Cancer Chemother Pharmacol (1993) 33: 171–175

Cancer Chemotherapy and Pharmacology

Postoperative PSK and OK-432 immunochemotherapy for patients with gastric cancer

Yoshihiko Maehara[1], Sadaaki Inutsuka[2], Hideya Takeuchi[2], Hideo Baba[2], Hiroki Kusumoto[2], Keizo Sugimachi[1, 2]

[1] Department of Surgery II, Faculty of Medicine, Kyushu University Fukuoka, Japan
[2] Cancer Center of Kyushu University Hospital, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Received 23 April 1993/Accepted 2 July 1993

Abstract. We evaluated the effects of chemotherapy given postoperatively with and without immunomodulators on the survival of patients who had undergone resection for gastric cancer. We conducted a retrospective survey of data on 963 Japanese patients treated at our department of surgery between 1965 and 1987. Data related to the duration of postoperative survival were calculated for those who received chemotherapy, i.e. an individualized combination of various agents given with or without the immunomodulators PSK, a protein extract of the fungus *Coriolus versicolor*, and/or OK-432, a preparation of an attenuated strain of *Streptococcus* (immunochemotherapy). Postoperative immunochemotherapy was more often prescribed for patients with advanced disease. The survival of patients who received immunochemotherapy was shorter than that of patients who received only chemotherapy. In a subgroup of patients adjusted for disease stage, the survival of those on chemotherapy versus immunochemotherapy did not differ significantly at any stage. For optimal results, a protocol for postoperative immunochemotherapy needs to be designed and investigated prospectively and according to the stage of gastric cancer. The stage III gastric cancers seem amenable to a favorable response.

Introduction

Postoperative long-term cancer chemotherapy for patients with gastric cancer has included a combination of mitomycin C (MMC), 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur), and an immunomodulator (PSK and/or OK-432) [1, 11, 14, 18, 21]. PSK is a protein-bound preparation extracted from *Coriolus versicolor*, a basidiomycete [29]. OK-432 is a lyophilized preparation of an attenuated strain of *Streptococcus* [30]. These two agents have exhibited marked effects on host defense mechanisms in Japanese cancer patients treated in Japan. We previously reported that the combined administration of mitomycin C, tegafur, and PSK for 1 year postoperatively prolonged the survival of patients with advanced gastric cancer following curative resection as compared with that of the no-chemotherapy group as determined in a retrospective study [18]. In an analysis based on factors of serosal invasion (ps) and lymph-node metastasis (n), this adjuvant chemotherapy is effective for patients with ps(+)n(–) and ps(–)n(+). As the effectiveness of postoperative immunochemotherapy has been investigated in only a limited subset of gastric cancers, the effectiveness of immunomodulators has remained to be defined [19]. As a retrospective analysis should aid in determining whether such drugs should be prescribed at each stage of gastric cancer, we examined our files concerning the duration of survival of patients with various stages of gastric cancer who had been given such drugs.

Patients and methods

Patients. Between 1965 and 1987, 963 Japanese patients with gastric cancer and no evidence of any other malignancy underwent gastric resection followed by the postoperative administration of anticancer drugs. All were treated in the Department of Surgery II, Kyushu University Hospital. Of those 963 patients, 627 (65.1%) were given postoperative chemotherapy and 336 (34.9%) were additionally given immunomodulators (immunochemotherapy). Pathological diagnosis and classification of the resected gastric cancer tissues were carried out according to the General Rules for the Gastric Cancer Study in Surgery and Pathology in Japan [8, 9]. Gastric resection based on lymph-node dissection was classified as follows: R0, gastric resection including the incomplete removal of group 1 lymph nodes; R1, gastric resection including the complete removal of group 1 lymph nodes alone; R2, gastric resection including the complete removal of group 1 and 2 lymph nodes; and R3, gastric resection including the complete removal of group 1, 2, and 3 lymph nodes [8].

Postoperative chemotherapy. A total of 627 patients received postoperative chemotherapy, including a combination of MMC; the fluorinated

Correspondence to: Y. Maehara, Department of Surgery II, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan

pyrimidines tegafur, UFT [uracil/tegafur (4 : 1)], and 1-hexylcarbamoyl-5-fluorouracil; thiotepa; cyclophosphamide; neocarzinostatin; carboquone; doxorubicin; aclarubicin; and bleomycin. Drug combinations and dosing varied from patient to patient. Postoperative immunochemotherapy was given to 336 patients by adding PSK (284 patients) and/or OK-432 (103 patients) to the chemotherapy.

Statistical analysis. The BMDP statistical package program (BMDP, Los Angeles, Calif.) for the IBM (Armonk, NY) 4381 mainframe computer was used for all analyses [2]. The BMDP P4F and P3S programs were used for the chi-square test and the Mann-Whitney test to compare data on patients who received immunochemotherapy versus those given chemotherapy alone. The BMDP P1L program was used to analyze survival data by the Kaplan-Meier method, and the generalized Wilcoxon test was used to test for equality of the survival curves. The level of statistical significance was $P < 0.05$.

Results

Clinicopathological factors

Table 1 shows clinicopathological data on the 627 patients who received chemotherapy and the 336 who were given immunochemotherapy. All had undergone gastric resection prior to treatment. For patients given immunochemotherapy, lymph-node metastasis was more prominent, and the rates of lymphatic involvement and peritoneal dissemination were higher. Thus, in this group the tumor was more advanced and the rate of noncurative resection was higher (38.1%). Stage distribution into two groups based on the General Rules for the Gastric Cancer Study in Surgery and Pathology in Japan [8] revealed that more advanced cases were prescribed immunochemotherapy ($P = 0.000$; Fig. 1).

Survival

The postoperative survival curve generated for patients who received immunochemotherapy was compared with the curve obtained for those given chemotherapy. Analysis of the postoperative survival curves determined for all patients excluded 10 patients (1.0%) who died within the first 30 postoperative days and 5 (0.5%) for whom data on survival duration could not be determined. The survival of patients who received immunochemotherapy was lower than that of patients given chemotherapy ($P = 0.000$; Fig. 2); the 10-year survival was 52.1% for patients given postoperative chemotherapy and 39.2% for those given postoperative immunochemotherapy. In a subgroup of patients stratified to adjust for disease stage, we observed no significant difference in survival at any stage of the disease (stage I, $P = 0.143$; stage II, $P = 0.371$; stage III, $P = 0.092$; stage IV, $P = 0.695$; Fig. 3).

Discussion

PSK given orally as a host-mediated, nonspecific immunomodulator blocks serum-suppressive factors [24], restores interleukin 2 (IL-2) production in the tumor-bearing host [12], and augments the cytotoxicity of lymphocytes [22].

Table 1. Clinicopathological factors in patients with gastric cancer treated with chemotherapy or immunochemotherapy

Variable	Chemotherapy ($n = 627$)	Immunochemotherapy ($n = 336$)	P value
Age (years)	56.9 ± 12.1[a]	59.7 ± 12.9	$P = 0.001$
Sex:			
M	416 (66.3%)	203 (60.4%)	$P = 0.067$
F	211 (33.7%)	133 (39.6%)	
Maximal tumor diameter (cm)	6.71 ± 3.99	8.39 ± 4.18	$P = 0.000$
Tumor location:			
Upper	131 (20.9%)	107 (31.8%)	$P = 0.000$
Middle	217 (34.6%)	94 (28.0%)	
Lower	279 (44.5%)	135 (40.2%)	
Serosal invasion:			
Negative	296 (47.2%)	92 (27.4%)	$P = 0.000$
Positive	331 (52.8%)	244 (72.6%)	
Histology:			
Differentiated	293 (46.8%)	145 (43.4%)	$P = 0.315$
Undifferentiated	333 (53.2%)	189 (56.6%)	
Others[a]	1	2	
Lymphatic involvement:			
Negative	249 (49.9%)	123 (37.3%)	$P = 0.000$
Positive	250 (50.1%)	207 (62.7%)	
Unknown[b]	128	6	
Vascular involvement:			
Negative	382 (80.4%)	255 (79.9%)	$P = 0.867$
Positive	93 (19.6%)	64 (20.1%)	
Unknown[b]	152	17	
Histological growth pattern:			
Expansive	101 (17.5%)	49 (15.0%)	$P = 0.427$
Intermediate	182 (31.5%)	97 (29.8%)	
Infiltrative	294 (51.0%)	180 (55.2%)	
Unknown[b]	50	10	
Histological lymph-node metastasis:			
Negative	251 (40.1%)	93 (27.7%)	$P = 0.003$
Positive	375 (59.9%)	243 (72.3%)	
Unknown[b]	1	0	
Peritoneal dissemination:			
Negative	574 (91.5%)	284 (84.5%)	$P = 0.001$
Positive	53 (8.5%)	52 (15.5%)	
Liver metastasis:			
Negative	595 (94.9%)	310 (92.3%)	$P = 0.102$
Positive	32 (5.1%)	26 (7.7%)	
Gastric resection:			
Partial	383 (61.7%)	169 (50.4%)	$P = 0.001$
Total	238 (38.3%)	166 (49.6%)	
Unknown[b]	6	1	
Lymph-node dissection:			
R1	122 (19.5%)	90 (26.8%)	$P = 0.203$
R2, R3	505 (80.5%)	246 (73.2%)	
Curability:			
Curative	451 (71.9%)	208 (61.9%)	$P = 0.001$
Noncurative	176 (28.1%)	128 (38.1%)	

NS, No significant difference

[a] Mean value ± SD

[b] Cases excluded from statistical analysis

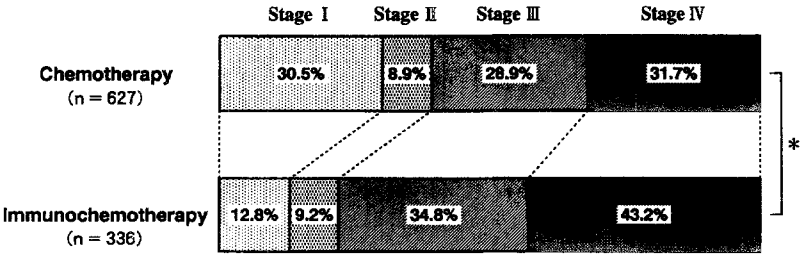

Fig. 1. Distribution of tumor stage between the chemotherapy and immunochemotherapy groups. Tumor size was more advanced in the immunochemotherapy group, with the difference reacting statistical significance (* $P = 0.000$)

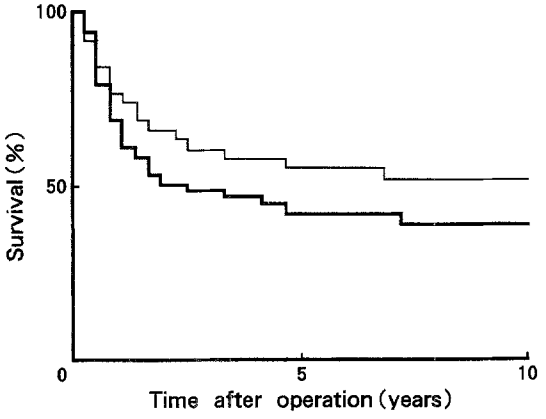

Fig. 2. Survival curve generated for patients with gastric cancer treated by gastric resection plus postoperative chemotherapy or immunochemotherapy. A total of 627 patients received postoperative chemotherapy (*thin line*) and 336 patients received postoperative immunochemotherapy (*thick line*). The difference in the duration of survival reached statistical significance ($P = 0.000$)

These factors may explain the antitumor activity of PSK [29]. OK-432 stimulates lymphocyte-mediated and macrophage-mediated immunity [7, 10] as well as direct cytostatic and cytotoxic activities against malignant cells [15]. In cases of gastric cancer, the intraperitoneal administration of OK-432 can lead to a reduction in or the disappearance of cancerous ascites and tumor cells [25]. This agent may also prevent peritoneal recurrence when the gastric cancer cells invade the serosa [27].

Our objective in conducting this retrospective study was to examine whether postoperative adjuvant immunochemotherapy, including the administration of PSK and/or OK-432, might lead to a prolongation of the survival of patients with gastric cancer. The approach to postoperative treatment in Japan is quite different from that in Western countries [3]. In Japan, chemotherapy, including immunotherapy, is initiated either intraoperatively or in the very early postoperative period. The protocol of the study we documented was as follows: MMC given at 20 mg by intravenous injection on the day of the operation and at 10 mg every 3 months thereafter for 1 year; tegafur at 600 mg and PSK at 3 g daily per os were prescribed from 7 to 10 days after the operation for as long as possible [18]. In Western countries, chemotherapy is usually not begun until 4–6 weeks postoperatively, and a delay in postoperative treatment has been found to lead to negative results [13]. Fielding et al. [5] found no positive effects for adjuvant chemotherapy with MMC plus 5-FU, but the survival of their patients was lengthened when treatment was begun within 1 month postsurgery. As the doubling time of tumor cells is often shorter in a small population focus than in a larger one, tumor foci remaining after surgery are expected to be more sensitive to anticancer drugs [6, 23]. Estape et al. [4] have reported that adjuvant MMC after curative resection is an effective treatment and that its effects remain evident after 10 years of follow-up.

Longer survival has been reported for patients who receive postoperative immunochemotherapy than for those who do not, particularly for a limited subset of gastric cancers, in studies using selected chemotherapeutic regimens [1, 11, 14, 18, 21]. The immunochemotherapy consisted of the combination of MMC, tegafur, and OK-432 for stage III gastric cancer [1], the combination of MMC, tegafur, and PSK for advanced gastric cancer [11, 18, 21], and tegafur and OK-432 for advanced gastric cancer [14]. In a previous report, we described that postoperative chemotherapy, including immunochemotherapy, was too closely associated with other prognostic covariants for it to have an independent prognostic significance for patients with gastric cancer as determined in a multivariate analysis [19]. In prescribing an immunomodulator for patients with gastric cancer, the character of the tumor and the immune response of the host must be considered, then the optimal chemotherapeutic regimen can be designed for each individual patient [16, 17, 19, 20].

Early-stage gastric cancer can be controlled either because the tumor is curatively resected or because the small number of residual tumor cells are destroyed by the host immune system. Advanced stage IV gastric cancer has a poor prognosis because immunochemotherapy is not very effective for unresectable tumors. Tsujitani et al. [28] analyzed the effects of PSK in patients with stage III gastric cancers at the point of infiltration of the tumor by dendritic cells. These cells function as accessory tissues that present antigens to sensitized T-cells and have the potential to stimulate antigen-specific T-cells [26]. In cases of a slight infiltration by dendritic cells, the survival was prolonged, as the ingestion of PSK apparently led to the activation of immune activity. Thus, stage III tumors would seem to be the gastric cancers most amenable to postoperative immunochemotherapy.

As our findings show that patients with stage III gastric cancer can respond favorably to immunochemotherapy including PSK and/or OK-432 ($P = 0.092$), a prospective study on the effects of immunotherapy in such patients should be informative.

Acknowledgements. We thank M. Ohara for helpful comments.

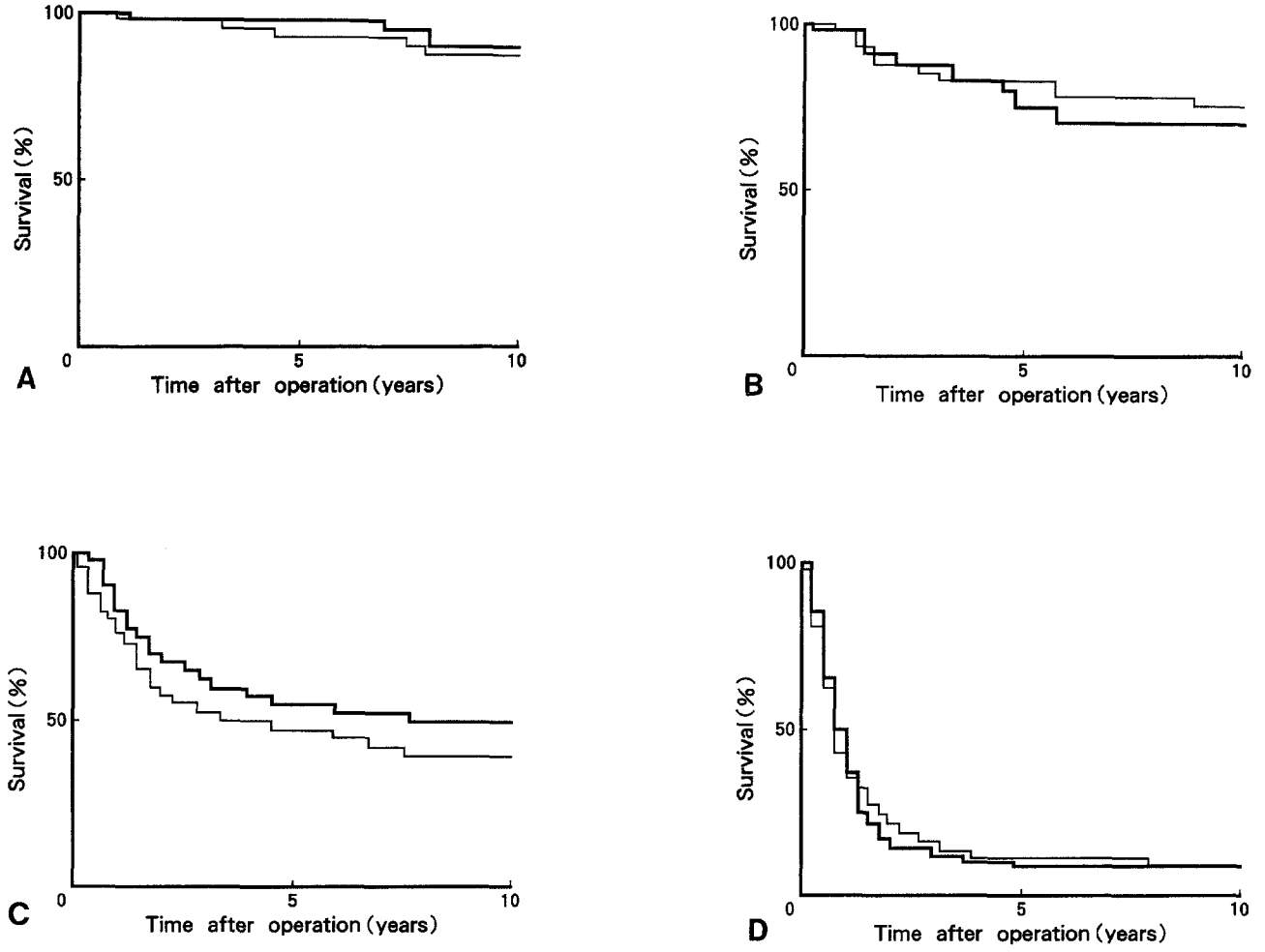

Fig. 3 A – D. Survival curves for patients with gastric cancer treated by chemotherapy or immunochemotherapy as generated at each stage of the disease. **A** Patients with stage I disease given chemotherapy ($n = 191$) versus those given immunochemotherapy ($n = 43$; $P = 0.143$). **B** Patients with stage II disease given chemotherapy ($n = 56$) versus those given immunochemotherapy ($n = 31$; $P = 0.371$). **C** Patients with stage III disease given chemotherapy ($n = 181$) versus those given immunochemotherapy ($n = 117$; $P = 0.092$). **D** Patients with stage IV disease given chemotherapy ($n = 199$) versus those given immunochemotherapy ($n = 145$; $P = 0.695$). *Thin lines*, patients given chemotherapy; *thick lines*, those given immunochemotherapy

References

1. Arinaga S, Karimine N, Takamuku K, Nanbara S, Inoue H, Abe R, Watanabe D, Matsuoka H, Ueo H, Akiyoshi T (1992) A trial of adjuvant chemoimmunotherapy with mitomycin C and OK-432 for stage III gastric carcinoma. J Surg Oncol 50: 187
2. Dixon WJ (ed) (1988) BMDP statistical software. University of California Press, Berkeley, p 229
3. Douglass HO (1985) Gastric cancer: overview of current therapies. Semin Oncol 12 [Suppl 4]: 57
4. Estape J, Grau JJ, Lcobendas F, Curto J, Daniels M, Vinolas N, Pera C (1991) Mitomycin C as an adjuvant treatment to resected gastric cancer. A 10-year follow-up. Ann Surg 213: 219
5. Fielding JWL, Fagg SL, Jones BG, Ellis D, Hockey MS, Minawa A, Brookes VS, Craven JL, Mason MC, Timothy A, Waterhouse JAH (1983) An interim report of a prospective, randomized, controlled study of adjuvant chemotherapy in operable gastric cancer: British Stomach Cancer Group. World J Surg 7: 390
6. Gunduz N, Fisher B, Saffer EA (1979) Effect of surgical removal on the growth and kinetics of residual tumor. Cancer Res 39: 3861
7. Ishii Y, Yamaoka H, Toh K, Kikuchi K (1976) Inhibition of tumor growth in vivo and in vitro by macrophages from rats treated with a streptococcal preparation, OK-432. Jpn J Cancer Res 67: 115
8. Japanese Research Society for Gastric Cancer (1981) The General Rules for the Gastric Cancer Study in Surgery and Pathology. I. Clinical classification. Jpn J Surg 11: 127
9. Japanese Research Society for Gastric Cancer (1981) The General Rules for the Gastric Cancer Study in Surgery and Pathology. II. Histological classification of gastric cancer. Jpn J Surg 11: 140
10. Kai S, Tanaka J, Nomoto K, Torisu M (1979) Studies on the immunopotentiating effect of a streptococcal preparation, OK-432. I. Enhancement of T-cell-mediated immune responses of mice. Clin Exp Immunol 37: 98
11. Kano T, Kumashiro R, Tamada R, Kodama Y, Inokuchi K (1981) Late results of postoperative long term cancer chemotherapy for advanced carcinoma of the stomach. Jpn J Surg 11: 291
12. Kikuchi Y, Kizawa I, Oomori K, Iwano I, Kita T, Kato K (1988) Effects of PSK on interleukin-2 production by peripheral lymphocytes of patients with advanced ovarian carcinoma during chemotherapy. Jpn J Cancer Res 79: 125
13. Krook JE, O'Connell MJ, Wieand HS, Beart RW Jr, Leigh JE, Kugler JW, Foley JF, Pfeifle DM, Twito DI (1991) A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer 67: 2454

14. Kuroda Y, Miura S, Asada Y, Iida A, Mitsui T, Jung Gi K, Katoh Y, Fujisawa K, Minagawa M, Fujisawa M (1989) Evaluation of long-term administration of OK-432 for gastric cancer patients who underwent curative resection – historical control study (in Japanese, with English abstract). Biotherapy 3: 723
15. Ono T, Kurata S, Wakabayashi K, Sugawara Y, Saito M, Ogawa H (1973) Inhibitory effect of a streptococcal preparation (OK-432) on the nucleic acid synthesis in tumor cells in vitro. Jpn J Cancer Res 64: 59
16. Maehara Y, Kusumoto T, Sakaguchi Y, Kusumoto H, Kido Y, Anai H, Sugimachi K (1989) Pyrimidine nucleotide synthesis is more extensive in poorly differentiated than in well-differentiated human gastric carcinoma. Cancer 63: 96
17. Maehara Y, Kusumoto T, Kusumoto H, Anai H, Sakaguchi Y, Kido Y, Okamura T, Korenaga D, Sugimachi K (1989) 5-Fluorouracil and UFT-sensitive gastric carcinoma has a high level of thymidylate synthase. Cancer 63: 1693
18. Maehara Y, Moriguchi S, Sakaguchi Y, Emi Y, Kohnoe S, Tsujitani S, Sugimachi K (1990) Adjuvant chemotherapy enhances long-term survival of patients with advanced gastric cancer following curative resection. J Surg Oncol 45: 169
19. Maehara Y, Emi Y, Moriguchi S, Takahashi I, Yoshida M, Kusumoto H, Sugimachi K (1992) Postoperative chemotherapy for patients with advanced gastric cancer. Am J Surg 163: 577
20. Maehara Y, Sugimachi K, Akagi M, Kakegawa T, Shimazu H, Tomita M (1992) Early postoperative chemotherapy following non-curative resection for patients with advanced gastric cancer. Br J Cancer 65: 413
21. Nakajima T, Inokuchi K, Hattori T, Inoue K, Taguchi T, Kondou T, Abe O, Kikuchi K, Tanabe T, Ogawa N (1989) Multi-institutional cooperative study of adjuvant immunochemotherapy for gastric cancer – five-year survival rate (in Japanese, with English abstract). Jpn J Cancer Chemother 16: 799
22. Nio Y, Shiraishi T, Tsubono M, Morimoto H, Tseng C-C, Imai S, Tobe T (1991) In vitro immunomodulating effect of protein-bound polysaccharide, PSK on peripheral blood, regional nodes, and spleen lymphocytes in patients with gastric cancer. Cancer Immunol Immunother 32: 335
23. Schabel FM (1975) Concepts for systemic treatment of micrometastases. Cancer 35: 15
24. Toge T, Yamaguchi Y, Kegoya Y, Baba N, Yanagawa E, Hattori T (1989) Blocking of lymphocyte surface binding sites for the soluble suppressor factor by protein-bound polysaccharide. PSK. Int J Immunopharmacol 11: 9
25. Torisu M, Katano M, Kimura Y, Itoh H, Takesue M (1983) New approach to management of malignant ascites with a streptococcal preparation. OK-432. I. Improvement of host immunity and prolongation of survival. Surgery 93: 357
26. Tsujitani S, Furusawa T, Tamada R, Okamura T, Yasumoto K, Sugimachi K (1987) Langerhans cells and prognosis in patients with gastric carcinoma. Cancer 59: 501
27. Tsujitani S, Abe Y, Korenaga D, Saitoh A, Watanabe A, Sugimachi K (1990) Intraperitoneal administration of the biological response modifier OK-432 and peritoneal recurrence following gastrectomy. Hepatogastroenterology 37: 498
28. Tsujitani S, Kakeji Y, Orita H, Watanabe A, Kohnoe S, Baba H, Anai H, Maehara Y, Sugimachi K (1992) Postoperative adjuvant immunochemotherapy and infiltration of dendritic cells for patients with advanced gastric cancer. Anticancer Res 12: 645
29. Tsukagoshi S, Hashimoto Y, Fujii G, Kobayashi H, Nomoto K, Orita H (1984) Krestin (PSK) Cancer Treat Rev 11: 131
30. Uchida A, Hoshino T (1980) Clinical studies on cell-mediated immunity in patients with malignant disease. I. Effect of immunotherapy with OK-432 on lymphocyte subpopulation and phytomitogen responsiveness in vitro. Cancer 45: 476