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=Abstract=

**Effect of 5-FU plus leucovorin for adjuvant chemotherapy according to dose related factors in colon cancer**

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**Background :** In patients with stage C colon cancer, surgery followed by adjuvant chemotherapy with 5-fluorouracil (5-FU)/leucovorin (LV) is considered to be the standard treatment. However, the objects of adjuvant therapy and the duration of treatment are still matters of controversy. We investigated the effect of dose related factor (delivered total dose of 5-FU per body square meter, actual dose intensity and relative dose intensity) of the adjuvant 5-FU/leucovorin regimen on survival in colon cancer.

**Methods :** Of the colon cancer patients with Duke's B2 and C stage diseases treated with curative resection from December, 1990 to December, 1996, 139 patients treated with 5-FU/LV as an adjuvant chemotherapy were evaluated. The delivered total dose of 5-FU per body square meter, actual dose intensity and relative dose intensity were obtained. The patients were divided into two groups according to the median value of each factor and the survival rates were compared.

**Results :** The total dose of 5-FU administered per body square meter had a significant effect on the 5-year disease free and overall survival in stage B2 and C colon cancer patients (B2;  $p=0.025$ ,  $p=0.045$ , respectively, C;  $p=0.011$ ,  $p=0.0002$ , respectively). But survival was not affected by the dose intensity. Multivariate analysis demonstrated that only the total dose of 5-FU administered per body surface area affected the 5-year disease free and overall survival ( $p=0.0016$ ,  $p=0.0007$ , respectively).

**Conclusion :** It can be concluded that the total dose of 5-FU administered is more important than the DI in adjuvant chemotherapy of colon cancer and the total dose of 5-FU had a significant

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 (1998)

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effect on the survival rate in colon cancer patients. To confirm the total dose effect of 5-FU on survival in this study, multi-institutional, prospective randomized studies should be carried out.(Korean J Med 59:290-299, 2000)

**Key Words** : Colonic neoplasms; Chemotherapy, Adjuvant; Fluorouracil; Dosage forms

5-FU leucovorin 1, 2 8, 9, 10, 20-40% 5-FU/leucovorin

가 , 5-FU/leucovorin

가

1), NSABP C-03 MOF Intergroup 0089

, 30% , 6 5-FU/leucovorin 12

2) 5-FU/levamisole 가

가 12) 5FU/levamisole 5-FU/leucovorin

5-Fluorouracil( 5-FU ) 1958

. 1960 5-FU Duke B2, C2 5-FU leucovorin

15-20% 3) 1970 (1) 5-FU total dose

5-FU methyl-CCNU, vincristine (2) 5-FU dose intensity

5-FU

4) 1988 National Surgical Adjuvant Breast and Bowel Project(NSABP) Duke B C 5-FU, semustine

vincristine(MOF) 1. 1990 1 1996 12

5) North Central Cancer Treatment Group(NCCTG) Intergroup 가 Duke B2, C 5-FU/leucovorin

5-FU levamisole , 가

40% 6) Duke C 가 ECOG 0-2 , , ,

가 1990 가 139

5-FU, levamisole Duke C 가

7) 1980 5-FU 가 2. 3-4

leucovorin 5-FU fluoro- 5-FU 400 mg/m2 leucovorin 20

deoxyuridine monophosphate(FdUMP)

mg/m<sup>2</sup> 1 5 . log-rank test ,  
 4 1 . CBC  
 , 가 3,000/ Cox-regression test . 5-FU  
 mm<sup>3</sup> , 가 100,000/mm<sup>3</sup>  
 1 Chi-square test t-test  
 가 3,000/mm<sup>3</sup> , 가 100,000/mm<sup>3</sup> , Chi-square test  
 5-FU 25% .  
 WHO grade III  
 , 5-FU 25%  
 . B2 6 , C 1.  
 12 .  
 3. 24-76 가 55 ,  
 87 (63%), 52 (37%) ,  
 ECOG 0-1 118 (85%)  
 . Duke B2가 81  
 , X , , (58%), C가 58 (42%) ,  
 5 6 CEA, 61 (44%), S 52 (37%) .  
 , 5ng/mL 가 93 (73%)  
 , 5ng/mL 가 34 (27%) .  
 . 27 101 well differentiated가 27 , moderately  
 50 differentiated가 85 , poorly differentiated가 13  
 4. 가 B2 6 , C  
 12 .  
 5-FU (total Table 1 .  
 dose) 5-FU 2. 5-FU ,  
 ( ; mg/m<sup>2</sup>) ,  
 (actual dose intensity)  
 5-FU가 가 5-FU B2  
 5-FU 가 12.9 g/m<sup>2</sup> ; 3.5-27.4 g/m<sup>2</sup>  
 ( ; ) ( ; mg/m<sup>2</sup>/week) C 20.6 g/m<sup>2</sup> ; 1.9-30.7  
 . (relative dose intensity) g/m<sup>2</sup> . B2  
 가 462 mg/m<sup>2</sup>/week( ; 353-598 mg/m<sup>2</sup>/week)  
 C 498 mg/m<sup>2</sup>/week( ;  
 293-678 mg/m<sup>2</sup>/week) . B2  
 , 92.4( ; 70.5-119.5) C  
 93.5( ; 58.5-135.5) .  
 (1999 3 )  
 3.  
 4. B2 5 86.2% C  
 5 68.9% (Figure 1A). B2  
 Kaplan-Meier method 5 87.1% C 5

**Table 1. Patients characteristics**

	Delivered 5-FU*		p- value	Total
	Below the median	Above the median		
Number of patients	70	69		139
Male:Female	1.3:1 (40:30)	2.1:1 (47:22)	0.181	1.7:1 (87:52)
Age				
Median(year)	56	51	0.259	55
Range	24- 73	30- 76		24- 76
ECOG status				
0	5	5	0.265	10
1	51	57		108
2	14	7		21
Primary lesion				
Rt	29	32		61
Transverse	4	8	0.484	12
Lt	8	6		14
Sigmoid	29	23		52
Differentiation				
Well	11	16		27
Moderately	45	40	0.732	85
Poor	7	6		13
Mucinous	7	7		14
Preop. CEA (ng/mL)				
< 5	44	49	0.251	93
5	20	14		34
Cycle in B2 stage				
Median	6	12	0.0001 †	6
Range	2- 7	6- 13		2- 13
Cycle in C stage				
Median	7	12	0.0001 †	12
Range	1- 13	9- 14		1- 14
Duke's stage				
B2	41	40	0.943	81
C	29	29		58

\* ; means the delivered total dose of 5-FU per body square meter

† ; significant difference

75.7% (Figure 1B).  
5-FU 80% (p=0.446).  
5, B2 4.  
C 5 † (p=0.045, p=0.0002) (Figure 2A, B).  
139 25 18.0%  
B2 9  
5 85%, (11.1%) †, C 16 (27.6%) †  
80% (p=0.446).  
5 (20%), 5 (20%), 13 (52%),

**Figure 1.** Survival in total patients according to Duke's stage. (A) DFS (B) OS.

**Figure 2.** Overall survival according to the total dose of 5-FU per body square meter (A) Duke's B2 stage (B) Duke's C stage.

Table 2	B2		C		Total	p-value
	n	%	n	%		
Overall survival	11	36%	5	7%	1,184	(p=0.004)
Grade 3 toxicity	6	70%	5	7%	11	(0.9%)
Grade 4 toxicity	2	8%	3	7%	5	(0.4%)
Grade 5 toxicity	1	14%	1	2%	2	(0.2%)
Grade 6 toxicity	1	14%	1	2%	2	(0.2%)
Grade 7 toxicity	1	14%	1	2%	2	(0.2%)
Grade 8 toxicity	1	14%	1	2%	2	(0.2%)
Grade 9 toxicity	1	14%	1	2%	2	(0.2%)
Grade 10 toxicity	1	14%	1	2%	2	(0.2%)
Grade 11 toxicity	1	14%	1	2%	2	(0.2%)
Grade 12 toxicity	1	14%	1	2%	2	(0.2%)
Grade 13 toxicity	1	14%	1	2%	2	(0.2%)
Grade 14 toxicity	1	14%	1	2%	2	(0.2%)
Grade 15 toxicity	1	14%	1	2%	2	(0.2%)
Grade 16 toxicity	1	14%	1	2%	2	(0.2%)
Grade 17 toxicity	1	14%	1	2%	2	(0.2%)
Grade 18 toxicity	1	14%	1	2%	2	(0.2%)
Grade 19 toxicity	1	14%	1	2%	2	(0.2%)
Grade 20 toxicity	1	14%	1	2%	2	(0.2%)
Grade 21 toxicity	1	14%	1	2%	2	(0.2%)
Grade 22 toxicity	1	14%	1	2%	2	(0.2%)
Grade 23 toxicity	1	14%	1	2%	2	(0.2%)
Grade 24 toxicity	1	14%	1	2%	2	(0.2%)
Grade 25 toxicity	1	14%	1	2%	2	(0.2%)
Grade 26 toxicity	1	14%	1	2%	2	(0.2%)
Grade 27 toxicity	1	14%	1	2%	2	(0.2%)
Grade 28 toxicity	1	14%	1	2%	2	(0.2%)
Grade 29 toxicity	1	14%	1	2%	2	(0.2%)
Grade 30 toxicity	1	14%	1	2%	2	(0.2%)
Grade 31 toxicity	1	14%	1	2%	2	(0.2%)
Grade 32 toxicity	1	14%	1	2%	2	(0.2%)
Grade 33 toxicity	1	14%	1	2%	2	(0.2%)
Grade 34 toxicity	1	14%	1	2%	2	(0.2%)
Grade 35 toxicity	1	14%	1	2%	2	(0.2%)
Grade 36 toxicity	1	14%	1	2%	2	(0.2%)
Grade 37 toxicity	1	14%	1	2%	2	(0.2%)
Grade 38 toxicity	1	14%	1	2%	2	(0.2%)
Grade 39 toxicity	1	14%	1	2%	2	(0.2%)
Grade 40 toxicity	1	14%	1	2%	2	(0.2%)
Grade 41 toxicity	1	14%	1	2%	2	(0.2%)
Grade 42 toxicity	1	14%	1	2%	2	(0.2%)
Grade 43 toxicity	1	14%	1	2%	2	(0.2%)
Grade 44 toxicity	1	14%	1	2%	2	(0.2%)
Grade 45 toxicity	1	14%	1	2%	2	(0.2%)
Grade 46 toxicity	1	14%	1	2%	2	(0.2%)
Grade 47 toxicity	1	14%	1	2%	2	(0.2%)
Grade 48 toxicity	1	14%	1	2%	2	(0.2%)
Grade 49 toxicity	1	14%	1	2%	2	(0.2%)
Grade 50 toxicity	1	14%	1	2%	2	(0.2%)

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5 90% , B 70% 12  
 C 5-FU/levamisole 6 5-FU/  
 50% , B C leucovorin .  
 가 NCCTG 5-FU/levamisole, 5-FU/levamisole/leu-  
 covorin 가 6 , 12 4  
 가 B, 1980 NSABP , 5-FU/levamisole/leucovorin  
 C-01 5-FU methyl-CCNU, vincristine 6 가  
 (MOF) 4 가 12  
 가 Moertel 18).  
 Duke C 5-FU  
 levamisole 1 40%, 5-FU  
 33% 9 1990  
 NIH Consensus Development Conference Duke C , B2  
 5-FU levamisole 1 5 95%, 95%  
 7). 78%, 80%  
 (p=0.025, p=0.045), C  
 가 5  
 가 90%, 97%  
 5-FU 52%, 55%  
 (p=0.011, p=0.0002)(Figure 2A, B).  
 N-(phosphonacetyl)-L-aspartic  
 acid(PALA)14, interferon15, leucovorin16  
 , 5-FU leucovorin 5-FU  
 5-FU/leucovorin , B2  
 가 1987 5 94%, 97%  
 . NSABP C-03 leucovorin 80%, 82%  
 500 mg 5-FU (p=0.036, p=0.028), C  
 (5-FU 500 mg/m2 leucovorin 500 mg/m2 every  
 week for 48 weeks). NSABP C-01 67%, 87% ,  
 가 MOF (p=0.169),  
 , 5-FU/leucovorin MOF 5 77%,  
 30% 3 96%  
 가 II). NCCTG (p=0.045).  
 20 mg leucovorin C 가 B2  
 5-FU/leucovorin  
 (5-FU 425 mg/m2 x 5 days IVB. leucovorin 20 mg/m2  
 x 5 days IVB every 4 weeks, 6 cycles).  
 6 가 .  
 5 17). IMPACT B2  
 40%, 33% 5-FU/ leucovorin

: 59 3 481 2000 -  
 5 5 85% 80%  
 73% 76% , 5 80% 가 5-FU  
 82% B2 가 60%  
 C-01 C-04 19), NSABP 가  
 B2 C 5-FU 가 61%  
 20), B2가 . 5-FU 5 가  
 C 5-FU B2 93% (p=0.542), 5-FU 가  
 C 5 5-FU 96% 5 71%, 69%  
 5 60-70% (p=0.987). 5-FU 가  
 B2 B2 5 6  
 5-FU 36% 7% 6 C 10  
 가 B2 (p=0.004). 9  
 가 (p=0.003).

**Table 2. Stepwise recurrence according to cycles**

No. of cycles	B2		C	
	No. of patients	No. of recur ( )*	No. of patients	No. of recur ( )*
1	-	-	1	0
2	1	0	3	2(1)
3	2	2(1)	3	2(1)
4	5	1	1	0
5	3	1	2	2(1)
6	35	2	4	1
7	3	2	1	0
8	4	1(1)	2	1(1)
9	2	0	5	3(3)
10	-	-	3	0
11	1	0	1	0
12	22	0	29	5
13	3	0	2	0
14	-	-	1	0
Total	81	9(2)	58	16(7)

( )\* ; means the number of recurrence during the adjuvant chemotherapy

**Table 3. Univariate and multivariate analysis of dose related factors influencing disease-free survival and overall survival**

factors	5- year DFS	p- value*	p- value †	5- year OS	p- value ‡	p- value §
5-FU dose		0.0018	0.0016		0.0011	0.0007
above the median	94			96		
below the median	71			79		
Actual DI		0.7576			0.4604	
above the median	81			90		
below the median	86			86		
Relative DI		0.7576			0.4604	
above the median	81			90		
below the median	86			86		
No. of cycles		0.0509			0.1673	
above the median	94			94		
below the median	79			86		

\* ; univariate analysis of 5-year DFS within each factor, † ; multivariate analysis of 5-year DFS, among the factors, ‡ ; univariate analysis of 5-year OS within each factor, § ; multivariate analysis of 5-year OS among the factors, ; means the delivered total dose of 5-FU per body square meter

, B2 6 (p=0.012), Duke C (p=0.275), 5-FU/levamisole 5-FU/LV 가 가 (Table 2).

Table 3 5-FU Duke B2, C 5-FU leucovorin (1) 5-FU total dose (2) 5-FU dose intensity : 1990 1 1996 12

가 Duke B2, C 5-FU/LV 139 5-FU/LV 5-FU 가 3-4 5-FU 400 mg/m2 leucovorin 20 mg/m2 1 5 4 1 : B2 5 86.2% C 5 68.9% B2 5 87.1% C 5



75.7% , B2 C 가 5 (B2;  $p=0.025$ ,  $p=0.045$ , C;  $p=0.011$ ,  $p=0.0002$ ).

5-FU , 5-FU : 가

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