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Abstract

Objective

The efficacy of oral fluoropyrimidine carmofur was evaluated for adjuvant use for breast cancer.

Methods

150 patients with breast cancer of T0N1, T1, N1, T2N0, and T2N1 were randomized to 100 for carmofur and 50 for carboquone. Both drugs were administered continuously for 28 days cyclically for 5 years with a cessation period of 28 days for carmofur and 56 days for carboquone.

Results

Overall survival excluding non-breast cancer death was 90% for the carmofur group and 88% for the carboquone group, adjusted by Cox's regression analysis. Difference in drug never affected survival. Leukocyte count was decreased in the carboquone group, but no change in serum transaminase was found in either group. Ten patients, 5 for carmofur and 5 for carboquone, suffered from second malignancy, more than expected in the normal population, but difference in the cumulative rate of each group was not significant.

Conclusion

Adjuvant use of carmofur as well as carboquone is beneficial for early breast cancer.

Key Words: Carmofur; Adjuvant use; Breast cancer

Introduction

Carmofur is one of the derivative precursors of 5-fluorouracil (5-FU). Activated not only by the liver but also by extrahepatic route, it yields a higher blood 5-FU level than oral use of tegafur or 5-FU. Leukocytopenia is seldom observed at its ordinary dose level. In order to confirm the efficacy for safe prophylaxis of recurrence for breast cancer, it was compared with carboquone as a standard.

Patients and Methods

We administered adjuvant chemotherapy to 150 postoperative patients with T0N1, T1, N1,

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T2N0, T2N1 breast cancer[1,2], who had 2.1 to 5.0 cm size tumor in longest diameter and had no axillary nodes with mutual or surrounding adhesion. All patients had to undergo mastectomy or total glandectomy with axillary dissection. For 100 patients, carmofur was given in a daily dose of 400 mg divided twice, for 28 consecutive days followed by 28 days of cessation. For 50 patients for comparison, carboquone was given in a daily dose of 0.5 mg divided twice, for 28 consecutive days followed by 56 days of cessation. These were continued for five years postoperatively unless recurrence was observed. Patients were enrolled in this study with random envelope method, after confirming their consent between December 1988 and August 2000. Patients who could not refrain from drinking alcohol were excluded from randomization. Survival rates were calculated by the Kaplan-Meier method. In the calculation of local relapse-free rates, patients for whom distant recurrence preceded a local one were regarded as censored. Expected number of second primary carcinoma was estimated by person-year method with Cancer Registry Data of internet[3].

Results

In August 2002, the median follow-up period was 74 months (range, 18 to 160). A total of 118 patients were alive without recurrence, 13 alive with recurrence, 18 had died of breast cancer and one patient had died of renal cancer. Six had bilateral breast cancer and four had other cancer (colon 2, renal 1 and thymoma 1).

The background of patients is shown in Table 1. The average number of metastatic nodes was

Table 1. Background of patients, number of patients or average ± SD for the two groups

		Carmofur	Carboquone	p-value
Number of patients enrolled		100	50	
Age, years		52.1 ± 9.4	52.2 ± 10.1	0.231
	39 or less	4	5	NS
	40-49	45	17	
	50-59	27	16	
	60-69	18	9	
	70-79	6	3	
Longest tumor diameter, cm		3.4 ± 0.9	3.3 ± 0.9	0.205
TN	T0N1	0	1	0.005
	T1N1	2	0	
	T2N0	80	43	
	T2N1	18	6	
Number of metastatic nodes		2.1 ± 4.2	1.2 ± 3.1	0.005
	0	53	33	0.005
	1-3 by level 2	24	11	
	4 or more by level 2	12	4	
	level 3	11	2	
Histology				NS
	In situ lobular	1	0	
	Invasive lobular	3	1	
	Medullary	2	0	
	Mucinous	1	0	
	Non-invasive	1	2	
	Papillotubular	31	18	
	Scirrhous	29	15	
	Solid tubular	32	14	
Body height, cm		154.0 ± 5.8	154.0 ± 5.6	0.255
Body weight, kg		54.7 ± 7.7	54.5 ± 6.2	0.204
Cumulative rate (percentages) of drug discontinuation at five years				
	Due to patient wish	26.5 ± 6.5	28.6 ± 9.5	0.496
	Due to all cause	42.6 ± 8.7	42.6 ± 12.3	0.387

Differences between two groups were calculated by Fishers direct calculation or chi-square test for contingency table, t-test for average and log-rank test for cumulative rate.

Table 2. Five-year survival rates calculated by Kaplan-Meier method

Type survival	Carmofur1 5 year survival	Carboquone 5 year survival	p-value
Overall	86 ± 4 (90)	96 ± 3 (88)	0.246 (0.149)
Relapse-free	77 ± 6 (81)	87 ± 6 (80)	0.150 (0.305)
Distant disease-free	79 ± 5 (82)	91 ± 5 (84)	0.135 (0.167)
Locally relapse-free	97 ± 2 (97)	93 ± 4 (93)	0.320 (0.158)

Numbers in parentheses are adjusted values calculated by Cox's regression analysis, taking into account the number of metastatic nodes, age, body height, body weight, longest tumor diameter, tumor mediality, and pectoral muscle resection.

Table 3. Multiple regression coefficient and p-values calculated by Cox's regression analysis

	Overall		Relapse-free		Distant disease-free		Local relapse-free	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Five-year result	90%		81%		83%		96%	
Number of metastatic nodes	-0.129	0.001	-0.105	0.001	-0.115	0.001	-0.041	0.149
Age, year	0.024	0.204	0.023	0.186	0.023	0.182	0.032	0.225
Body height, cm	-0.027	0.192	0.013	0.298	0.017	0.252	-0.036	0.214
Body weight, kg	0.009	0.354	0.012	0.292	-0.003	0.436	0.017	0.324
Longest tumor diameter, cm	-0.014	0.274	-0.009	0.312	-0.008	0.342	-0.027	0.225
Tumor mediality, 1=yes; 0=no	-0.047	0.038	-0.017	0.220	-0.006	0.378	-0.046	0.133
Pectoral muscle resection, 1=removed; 0=preserved	0.018	0.228	0.013	0.260	0.023	0.155	-0.043	0.143

significantly larger in the carmofur group than in the carboquone group. Rate of drug discontinuation was same in each group and it was not due to leucocytopenia.

Four types of survival at five years postoperatively are shown in Table 2. No significant difference was found in these survivals between two groups with or without Cox's regression analysis. Overall survival excluding non-breast cancer death was 86% for the carmofur group and 96% for the carboquone group. With adjustment by Cox's regression analysis, these values were reversed, as 90% and 88%. In Cox's regression analysis, number of metastatic nodes was the only significant prognostic factor, while age, body height, body weight, longest tumor diameter, tumor mediality, and pectoral muscle resection were not (Table 3).

Nine patients suffered second primary cancer, a rate significantly higher than that from the incidence in Osaka Prefecture (Table 4). However the number of second cancer for the two groups did not significantly differ.

Yearly change in laboratory data is shown in Table 5. Postoperative leukocyte count was significantly lower for the carboquone group during the 5 years of drug taking. Aspartic aminotransferase (AST) exhibited no change during the 5 postoperative years.

Discussion

Carmofur is an oral fluoropyrimidine yielding a higher plasma 5-FU level than other fluoropyrimidines[4]. Sporadic reports of liver damage by fluoropyrimidine[5-8] suggest that it is beneficial for low dose and long-term use[9,10]. The efficacy of carmofur was established by an objective response in breast cancer[11], and colon cancer[12], pancreatic cancer[13], and stomach cancer[14], but not by adjuvant use. Adjuvant use for hepatocellular carcinoma was not successful[15,16]. Despite a negative report[17], many hopeful findings have been reported for head and neck carcinoma[18],

Table 4. Number of second primary cancer observed and expected from the incidence in Osaka Prefecture

Second primary	Postoperative adjuvant	Number of expected	Number of observed	Percetage of Observed/Expected	p-value	5-year percentage cumulative rate	p-value
All kinds	Total	3.53	10	11.9	0.007	4.3	
(Breast)		(0.87)	(6)	(30.2)	(0.001)	(2.1)	
	Carboquone	1.26	5	11.0	0.019	8.2	0.224
		(0.29)	(3)	(25.0)	(0.007)	(4.0)	0.274
	Carmofur	2.27	5	3.3	0.160	3.4	
		(0.58)	(3)	(10.2)	(0.042)	(1.2)	

p-values were calculated by Poisson distribution according to person-year for O/E ratio and Logrank-test for cumulaitve rates between two groups.

Table 5. Yearly changes in white blood cell count (WBC) and aspartic aminotransferase (AST)

			Before	Postperative years						
			mastectomy	1	2	3	4	5	6	>6
WBC	Carmofur	No. of data	72	89	82	78	69	63	26	22
		Average	55	54	51	51	50	50	55	55
		SD	8	8	7	7	7	7	8	8
	p-value*1			0.495	0.061	0.056	0.06	0.102	0.088	0.104
	Carboquone	No. of data	34	45	44	42	38	30	16	13
		Average	56	47	45	43	43	45	53	50
		SD	8	7	7	7	7	7	8	7
	p-value*1			0.006	0.275	0.248	0.256	0.264	0.211	0.108
	p-value*2		0.218	<0.001	0.008	0.005	0.003	0.01	0.205	0.164
AST	Carmofur	No. of data	72	89	82	78	69	63	23	23
		Average	23	23	24	24	25	28	27	25
		SD	5	5	5	5	5	6	5	5
	p-value*1			0.365	0.092	0.073	0.067	0.109	0.166	0.152
	Carboquone	No. of data	34	45	44	42	37	30	16	14
		Average	26	25	25	26	27	26	26	27
		SD	6	5	5	5	5	5	5	5
	p-value*1			0.371	0.035	0.026	0.051	0.072	0.167	0.14
	p-value*2		0.131	0.131	0.151	0.054	0.128	0.191	0.146	0.127

p-values were calculated by Student's t-test.
*1, compared with preoperative data; *2, compared between two groups

colon cancer[19-23] and stomach cancer[24]. Experimental data have suggested the possibility of a wider spectrum of efficacy for carmofur than for 5-FU[25]. Adjuvant efficacy for breast cancer has not been reported but was expected based on these encouraging findings. Because of these highly optimistic data, we adopted the twice rate allocation for carmofur.

As a standard for comparison, we used carboquone, because we found it to be effective for breast cancer for adjuvant use[26]. Since about 10% odds reduction for cancer death is expected with the adjuvant use of cytotoxic chemotherapy for breast cancer[27], carboquone is a reasonable drug for use as an adjuvant.

Because it increases the risk of liver metastasis[28], alcohol intake is not recommended. Carmofur inhibits aldehyde dehydrogenase more than methylthiotetrazole[29] and enhances

alcohol toxicity. We found that some patients could not refrain from drinking alcohol during carmofur treatment, even with a repeated explanation of its risk.

Heat sensation, a central nervous system effect of carmofur itself, is decreased by simultaneous oral use of hydroxyaluminium gel without decrease of 5-FU level[30].

The neurotoxicity of carmofur appears to be a direct effect of fluoro-β-alanine on myelinated neural fibers[31]. Although its true incidence is not known, leucoencephalopathy is often reported during or after use of carmofur[32-34], and magnetic resonance imaging appears to be effective for earlier detection of and diagnostic differentiation from geriatric brain damage[35-37].

We experienced 10 patients who suffered second primary malignancy, a slightly higher incidence than in the normal population. Although the difference was not significant, the cumulative rate in the carboquone group was twice that in the carmofur group. This complication was found to have a major impact on survival in early breast cancer[38]. Among breast cancer after mastectomy contralateral breast cancer and stomach cancer were most common[39,40] and mitomycin C appeared to have a major effect on the rate of occurrence of second cancer, as did radiation on those of leukemia and esophageal cancer[40]. On the other hand, chemoradiotherapy appears never to affect the risk of second cancer[41,42].

Despite the potential hepatotoxicity of carmofur[43], our patients exhibited no change in transaminase levels. Several patients had their drug discontinued, but the number of such patients was the same in each group. Discontinuation of adjuvant use of oral fluoropyrimidine was more common than for CAF or CMF[44], although simple oral use seems to be well-accepted. Fortunately, we have experienced no neurotoxicity or liver dysfunction, probably because we prescribed carmofur with intervals of cessation. Leukocytopenia was apparent in the carboquone group, but it did not increase the rate of discontinuation of adjuvant chemotherapy. Although a care might be needed to avoid serious toxicity, carboquone is never a drug to be abondoned for adjuvant use.

Adjuvant use of carmofur as well as carboquone thus appears to be beneficial for early breast cancer.

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