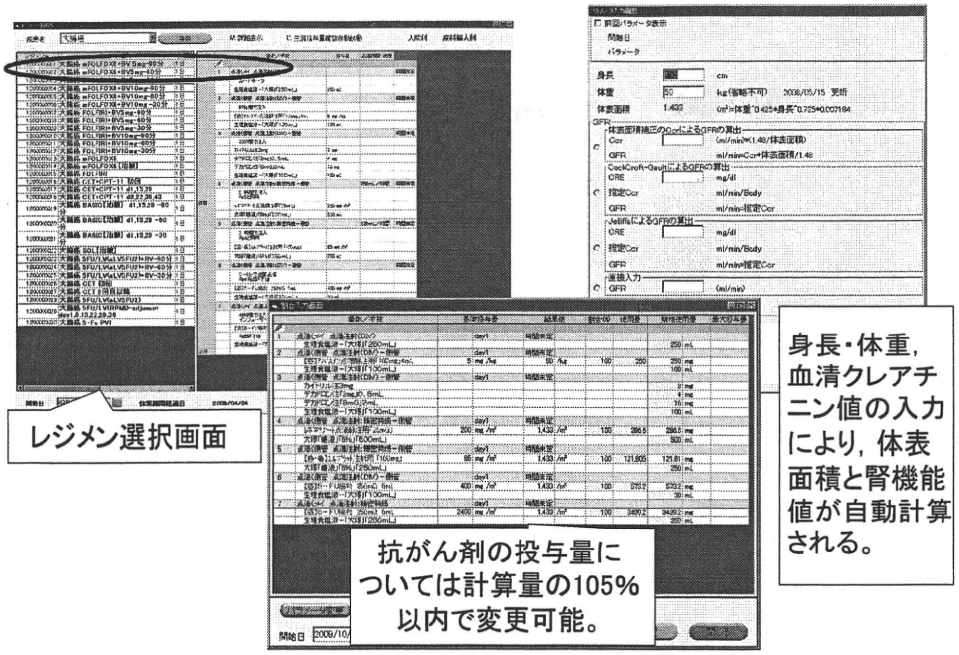


図2　レジメンオーダシステム処方画面

急性白血病と卵巣がんが各20件の順で多かった。エビデンスレベルをみると，総レジメン登録件数に対してエビデンスレベルⅡ以上のものが74.3%であった。一方，皮膚がん，原発性肝がん，骨・軟部腫瘍などでは比較的エビデンスレベルが低いものが標準的に使用されていることがわかった（**表2**）。また，レジメン事前審査後の申請科への照会内容として，エビデンスレベルやシステム登録するための内容確認が，総照会件数に対して，それぞれ約70%，50%を占めていた（**表3**）。

2．レジメンオーダ導入前後における疑義照会内容の比較

レジメンオーダ導入前後における疑義照会件数は，導入前の全処方件数713件中30件（4.2%）であったのに対して，導入後では661件中21件（2.8%）に減少していた。また，処方変更件数も導入前の22件（3.2%）から導入後は7件（0.9%）へ減少していた。照会内容としては，導入前に比較して導入後では，抗がん剤の投与量確認に関することが多くなっていたが，制吐剤・ステロイド剤の不足など前投薬に関することや複数規格薬品の選別に関する項目は減少していた（**表4**）。

表2　登録レジメンの内容とエビデンスレベル

(a) がん種別登録レジメン一覧

分類	エビデンスレベル				臨床試験	総登録数	Ⅱ以上	
	Ⅰ	Ⅱ	Ⅲ	Ⅳ以下			件数	%
皮膚がん		8	3	19		30	8	26.7
肺がん	22	5			1	28	27	96.4
リンパ増殖性疾患		23	2			25	23	92.0
急性白血病	14	4		2		20	18	90.0
卵巣がん	5	13			2	20	18	90.0
結腸・直腸がん	10				2	12	10	83.3
子宮がん	3	5	1		3	12	8	66.7
胃がん	4	4			1	9	8	88.9
頭頸部がん	6	2				8	8	100.0
乳がん	6	2				8	8	100.0
原発性肝がん	1	1	5			7	2	28.6
骨・軟部腫瘍			6			6	0	0.0
食道がん		6				6	6	100.0
造血幹細胞移植		1	4			5	1	20.0
多発性骨髄腫		2	3			5	2	40.0
尿路上皮がん	3	1				4	4	100.0
中枢神経系腫瘍	1	3				4	4	100.0
中皮腫	1	2				3	3	100.0
内分泌がん				3		3	0	0.0
膵がん	2					2	2	100.0
精巣がん	2					2	2	100.0
胆道系がん		2				2	2	100.0
前立腺がん	1					1	1	100.0
合計	81	84	24	24	9	222	165	74.3

(b) 登録レジメン例

分類	がん種	レジメン名	薬剤	エビデンスレベル
骨・軟部腫瘍	骨肉腫	HD-MTX	MTX	Ⅲ
骨・軟部腫瘍	骨肉腫・Ewing肉腫	CDDP+DXR	CDDP, DXR	Ⅲ
骨・軟部腫瘍	軟部肉腫	MAI	IFO, DXR	Ⅲ
皮膚がん	有棘細胞がん，基底細胞がん	CA	CDDP, DXR	Ⅳ
皮膚がん	菌状息肉症成人T細胞白血病	IFN-γ	IFN-γ	Ⅴ
内分泌がん	神経内分泌腫瘍	IP	CPT-11, CDDP	Ⅴ
内分泌がん	神経内分泌腫瘍	PE	VP-16, CDDP	Ⅴ

MTX：メソトレキセート，CDDP：シスプラチン，
DXR：ドキソルビシン，IFO：イオフォスファマイド，
IFN-γ：インターフェロンγ，CPT-11：イリノテカン，
VP-16：エトポシド

考　察

がん化学療法に携わるすべての医療スタッフは，医療事故を起こさないための安全管理システムの確立と良質な医療を提供できる環境を整備する必要がある。そのためにも厳格なレジメン管理体制の構築が重要であり，その管理を担うレジメン審査委員会が高い水準で機能していることが，安全管理上，必要不可欠とされている。

表3　レジメン登録制導入後のレジメン審査による照会内容と件数

審査結果	照会件数（延べ数）
エビデンスレベルの確認	44
レジメンオーダ設定関連	32
投与基準の記載事項	20
レジメン分類の記載	20
誤字・記入間違い	15
投与スケジュール	3
申請理由が不明	2
その他	21
総件数	61
レジメン申請件数	223
レジメン登録件数	222

登録されたレジメンのうち70%以上がエビデンスレベルⅡ以上であった。そのエビデンスレベルⅡ以上のレジメンが，2009年４～６月までで全がん化学療法件数1,374件中1,258件（91.6%）で実施されており，当院では標準治療を基本としていることが示唆された。一方，皮膚がんや骨・軟部腫瘍のような，エビデンスレベルが低いレジメンを治療に使用するがん種も多く存在していることがわかった。このようなレジメンは，レジメンオーダ導入までの時間的制約によりすべて「仮承認」となっているため，その使用目的や今後も優先的に使用するレジメンか否かを申請科へ再度通知し，再検討する必要があると考えられる。現在，当院ではエビデンスレベルがⅢ以下のもの，臨床研究審査委員会の承認が必要なもの，そして保険適応外使用を含むような見直しが必要と判断される仮承認レジメンを申請した診療科へ通知し，レジメンを見直す作業を行っている（**図3**）。今後は，承認されているレジメンについても，このように組織的に定期的な見直しを行う管理体制を構築することが重要であると考えられる。

当院では外来化学療法室の開設に伴い，薬剤部におけ

表4　レジメンオーダ導入前・後における疑義照会内容と照会・変更件数の比較

(a) 疑義照会内容

内容	レジメンオーダ			
	導入前（2009年１～３月）		導入後（2009年４～６月）	
	疑義照会件数	処方変更件数	義疑照会件数	処方変更件数
投与量（増量・減量・初回投与）	9	5	12	2
前投薬（制吐剤・ステロイド等）	4	2	1	0
抗がん剤希釈液の選択・量	6	5	1	1
複数規格薬品の選別	5	5	0	0
レジメンの選択	0	0	3	0
その他	6	5	4	3
総件数	30	22	21	6
全処方件数	713		661	
全処方件数に対する割合（%）	4.2	3.1	3.2	0.9

(b) 疑義照会例（導入前，導入後）

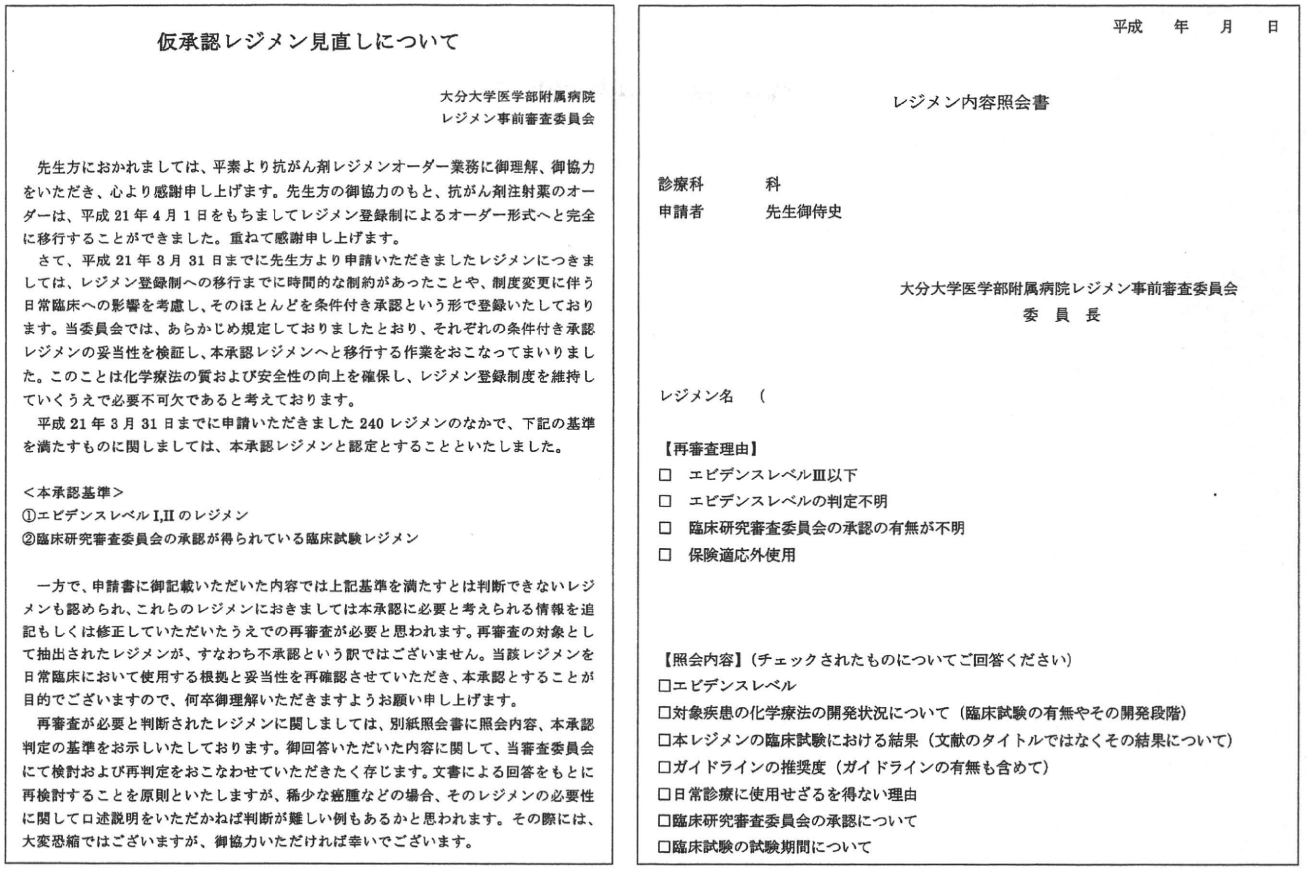
●導入前

分類	がん種	レジメン名	照会内容	回答	照会後の処方変更
投与量	大腸がん	mFOLFOX6	5-Fuの投与量が前回2,500mgであるが，今回2,750mgとなっている	2,500mgの間違い	変更
前投薬	悪性リンパ腫	CHOP	前投薬にメスナが処方されている（出血性膀胱炎予防）	メスナ中止	変更
抗がん剤希釈液	大腸がん	mFOLFOX6	オキサリプラチンの希釈液が生食	５%糖液へ変更	変更

●導入後

分類	がん種	レジメン名	照会内容	回答	照会後の処方変更
レジメンの選択	卵巣がん	CPT-P	子宮体がんCPT-11で処方	処方ミス	変更
レジメンの選択	食道がん	CPT-11	胃がんCPT-11にて処方。適応がん種未登録	4 th lineとして使用。登録手続きを行う	変更なし
投与量	悪性リンパ腫	CE	クレアチニンクリアランスが49.5であるため，VP-16の減量が必要	75%へ減量	変更

mFOLFOX6：fluorouracil, leuovorin, oxaliplatin



仮承認レジメン見直しについて

大分大学医学部附属病院
レジメン事前審査委員会

先生方におかれましては、平素より抗がん剤レジメンオーダー業務に御理解、御協力をいただき、心より感謝申し上げます。先生方の御協力のもと、抗がん剤注射薬のオーダーは、平成21年4月1日をもちましてレジメン登録制によるオーダー形式へと完全に移行することができました。重ねて感謝申し上げます。

さて、平成21年3月31日までに先生方より申請いただきましたレジメンにつきましては、レジメン登録制への移行までに時間的な制約があったことや、制度変更に伴う日常臨床への影響を考慮し、そのほとんどを条件付き承認という形で登録いたしております。当委員会では、あらかじめ規定しておりましたとおり、それぞれの条件付き承認レジメンの妥当性を検証し、本承認レジメンへと移行する作業をおこなってまいりました。このことは化学療法の質および安全性の向上を確保し、レジメン登録制度を維持していくうえで必要不可欠であると考えております。

平成21年3月31日までに申請いただきました240レジメンのなかで、下記の基準を満たすものに関しましては、本承認レジメンと認定とすることといたしました。

＜本承認基準＞
①エビデンスレベルI,IIのレジメン
②臨床研究審査委員会の承認が得られている臨床試験レジメン

一方で、申請書に御記載いただいた内容では上記基準を満たすとは判断できないレジメンも認められ、これらのレジメンにおきましては本承認に必要と考えられる情報を追記もしくは修正していただいたうえでの再審査が必要と思われます。再審査の対象として抽出されたレジメンが、すなわち不承認という訳ではございません。当該レジメンを日常臨床において使用する根拠と妥当性を再確認させていただき、本承認とすることが目的でございますので、何卒御理解いただきますようお願い申し上げます。

再審査が必要と判断されたレジメンに関しましては、別紙照会書に照会内容、本承認判定の基準をお示しいたしております。御回答いただいた内容に関して、当審査委員会にて検討および再判定をおこなわせていただきたく存じます。文書による回答をもとに再検討することを原則といたしますが、稀少な癌腫などの場合、そのレジメンの必要性に関して口述説明をいただかねば判断が難しい例もあるかと思われます。その際には、大変恐縮ではございますが、御協力いただければ幸いでございます。

平成　年　月　日

レジメン内容照会書

診療科　　科
申請者　　先生御侍史

大分大学医学部附属病院レジメン事前審査委員会
委員長

レジメン名　（

【再審査理由】
□　エビデンスレベルIII以下
□　エビデンスレベルの判定不明
□　臨床研究審査委員会の承認の有無が不明
□　保険適応外使用

【照会内容】（チェックされたものについてご回答ください）
□エビデンスレベル
□対象疾患の化学療法の開発状況について（臨床試験の有無やその開発段階）
□本レジメンの臨床試験における結果（文献のタイトルではなくその結果について）
□ガイドラインの推奨度（ガイドラインの有無も含めて）
□日常診療に使用せざるを得ない理由
□臨床研究審査委員会の承認について
□臨床試験の試験期間について

図3　仮承認レジメン見直し通知文と内容照会書

るレジメンに基づいた注射処方せんの処方監査が可能となった。しかしながら，入院においては各専門領域において標準的ではないレジメンが使用される現状があり，十分な監査が実施されているとは言い難い状況であった。今回，レジメン審査委員会の設置と院内のレジメン完全登録制を契機として，抗がん剤を含む注射オーダを全面的にレジメンオーダへ移行したことにより，処方内容が標準化されたと考えられる。また，調査期間において，前投薬の有無や抗がん剤希釈液の種類や量に関する薬剤部からの疑義照会件数がレジメンオーダ導入後で減少していたことからも，本システムの導入は薬剤師の業務効率化の観点からも有用といえる。しかしながら，現在のシステムは病名とレジメンオーダとの整合性や，レジメンの選択・適応（一次・二次治療，術前・術後化学療法など）と処方との照合機能を有していない。これらの点はシステムによるチェックの限界を示しており，薬剤師による治療計画と処方との照合が必要である。レジメンオーダの導入前は，薬剤師による抗がん剤無菌調製率が全抗がん剤処方の約30%であった。しかしながら，システム導入に伴い，薬剤部における抗がん剤無菌調製業務を入院・外来へ全面的に拡大したことにより，すべてのレジメン処方のチェックを調製担当薬剤師が行えるようになった。そして，レジメンオーダ導入前は疑義照会件数が0件（2009年1～3月）であったレジメンの選択については，導入後3件（2009年4～6月）に増加していたことから，タイムリーな処方監査も行えるようになったと考えられる。

血液疾患や小児疾患のレジメンは，投与スケジュールや投与方法が複雑であるためレジメンオーダのみでは管理が困難であり，運用面で柔軟に対応することが必要である。レジメンオーダを全面的に運用することは以上のような検討課題も含むが，レジメン登録制を効率的に導入でき，また，処方を標準化することができるという点においては有用であると思われる。今後は，がん化学療法に関するインシデントやアクシデントを集計し，リスクマネジメントの観点からもレジメンオーダの有用性を検討する予定である。

引用文献

1）牧野好倫，横手信昭ほか：レジメン審査委員会の運営，日本病院薬剤師会雑誌，**45**，1084-1085 (2009).
2）山本弘文，加藤裕久ほか:“抗がん剤レジメン管理ガイド”，じほう，東京，2008，pp. 21-33.

Cancer Chemother Pharmacol
DOI 10.1007/s00280-010-1358-1

ORIGINAL ARTICLE

Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC)

Tetsuya Hamaguchi · Kuniaki Shirao · Yoshihiro Moriya · Shigeaki Yoshida · Susumu Kodaira · Yasuo Ohashi · The NSAS-CC Group

Received: 20 October 2009 / Accepted: 1 May 2010

Abstract
Objective In the latter 1990s, adjuvant chemotherapy for completely resected Stage III colorectal cancer remained controversial in Japan. We conducted two independent randomized controlled trials in patients with Stage III colon and rectal cancer.

Methods Patients were randomly assigned to receive surgery alone or surgery followed by treatment with UFT (400 mg/m^2/day), given for five consecutive days per week for 1 year. The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS).

Results A total of 334 patients with colon cancer and 276 with rectal cancer were enrolled. The patients' characteristics were similar between the UFT group and the Surgery-alone group. There was no significant difference in RFS or OS in colon cancer. In rectal cancer, however, RFS and OS were significantly better in the UFT group than in the Surgery-alone group. The only grade 4 toxicity in the UFT group was diarrhea, occurring in one patient with colon cancer and one patient with rectal cancer.

Conclusions Postoperative adjuvant chemotherapy with UFT is successfully tolerated and improves RFS and OS in patients with Stage III rectal cancer. In colon cancer, the expected benefits were not obtained (hazard ratio = 0.89).

Keywords Stage III colon cancer · Stage III rectal cancer · UFT · Surgery alone · Randomized controlled trial

The Members of the National Surgical Adjuvant Study of Colorectal Cancer are listed in "Appendix".

T. Hamaguchi (✉)
Department of Gastrointestinal Oncology,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: thamaguc@ncc.go.jp

K. Shirao
Department of Medical Oncology, Faculty of Medicine,
Oita University, 1-1 Idaigaoka, Hasama, Yufu,
Oita 879-5593, Japan

Y. Moriya
Department of Surgical Oncology,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan

S. Yoshida
Aomori Prefectural Central Hospital,
2-1-1 Higashitsukurimichi, Aomori,
Aomori 030-8553, Japan

S. Kodaira
Department of Surgery, Nerima General Hospital,
1-24-1 Asahigaoka, Nerima-ku, Tokyo 176-8530, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health,
University of Tokyo, 7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan

Introduction

In Japan, the westernization of lifestyles has become associated with an annual increase in the incidence of colorectal cancer. In 2006, a total of 41,097 persons died of colorectal cancer, accounting for 12.6% of all deaths from malignant tumors. In 2004, 100,137 patients were diagnosed with colorectal cancer (17.6% of all patients with cancer). Colorectal cancer is forecast to become the most prevalent type by 2015, surpassing gastric cancer and lung

Published online: 19 May 2010

cancer [1]. In Europe and North America, colorectal cancer is the second leading cause of death from cancer [2]. Globally, the prevention, early diagnosis, and development of improved treatments for colorectal cancer are thus very important tasks.

In Europe and North America, 40–50% of patients with colorectal cancer who undergo surgery alone die of metastasis or recurrence. In patients with Stage III colon cancer, postoperative adjuvant chemotherapy with fluorouracil (FU) and levamisole (LEV) can cut mortality by 33% [3]. The 1990 National Institutes of Health Consensus Conference thus recommended a combination of FU and LEV (FULEV) as standard adjuvant therapy for Stage III colon cancer. In addition, radiotherapy combined with chemotherapy was recommended as a standard adjuvant therapy for rectal cancer [4]. Subsequent studies reported that FU plus leucovorin (LV) is superior to FU plus LEV for the adjuvant therapy of colon cancer [5]. In the late 1990s, FU plus LV (FULV) was positioned as standard adjuvant therapy for Stage III colon cancer.

In Japan, clinical trials of postoperative adjuvant chemotherapy have focused mainly on oral fluoropyrimidine-based regimens in both colon and rectal cancer. Although meta-analyses suggest that oral FU derivatives were effective [6, 7], standard adjuvant regimens were not established for either colon or rectal cancer until the early 2000s. Preoperative or postoperative radiation was considered unnecessary, since lateral nodal dissection is the standard procedure in Japan. Furthermore, FULV, regarded as more effective than FU alone in Western countries, was not available in Japan until 1999; however, in one comparative study of FU alone and FULV in advanced cancer, there was a difference in overall response rate, but the difference in overall survival was not significant [8]. This prompted us to perform a randomized, controlled study, the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC), to examine whether postoperative adjuvant chemotherapy with uracil–tegafur (UFT) alone is useful for the treatment of Stage III colon and rectal cancer. Phase II studies found that UFT, which is widely used in Japan, is effective for the management of advanced cancers of the stomach, colon, rectum, breast, and other organs [9]. UFT monotherapy was used because LV was not available in Japan at the time of planning this study.

Methods

The present study was designed to examine the usefulness of postoperative adjuvant chemotherapy with UFT in patients with curatively resected Stage III colon or rectal cancer. The protocol was approved by the institutional review board at each participating center.

Patients and study design

The eligibility criteria in the study were as follows: (1) histologically confirmed adenocarcinoma; (2) curatively resected (R0 surgery) Stage III (any T, n1 or n2, M0) colon cancer and rectal cancer; (3) a performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (4) an age of 20–75 years; (5) adequate function of main organs (white-cell count $\geq$ 4,000/mm^3, platelet count $\geq$ 100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels within twice the normal upper limit, serum total bilirubin level $\leq$ 1.2 mg/dL, blood urea nitrogen level $\leq$ 25 mg/dL, serum creatinine concentration $\leq$ 1.5 mg/dL, normal electrocardiogram), and (6) written informed consent obtained from the patient.

Patients who met the eligibility criteria were enrolled at the NSAS data center by telephone or fax within 6 weeks of after surgery and were randomly assigned to receive adjuvant chemotherapy with UFT (the UFT group) or surgery alone (Surgery-alone group) according to whether they had been diagnosed with colon cancer or rectal cancer. This was a non-blind study, and treatment was assigned by the minimization technique. Adjustment factors were T stage (T1/T2 vs. T3/T4) and N stage (n1 vs. n2/n3). In rectal cancer, the tumor site (upper vs. lower) was also used as an adjustment factor. Zelen's adjustment [10] was performed to balance the number of patients assigned to each treatment group according to center. Colon cancer, rectal cancer, and N stage were classified according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers arising from the rectosigmoid were classified as rectal cancer (see the footnote to Table 1).

The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS). Both endpoints were evaluated separately for colon cancer and rectal cancer.

Treatment plan

In advanced recurrent colorectal cancer, UFT 400 mg/m^2/day in two divided doses is the recommended dosage according to Japanese Phase I/II study [12]. Therefore, we judged that UFT at 400 mg/m^2/day would be an optimum dosage for postoperative chemotherapy for colorectal cancer. UFT at 600 mg/day has been approved as the upper daily dosage limit in Japan, so we did not wish to use dosages at or above this limit. Although UFT has been given two or three times daily, we considered that the twice-daily dosage would be superior in terms of compliance. A 1-year treatment was chosen in reference to previous Japanese studies of oral FU [6, 7, 13]. In the UFT group, UFT (tegafur, 400 mg/m^2/day; 600 mg/day in patients with a body surface area of $\geq$1.25 m^2

Table 1 Patient characteristics

	Colon		Rectum	
	UFT ($n = 168$)	Surgery alone ($n = 164$)	UFT ($n = 139$)	Surgery alone ($n = 135$)
Sex				
Male	91	98	83	82
Female	77	66	56	53
Age				
Years, median (range)	62 (30–75)	61 (35–75)	59 (32–75)	58 (30–75)
Tumor location				
Right colon	73	72	–	–
Left colon	95	92	–	–
Upper rectum	–	–	82	82
(Rs)[a]			(43)	(39)
(Ra)[a]			(39)	(43)
Lower rectum	–	–	57	53
(Rb)[a]			(55)	(51)
(P)[a]			(2)	(2)
Depth of tumor invasion (T stage)				
T1	11	10	8	11
T2	13	14	21	16
T3	102	95	94	90
T4	42	45	16	18
Extent of positive lymph nodes (N stage: Japanese classification)[b]				
n1	138	133	110	105
n2	25	25	26	25
n3	5	6	3	5
No. of positive lymph nodes				
1–3	134	125	99	98
4-	34	39	40	37

n0 no lymph node metastasis, *n1* metastasis to group 1 lymph nodes, *n2* metastasis to group 2 lymph nodes, *n3* metastasis to group 3 lymph nodes, *n4* metastasis to group 4 lymph nodes

[a] The rectosigmoid surgically is classified as "Rs," which is defined as the bowel at the level between the promontorium and the lower margin of the second sacral vertebra. The border between "Ra" and "Rb" is defined as the bowel at the level of the peritoneal reflection, which corresponds approximately to the level of the middle Houston valve (Kohlrausch valve). The proctos ("P"), the anal canal, is defined as the portion between the upper edge of the puborectal muscle and anal verge

[b] Lymph nodes are grouped according to the independent lymphatic spread (groups 1–4). In the colon, two modes of lymphatic drainage are present: lymphatic drainage along to the intestine (paraintestinal drainage) and toward the mesenteric main lymph node (mesenteric drainage). In the rectum, three modes of lymphatic drainage are present: lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall (lateral drainage)

and 500 mg/day in those with a body surface area of $<1.25\ m^2$) was given orally twice daily on weekdays (5 days per week) for 1 year, starting within 6 weeks after surgery.

Adverse events were graded according to the criteria of the Japan Clinical Oncology Group (JCOG) [14] as follows: grade 1, mild; grade 2, moderate; grade 3, severe; and grade 4, life-threatening. In the UFT group, the dose of UFT was decreased to 250 mg/m^2/day (400 mg/day in patients with a body surface area of $\geq 1.25\ m^2$ and to 300 mg/day in those with a body surface area of $<1.25\ m^2$) if grade 2 or higher adverse events occurred during treatment. In Japan in the 1990s, surgeons were responsible for chemotherapy. Therefore, the dosage was reduced upon the occurrence of grade 2 toxicity, as safety was of the utmost importance.

Treatment was discontinued if the attending physician ruled out the continuation of treatment with UFT due to complications or adverse events, or if recurrence was confirmed.

In the Surgery-alone group, anticancer therapy was withheld until the confirmation of recurrence during follow-up.

Follow-up

All patients underwent blood cell count, serum chemical tests, urinalysis, CEA and CA 19-9 as tumor marker tests, chest radiography, and abdominal ultrasonography or computed tomography at 4-month intervals during the first 2 years and at 6-month intervals thereafter. Patients with rectal cancer additionally underwent computed tomography of the pelvis at 6-month intervals. In the UFT group, blood cell count, serum chemical tests, and urinalysis were performed every month during treatment.

Diagnosis of recurrence was based on the results of imaging studies. Cytologic or histologic examinations were performed if necessary. Elevated levels of CEA alone were not regarded as adequate evidence of recurrence. If the CEA was elevated, we checked for signs or symptoms suggestive of tumor recurrence and considered using further imaging studies (i.e., CT scan, MRI, and/or bone scintigram) as needed.

Case report forms for individual patients were submitted to the independent NSAS data center at 6-month intervals during the first 5 years and at yearly intervals thereafter. All events related to the study endpoints, such as recurrence, were evaluated by the Evaluation Committee; treatment assignments were masked at the time of evaluation.

Statistical analysis

There was a wide range in the results that were used as the basis for calculating the target number of subjects; therefore, it was difficult to identify the exact number of cases needed. We set the number in consideration of feasibility. We chose a sample size that would ensure at least 70% detection power even in the most disadvantageous case.

The method of Schoenfeld and Richer was used to estimate sample size. It was assumed that the RFS at 5 years in the Surgery-alone group would be 60–75% for colon cancer and 50–65% for rectal cancer, the enrollment period 2 years, and follow-up period after enrollment 5 years. We then estimated that samples of 390–624 patients with colon cancer and of 312–446 patients with rectal cancer would be required to show a significant difference in endpoints between the groups with an alpha level of 0.05 (one-sided), a statistical power of 80% ($\beta = 0.2$), and a hazard ratio of 0.67 (hazard decreased to 2/3 after treatment with UFT). In the present study, the target number of patients was, therefore, set at 500 for colon cancer and 400 for rectal cancer.

An interim analysis was planned 2 years after completion of enrollment. Early termination would be considered at the time of the interim analysis if the one-sided P value of log-rank test for primary endpoint fell below 0.005, according to the Lan and DeMets spending function method.

For RFS, either recurrence or death, whichever occurred earlier, was defined as an event. The survival time was defined as the period from the date of surgery until the date of an event. OS was defined as the period from the date of surgery to the date of death. All deaths, including deaths from other causes, were regarded as events. Data on patients showing event-free survival were censored at the time of the last follow-up visit. Survival was estimated using the Kaplan–Meier method. The log-rank test was used to compare differences in survival. Hazard ratios were calculated using Cox proportional hazards models. All P values were two sided.

Statistical analysis was performed by statistical analysts and the NSAS data center. All analyses were done using the Statistical Analysis System (SAS, version 8, SAS Institute Inc., Cary, NC, USA).

Results

Accrual and interim analysis

From October 1996 through April 2001, we enrolled 334 patients with colon cancer and 276 with rectal cancer. Although the numbers of enrolled patients fell short of the initially set goals, the enrollment period was not prolonged, since about 5 years has elapsed since the start of the study, and it was judged that the effectiveness of postoperative adjuvant chemotherapy could be evaluated by a meta-analysis with other studies.

An interim analysis was performed in 2003. Data and safety were assessed by an independent data monitoring committee (IDMC). The IDMC recommended publishing the results of the analysis, since the criteria for early termination had been met for rectal cancer and their effectiveness confirmed. On the basis of this recommendation, the results of the interim analysis for rectal cancer were published (median follow-up period, 3.0 years) [15].

The results of the present analysis are based on follow-up data received as of March 2006, 5 years after the completion of enrollment (median follow-up period, 6.2 years).

Patients' characteristics

Four registered patients were confirmed not to meet the eligibility criteria after enrollment (registration before

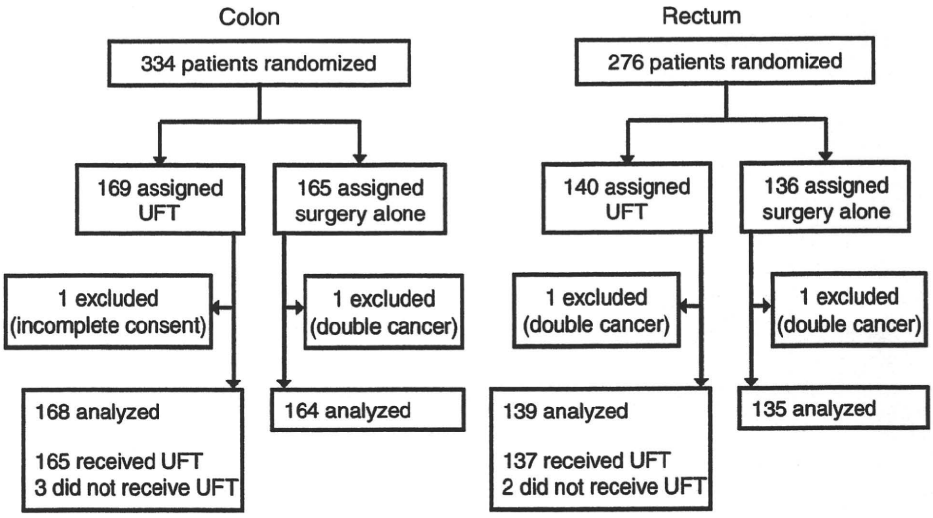


Fig. 1 CONSORT diagram

Table 2 Adverse events: grade 3/4

	Colon		Rectum	
Any events (grade 3/4)	UFT 19.4%/0.6%	Surgery alone 3.1%/0%	UFT 15.3%/0.7%	Surgery alone 2.2%/0.7%
Leukocytes	0%/0%	0%/0%	0%/0%	0%/0%
Neutrophils	2.6%/0%	0%/0%	0%/0%	0%/0%
Hemoglobin	0.6%/–	1.3%/–	0%/–	0%/–
Platelets	0%/0%	0%/0%	0%/0%	0%/0%
AST	2.5%/0%	0.6%/0%	2.2%/0%	0%/0%
ALT	3.1%/0%	0.6%/0%	2.2%/0%	0.8%/0%
Total bilirubin[a]	8.1%/0%	0%/0%	9.0%/0%	0.8%/0%
Anorexia	2.4%/–	0.6%/–	1.5%/–	0.7%/–
Nausea/vomiting	0.6%/–	0%/–	0.7%/–	0.7%/–
Diarrhea	0.6%/0.6%	0.6%/0%	0.7%/0.7%	0%/0.7%
Stomatitis	1.2%/0%	0%/0%	0%/0%	0%/0%
Rash	0.6%/0%	0%/0%	1.5%/0%	0%/0%
Fatigue	1.2%/0%	0%/0%	0.7%/0%	0%/0%

Japan clinical oncology group (JCOG) criteria

[a] Grade 3: > 2 × ULN (upper limit of normal)

obtaining informed consent, a history of breast cancer, synchronous esophageal cancer, and synchronous bladder cancer in one patient each). These patients were judged ineligible and excluded from the analysis. Data on 332 patients with colon cancer (UFT group, 168; Surgery-alone group, 164) and 274 with rectal cancer (UFT group, 139; Surgery-alone group, 135) were analyzed (Fig. 1).

The clinical characteristics of the patients, surgical procedures, and pathological findings were well balanced between the treatment groups (Table 1).

Adverse events and compliance

Adverse events were assessed according to the JCOG criteria [14]. In both the colon cancer and rectal cancer patients, the incidence of grade 3 or more severe adverse events was higher in the UFT group. However, grade 4 adverse events occurred in only one patient with colon cancer in the UFT group, one patient with rectal cancer in the UFT group, and one patient with rectal cancer in the Surgery-alone group (Table 2). There were no treatment-related or other deaths within 60 days of completion of treatment.

In the UFT group, the main reasons for treatment withdrawal were recurrence (16 patients), adverse events (17 patients), and refusal of the patient to continue treatment due to adverse events (16 patients) in patients with colon cancer; and recurrence (18 patients), adverse events (9 patients), and refusal of the patient to continue treatment because of adverse events (10 patients) in patients with rectal cancer. After excluding patients who discontinued treatment because of recurrence, the rate of treatment

completion was 72% in patients with colon cancer and 80% in those with rectal cancer. The median initial daily dose of UFT was 397 mg/m^2/day in patients with colon cancer and 395 mg/m^2/day in those with rectal cancer.

Relapse-free survival

At the time of the last follow-up, 49 patients with colon cancer in the UFT group, 51 with colon cancer in the Surgery-alone group, 46 with rectal cancer in the UFT group, and 59 with rectal cancer in the Surgery-alone group suffered recurrence or died. In patients with colon cancer, the 5-year RFS was 71.3% in the UFT group (95% confidence interval, 64.3–78.2%) and 69.6% in the Surgery-alone group (95% confidence interval, 62.4–76.7%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.89 (95% confidence interval, 0.60–1.32), with no significant differences between the groups ($P = 0.56$). In patients with rectal cancer, the 5-year RFS was 68.9% in the UFT group (95% confidence interval, 61.1–76.8%) and 56.3% in the Surgery-alone group (95% confidence interval, 47.9–64.8%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.66 (95% confidence interval, 0.45–0.97). The RFS was significantly better in the UFT group ($P = 0.033$; Fig. 2).

Overall survival

Overall, 36 patients with colon cancer in the UFT group, 42 with colon cancer in the Surgery-alone group, 29 with rectal cancer in the UFT group, and 43 with rectal cancer in the Surgery-alone group died. In patients with colon cancer, the 5-year overall survival (OS) was 81.3% in the UFT group (95% confidence interval, 75.4–87.3%) and 76.7% in the Surgery-alone group (95% confidence interval, 70.2–83.2%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.82 (95% confidence interval, 0.53–1.29), with no significant difference between the groups ($P = 0.39$). In patients with rectal cancer, the 5-year OS was 85.3% in the UFT group (95% confidence interval, 79.4–91.3%) and 72.1% in the Surgery-alone group (95% confidence interval, 64.4–79.7%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.60 (95% confidence interval, 0.38–0.97). OS was significantly better in the UFT group ($P = 0.034$; Fig. 3).

Patterns of relapse

As of the last follow-up, recurrence was diagnosed in 45 (26.8%) patients with colon cancer in the UFT group, 47 (28.7%) with colon cancer in the Surgery-alone group, 41 (29.5%) with rectal cancer in the UFT group, and 57 (42.2%) with rectal cancer in the Surgery-alone group. Analysis of patterns of relapse indicated that the rate of distant metastasis in patients with rectal cancer was lower in the UFT group (Table 3).

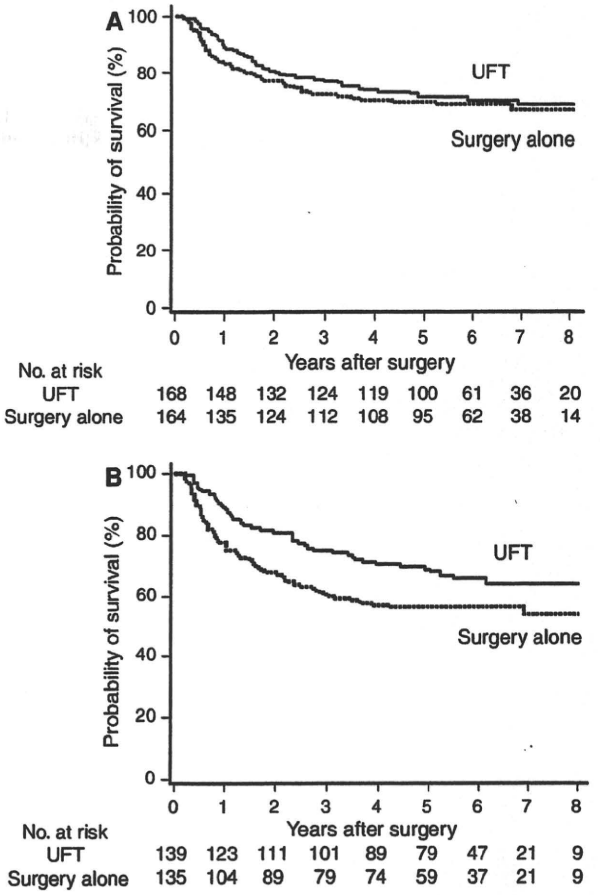


Fig. 2 Kaplan–Meier estimates of relapse-free survival by treatment, **a** colon cancer, **b** rectal cancer

Ancillary analysis

In the present study, we classified patients according to whether they had colon cancer or rectal cancer as defined by the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers developing in the rectosigmoid were classified as rectal cancer. In Europe and North America, cancers arising from the rectosigmoid are usually included in clinical studies of postoperative adjuvant chemotherapy for colon cancer. Some studies have also included tumors with their lower margins located above the peritoneal reflection. To facilitate a comparison of our results with those of Western studies, we calculated RFS and OS for patients with colon cancer plus those with tumors arising

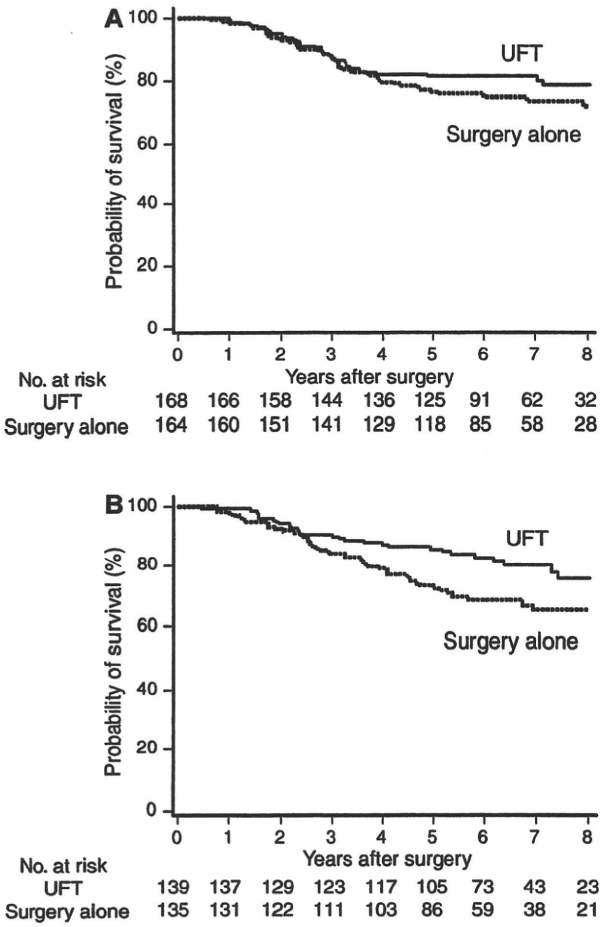


Fig. 3 Kaplan–Meier estimates of overall survival by treatment, **a** colon cancer, **b** rectal cancer

Table 3 Pattern of first relapse

	Colon		Rectum	
	UFT ($n = 168$)	Surgery alone ($n = 164$)	UFT ($n = 139$)	Surgery alone ($n = 135$)
Number of relapses	45	47	41	57
Local	1	1	9	11
Distant	44	44	30	42
Local and distant	0	2	2	4

from the rectosigmoid and for patients with colon cancer plus those with tumors located above the peritoneal reflection (upper rectal cancer). In patients with colon cancer plus those with rectosigmoid cancer, the 5-year RFS and OS were 74.2 and 85.1% in the UFT group and 67.4 and 76.2% in the Surgery-alone group, respectively. The hazard ratio was 0.73 (95% confidence interval, 0.51–1.04) in RFS and 0.69 (95% confidence interval, 0.46–1.05) in OS. In patients with colon cancer plus those with upper rectal cancer, the 5-year RFS and OS were 73.7 and 85.3% in the UFT group and 67.2 and 77.4% in the Surgery-alone group, respectively. The hazard ratio was 0.74 (95% confidence interval, 0.54–1.02) in RFS and 0.67 (95% confidence interval, 0.46–0.98) in OS. When cancers arising from the rectosigmoid or the upper rectum were included in the analysis, the difference in response between the treatment groups thus tended to increase.

Discussion

The regimen for UFT alone was either 2 years of treatment with continuous administration of 400 mg/m^2/day [16] or 1 year of treatment with 400 mg/m^2/day for 5 days followed by a 2-day washout (the present study and [13]). The latter has been more widely adopted in Japan because of superior compliance. The regimen for UFT + LV was five courses of 6 months of treatment consisting of UFT 300 mg/m^2/day for 28 days plus a 7-day washout. Improvement in efficacy was achieved with concurrent use of LV. When this study was carried out, LV tablets could not be used as they had not been approved in Japan; therefore, we used UFT alone.

In our study, RFS and OS did not differ significantly between the treatment groups in patients with colon cancer but were significantly better in the adjuvant chemotherapy group in patients with rectal cancer. These findings were consistent with the results obtained by the Tokai Adjuvant Chemotherapy Study Group for Colorectal Cancer [16], which also evaluated postoperative adjuvant chemotherapy with UFT. There were few grade 3 or higher adverse events, patient compliance was good, and chemotherapy with UFT was easily manageable.

An interim analysis showed that postoperative adjuvant chemotherapy with UFT was effective in patients with rectal cancer [15]. This finding was confirmed in the final analysis. In Japan, mesorectal excision with partial lateral lymph node dissection is performed as standard surgery; however, radiotherapy, considered a standard procedure in Europe and North America, has not been performed aggressively. Some studies have reported that preoperative radiotherapy (combined with chemotherapy) improves outcomes in patients with locally progressive disease [17]. Further studies of adjuvant chemoradiotherapy may thus be required to improve treatment outcomes in patients with locally advanced rectal cancer.

In patients with colon cancer, postoperative adjuvant chemotherapy with UFT was not confirmed to be effective, in contrast to the results obtained in patients with rectal cancer. This outcome may be due to the fact that only 334

of the initially scheduled 500 patients were enrolled and that the 5-year RFS in the Surgery-alone group was higher in patients with colon cancer (about 70%) than in those with rectal cancer. The study may, therefore, have been not sensitive enough to detect the effect of UFT in patients with colon cancer. Studies performed in Europe and North America in the 1980s have shown that adjuvant chemotherapy with methyl-CCNU, vincristine and FU (MOF), FULEV, or FULV was more effective than surgery alone in patients with colon cancer [3, 18–21]. Subsequent controlled studies comparing MOF with FULV [22] and FULEV with FULV [5] showed that DFS was significantly better with FULV. Combined chemotherapy with FULV was established as standard treatment for Stage III colon cancer in the latter half of the 1990s. More recently, controlled clinical trials comparing FULV with FULV with oxaliplatin (OX) (MOSAIC, NSABP C-07) in patients with Stage II/III colon cancer demonstrated that DFS was significantly better in the FULV plus OX group [23, 24]. At present, regimens combining FULV with OX with molecular targeted agents (bevacizumab, cetuximab) are being evaluated. FULV has also been compared with oral fluoropyrimidines (capecitabine, UFT and LV), and these treatments have been found to be equivalent in terms of efficacy [25, 26]. Oral fluoropyrimidines are now regarded as an alternative treatment to FULV. With respect to survival benefit, the adoption in Japan of FULV with OX regimens confirmed to be effective by clinical trials performed in Europe and North America, appears to be warranted.

Comparison of the results of Japanese clinical studies with those of studies performed in Europe and North America must take into account differences in surgical procedures and outcomes. Although direct comparisons are not feasible, the outcomes (RFS [DFS]) of patients with colon cancer in the Surgery-alone group of our study were superior to those of patients with Stage III colon cancer who received FULV and comparable to those in patients who received FULV with OX in the MOSAIC and NSABP C-07 studies [27]. We considered there seem to be two factors why the difference of the outcome between the western population and our results is [28]. The first is a difference in the standard nodal dissection procedures used in Japan and in the West. In Japan, D2 or D3 nodal dissection is conducted by dividing the dissection procedure into three parts (D1, D2, and D3) along the main surgical trunk artery root. In Western countries, dissection of the main trunk artery root is not performed, and only dissection below the D2 level is implemented. A retrospective multicenter study analysis by the Japanese Society for Cancer of the Colon and Rectum has revealed a 5–10% incidence of nodal metastasis in the region in which the dissection procedure differs between Japan and the West [29]. This difference in the dissection procedure may have caused the difference in surgical results.

The other factor was a substantial difference in the handling of surgical specimens. In Japan, the median number of lymph nodes examined was 17, and the number examined was less than 12 in 32% of surgical cases. According to the American SEER report, the median number of lymph nodes examined was nine, and the number examined was less than 12 in 63% of surgical cases [30]. Thus, a substantial difference in treatment results was likely to have been caused by "stage migration".

The Japanese Clinical Oncology Group (JCOG) is conducting a comparative study of the safety and efficacy of adjuvant oral fluoropyrimidines (UFT and LV) with FULV in patients with Stage III colon cancer (including tumors located in the upper rectum) [31]. Recruitment of 1,101 patients is complete. An interim analysis has demonstrated a 3-year DFS (FU+LV or UFT+LV) of about 75% [32]. Combination therapy of FULV with OX should also be critically evaluated, not only for survival benefit but also for adverse effects and economic factors.

Acknowledgments We thank the patients and investigators who participated in these two trials. We also thank Mr. Takayuki Aki for his assistance and advice on this paper. This study was supported by the Japan Health Sciences Foundation and by Taiho Pharmaceutical Company, Tokyo, Japan.

Conflict of interest statement None declared.

Appendix

Members of the National Surgical Adjuvant Study of Colorectal Cancer

Study Chairpersons—S. Yoshida; S. Kodaira;

Study Coordinators—K. Shirao; Y. Shimada;

Statistical Analyst—Y. Ohashi;

Evaluation Committee—Y. Moriya; S. Imaoka; T. Kato; S. Kodaira; E. Ikeda; T. Takahashi;

Independent Data and Safety Monitoring Committee—N. Saijo; Y. Ariyoshi; S. Ebihara; H. Origasa; M. Fukuoka; T. Mitsuishi; T. Tsuruo;

Participating Centers—Keiyukai Sapporo Hospital, Hokkaido; Sapporo Kosei General Hospital, Hokkaido; National Hospital Organization Hirosaki National Hospital, Aomori; National Hospital Organization Sendai Medical Center, Miyagi; Miyagi Cancer Center, Miyagi; Yamagata Prefectural Central Hospital, Yamagata; Ibaraki Prefectural Central Hospital, Ibaraki; Tochigi Cancer Center, Tochigi; Gunma Prefectural Cancer Center, Gunma; National Cancer Center Hospital East, Chiba; Cancer Institute Hospital, Tokyo; National Cancer Center Hospital, Tokyo;

International Medical Center of Japan, Tokyo; Teikyo University Hospital, Tokyo; Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo; Toranomon Hospital, Tokyo; Social Insurance Central General Hospital, Tokyo; National Hospital Organization Tokyo Medical Center, Tokyo; Kanagawa Cancer Center, Kanagawa; Niigata Cancer Center Hospital, Niigata; Aichi Cancer Center Hospital, Aichi; Aichi Cancer Center Aichi Hospital, Aichi; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; National Hospital Organization Osaka National Hospital, Osaka; Hyogo Cancer Center, Hyogo; Okayama Saiseikai General Hospital, Okayama; Kagawa University Hospital, Kagawa; National Hospital Organization Shikoku Cancer Center, Ehime; National Hospital Organization Kyushu Cancer Center, Fukuoka; Kurume University Medical Center, Fukuoka.

References

1. Statistics of Cancer, Center for Information Services, National Cancer Center, Japan. http://www.ganjoho.ncc.go.jp/public/statistics/pub/update.html
2. Pisani P, Parkin DM, Ferlay J (1993) Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer 55:891–903
3. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH et al (1990) Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 322:352–358
4. NIH consensus conference (1990) Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444–1450
5. Wolmark N, Rockette H, Mamounas E, Jones J, Wieand S, Wickerham DL, Bear HD, Atkins JN, Dimitrov NV, Glass AG, Fisher ER, Fisher B (1999) Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 17:3553–3559
6. Sakamoto J, Hamada C, Kodaira S, Nakazato H, Ohashi Y (1999) Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. Jpn J Clin Oncol 29:78–86
7. Sakamoto J, Ohashi Y, Hamada C, Buyse M, Burzykowski T, Piedbois P (2004) Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. J Clin Oncol 22:484–492
8. Advanced Colorectal Cancer Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10:896–903
9. Ota K, Taguchi T, Kimura K (1988) Report on nationwide pooled data and cohort investigation in UFT phase II study. Cancer Chemother Pharmacol 22:333–338
10. Zelen M (1974) The randomization and stratification of patients to clinical trials. J Chronic Dis 27:365–375
11. Japanese Society for Cancer of the Colon and Rectum (ed) (1997) General rules for clinical and pathological studies on cancer of the colon, rectum, and anus. Kanehara & Co., Ltd, Tokyo
12. Ikeda E, Kodaira S, Teramoto T, Okuda M, Takahashi T, Kato T, Yamamoto Y, Isomoto H (1996) Optimal dosage of UFT+MMC combination chemotherapy for advanced colorectal cancer—Phase I/II study of combination chemotherapy of MMC with 2-week intervals and intermittent UFT Administration. Jpn J Cancer Chemothr 23:1291–1298
13. Sadahiro S, Ohki S, Yamaguchi S, Takahashi T, Otani Y, Tsukikawa S, Yamamura T, Takemiya S, Nagasaki H, Nishiyama K, Fukujima T, Hiki Y, Yamaguchi S, Kamada K, Shimada H, Mitomi T, Makuuchi H (2000) Optimal dosage of UFT in a weekday-on/weekday-off schedule as a postoperative adjuvant chemotherapy for colorectal cancer. Jpn J Cancer Chemothr 27:2223–2230
14. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, Narabayashi M, Fukutomi T, Kondo H, Shimoyama M et al (1993) Toxicity grading criteria of the Japan clinical oncology group. The clinical trial review committee of the Japan clinical oncology group. Jpn J Clin Oncol 23:250–257
15. Akasu T, Moriya Y, Ohashi Y, Yoshida S, Shirao K, Kodaira S, National Surgical Adjuvant Study of Colorectal C (2006) Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. Jpn J Clin Oncol 36:237–244
16. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A (2002) Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. Langenbecks Arch Surg 386:575–581
17. Sadahiro S, Suzuki T, Ishikawa K, Fukasawa M, Saguchi T, Yasuda S, Makuuchi H, Murayama C, Ohizumi Y (2004) Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3–4Nx rectal cancer. Eur J Surg Oncol 30:750–758
18. Wolmark N, Fisher B, Rockette H, Redmond C, Wickerham DL, Fisher ER, Jones J, Glass A, Lerner H, Lawrence W et al (1988) Postoperative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C-01. J Natl Cancer Inst 80:30–36
19. Francini G, Petrioli R, Lorenzini L, Mancini S, Armenio S, Tanzini G, Marsili S, Aquino A, Marzocca G, Civitelli S et al (1994) Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. Gastroenterology 106:899–906
20. O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS (1997) Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol 15:246–250
21. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) Investigators (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 345:939–944
22. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, Jones J, Mamounas EP, Ore L, Petrelli NJ et al (1993) The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 11:1879–1887
23. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A, the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer Investigators (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351

24. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25:2198–2204
25. Twelves C, Wong A, Nowacki MP, Abt M, Burris H III, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz J-F, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J, Scheithauer W (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704
26. Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N (2006) Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from national surgical adjuvant breast and bowel project protocol C-06. J Clin Oncol 24:2059–2064
27. Allegra C, Sargent DJ (2005) Adjuvant therapy for colon cancer—the pace quickens. N Engl J Med 352:2746–2748
28. Ishiguro M, Sugihara K (2010) Difference in treatment and outcome of colorectal cancer between japan and western countries. Frontiers in colorectal cancer. Medical Review Co., Ltd, Japan, pp 14–19
29. Japanese Society for Cancer of the Colon and Rectum (ed) (2009) JSCCR guidelines 2009 for the treatment of colorectal cancer. Kanehara & Co., Ltd
30. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA (2005) Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 97:219–225
31. A Trial Comparing Adjuvant Oral UFT/LV to 5-FU/l-LV in Stage III Colorectal Cancer (JCOG-0205-MF)
32. http://www.jcancer.jp/ronbun_db/pdf/40.pdf (in Japanese)