A randomized trial of immunotherapy in combination with chemotherapy for gastric cancer with peritonitis carcinomatosis.

ORIGINAL ARTICLE Annals of Cancer Research and Therapy

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We evaluated the effect of immunotherapy using OK-432 in 67 gastric cancer patients with peritonitis carcinomatosis and investigated markers predicting the response to immunotherapy. All patients were followed up until death. The study enrolled 67 patients with biopsy-proved adenocarcinoma of the stomach associated with peritonitis carcinomatosis, of whom 56 underwent operation and 29 underwent gastrectomy. Seven were inoperative and 4 had recurrence with ascites due to peritonitis carcinomatosis. They were randomly assigned to receive chemotherapy with or without a streptococcal biological response modifier, OK-432.

Overall survival was not improved by OK-432. However, among the patients with a negative SUPS skin reaction before treatment, those who received OK-432 had a significantly better outcome than those without OK-432. Cox multivariate regression analysis indicated that postoperative therapy with or without OK-432 was a significant prognostic factor for patients receiving chemotherapy and immunochemotherapy who had a positive and negative SU-PS skin reaction, respectively.

These results indicate that the pretreatment SUPS skin reaction is a possible predictor of the effectiveness of immunotherapy using OK-432.

Ann Cancer Res Ther 3 (1) : 35~39, 1994 / Received 1 Mar 1994, Accepted 22 Mar 1994

Key words: gastric cancer with peritonitis carcinomatosis, OK-432 SUPS skin reaction

Peritonitis carcinomatosis due to advanced gastric cancer is associated with the worst prognosis along with hepatic metastasis, and many oncological and surgical methods have been tried to improve survival. The effectiveness of immunotherapy has been reported for gastric^{1,2)} and esophageal³⁾ cancer when used in combination with chemotherapy in Japan and as well as for colon cancer in Japan⁴⁾ and the USA⁵⁾. Mitomycin C (MMC), bleomycin (BLM), fluoropyrimidines, PSK, OK-432, and levamisole were used as the chemotherapeutic or immunomodulating agents in these trials.

Torisu et al. reported the resolution of massive ascites induced by peritonitis carcinomatosis after OK-432 was given intraperitoneally, suggesting that this agent may have a beneficial effect on such patients⁶⁾.

OK-432 is a biological response modifier prepared from a low-virulence SU strain of *Streptococcus pyogenes* (group A) of human origin. It has been shown to exert an antitumor effect and to potentiate the cytotoxic

activity of various effector cells as well as inducing various cytokines^{7,8)}.

In Japanese clinical trials, a beneficial effect of OK-432 on gastric cancer was obtained in combination with chemotherapy, but most of the studies performed were not randomized trials. There are many tumor markers available for monitoring disease progression and the effectiveness of treatment, but they are unable to predict the response to therapy⁹⁾.

The present study investigated the efficacy of immunotherapy using OK-432 for gastric cancer associated with peritonitis carcinomatosis, and evaluated the clinical usefulness of the following markers: α 1 antichymotrypsin (ACT)¹⁰⁾, sialic acid (SA)¹¹⁾, immunosuppressive acidic protein (IAP)¹²⁾, and acid soluble glycoproteins (ASP)¹³⁾. These are acute phase reactants (APRs) and have an immunosuppressive effect. In addition, the value of skin tests with purified protein derivative (PPD) and a polysaccharide extracted from the SU strain of *Streptococcus pyogenes* (SUPS) was assessed.

Materials and methods

A randomized controlled study of gastric cancer was undertaken from October 1986 to December 1988 at 16 institutions in Kanagawa Prefecture, Japan. The 67

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Table 1 Variables used in the Cox regression model,

Prognostic factor	Value/score
Sex	① male, ② female
Ascites	① (-), ② (+)
Histopathological types	① well, ② undifferentiated
Therapy	① without OK-432, ② with OK-432

well : papillary, well differentiated or moderately differentiated adenocarcinoma.
undifferentiated : mucinous carcinoma, poorly differentiated adenocarcinoma and signet ring cell carcinoma.

Fig.1 Survival of patients with (—) and without (·····) OK-432 therapy

patients eligible for enrollment in the trial had biopsy-proven adenocarcinoma of the stomach associated with peritonitis carcinomatosis. All the patients gave informed consent to the study. Patients who had a history of other malignancies or double cancer were excluded. Patients with recurrence who had received chemotherapy within 4 weeks were also excluded. Normal serum electrolytes, blood urea nitrogen, and serum creatinine levels, and no cardiac failure were also required. In addition, a white blood cell count of at least 2,000/mm³ and a platelet count of at least 50,000/mm³ were required prior to starting treatment.

Patients were stratified according to sex, resection or non-resection and the nonoperation or recurrence, and then were randomized to receive a treatment regimen with or without OK-432 (Picibanil, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan).

In the immunochemotherapy+surgery group, patients were intraoperatively underwent intraperitoneal administration of OK-432 at a dose of 10 KE (1 KE=0.1mg of dried streptococcal cells) with concomitant intravenous injection of mitomycin (MMC) (Kyowa Hakko Co., Ltd., Tokyo, Japan) at a dose of 0.4mg/Kg. MMC was

Fig.2 Survival of patients with and without gastrectomy according to therapy
Gastrectomy group : patients with (—) and without (·····) OK-432. Nongastrectomy group : patients with (---) and without (-·-·-) OK-432

Fig.3 Survival of 32 patients undergoing SUPS skin testing according to the treatment
Positive SUPS skin reaction group : patients with (·····) and without (---) OK-432. Negative SUPS skin reaction group : patients with (—) and without (-·-·-) OK-432

also given on postoperative day 1. This was followed by oral administration of 1-hexylcarbamoyl-5-fluorouracil (HCFU) (Mitsui Pharmaceutical Co., Ltd., Tokyo, Japan) (400mg/day) from day 14 after surgery. The starting dose of OK-400 was 1 KE on postoperative day 1. The drug was injected intradermally and the dose was increased at 2-day intervals to 3 and 5 KE, after which 5 KE was given at 2-day intervals throughout the hospital stay. After discharge, maintenance therapy was continued with 5 KE once a week for a period of at least 3 months unless there was progression of the cancer. In the patients without surgery, treatment protocol was the

Table 2 Multivariate analysis of factors related to survival in 32 patients with a positive or negative SUPS skin reaction

	SUPS skin test(+)		SUPS skin test(-)		Total	
	Coefficient p value		Coefficient p value		Coefficient p value	
Sex	-1.610	0.098	-1.731	0.016	-0.506	NS
Ascites	2.290	0.020	0.716	NS	0.295	NS
Histology	-1.225	NS	-0.054	NS	-0.464	NS
Therapy	1.933	0.049	-2.191	0.005	-0.841	NS

NS : $p > 0.1$

same except for no operation.

Among the 67 patients enrolled, 6 (8.9%) patients died within 30 days of starting treatment because of tumor progression, and 2 (3.0%) were lost to follow up.

Thirty-five patients were assigned to the chemotherapy group (18 received gastrectomy, 12 were not resected, and 5 had recurrent or inoperable disease) and 32 to the immunochemotherapy group (11 received gastrectomy, 14 were not resected, and 7 had recurrent or inoperable disease). Four patients died within 30 days and one was lost to follow up in the immunochemotherapy group, while the respective numbers were 2 and 1 in the chemotherapy group.

Pretreatment blood samples were collected from each hospital and taken to Mitsubishi Yuka BCL Co., Ltd., where the serum levels of APRs were examined. Forty-one patients had the serum levels of APRs determined. The serum ACT levels was determined by the single radial immunodiffusion method using antisera and standards supplied by the Department of Molecular Life Science (Tokai University, Japan). The serum SA level was determined using a modified resorcinol reagent kit (Kyokuto sialic acid test, Kyokuto Pharmaceutical Co., Ltd., Tokyo, Japan). The level of IAP, which is closely related to α -1-acid glycoprotein, was determined using a commercial kit (IP plate, Sanko Junyaku Co., Ltd., Tokyo, Japan). The level of ASP, a perchloric acid soluble glycoprotein, was determined with an ASPRO-GP kit (Otsuka Assay Laboratories Co., Ltd., Tokushima, Japan). ASP is almost identical to the seromucoid determined by Winzler's method.

In this study, the reference value for ACT, SA, IAP, and ASP were defined as $280\mu\text{g/ml}$, $85.3\mu\text{g/dl}$, $558\mu\text{g/ml}$ and 148mg/ml , respectively¹³⁻¹⁶.

Among the 67 patients, 32 were tested for their skin reaction to PPD and SUPS. SUPS (Chugai Pharmaceutical Co., Ltd.), or PPD was injected intradermally at dose of $20\text{ mg}/0.1\text{ml}$ and $0.05\text{mg}/0.1\text{ml}$, respectively. The erythematous skin reaction was measured after 48 hours and 24 hours, respectively, with erythema greater than 10 mm wide taken as positive.

Survival was assessed from the day of operation or

initiation of treatment until death. Sixty-five patients were followed up until death. Survival curves were produced using the Kaplan-Meier method and differences in survival were assessed by the log-rank test.

In 32 patients who were assessed for the SUPS skin reaction, multivariate analysis utilizing Cox's model was performed with four variables : sex, histological grade, ascites, and treatment with or without OK-432. The variables employed in the Cox regression model are shown in Table 1.

Results

The patients ranged from 33 to 78 years old (median : 58 years) and 59.7% were men.

It was difficult to determine the toxicity related to treatment, because of the death of some patients within 30 days due to tumor progression. In the chemotherapy group, nausea was noted in 2 patients. Nausea and high fever were noted in one patient from the immunochemotherapy group. These patients could not continue therapy until death.

The 2-year survival rates of the patients with and without OK-432 therapy were 6.5% and 2.9%, respectively (Fig.1). There was no significant difference in survival between the immunochemotherapy group and the chemotherapy group. For patients with or without gastrectomy, there were no significant differences in survival between the chemotherapy and immunochemotherapy groups (Fig.2). There was also no significant difference in survival between the patients with abnormal or normal APR levels and those with or without a normal PPD skin reaction.

Among the 19 patients with a negative skin reaction to SUPS, the 2-year survival rate for those with or without OK-432 therapy was 16.7% and 0.0%, respectively. There was a significant difference in survival between these groups (log-rank test, $p < 0.05$). On the other hand, among the 13 patients with a positive reaction to SUPS, there was no significant difference in survival between those with or without OK-432 therapy (Fig.3).

Tables 2 shows the results of multivariate analysis of

the factors related to survival among the patients receiving SUPS skin testing. In the whole group of patients, there were no factors with a significant influence on survival. However, ascites and postoperative adjuvant therapy were significantly related to survival in the patients with a positive SUPS skin reaction. On the other hand, in the patients with a negative skin reaction, postoperative adjuvant therapy and sex were significantly related to survival. Postoperative chemotherapy was more effective in the patients with a positive reaction to SUPS and postoperative chemotherapy+OK-432 was more effective in those with a negative reaction to SUPS.

Discussion

Several clinical studies of gastric cancer have demonstrated the clinical effectiveness of immunotherapy using OK-432^{2,14)}, but, the value of OK-432 for patients with malignant ascites was not clear. A randomized study of patients with peritonitis carcinomatosis due to gastric cancer by the Japanese Foundation for Multidisciplinary Treatment of Cancer¹⁵⁾ found no difference in survival between patients receiving chemotherapy with or without OK-432, and the same result was noted in our trial.

When we started this trial in 1986, combination therapy with OK-432 and HCFU had been reported to produce better results for peritonitis carcinomatosis, because the concentration of HCFU is high in ascitic fluid¹⁶⁾ and because OK-432 directly kills cancer cell in ascites^{17,18)}.

Individual patients should receive rationally designed adjuvant therapy, but this necessitates the evaluation of parameters that can predict the treatment response and prognosis.

Many tumor-associated markers may be useful in assessing the effectiveness of cancer therapy. We have reported that both gastric and esophageal cancer patients with abnormal SA levels showed a better prognosis than those with normal SA levels if they received immunotherapy using protein-bound polysaccharide K (PSK), an immunopotentiator prepared from *Coriolus vesicolor* (Fr.) Quel, in combination with chemotherapy^{19,20)}. We also found that gastric cancer patients with abnormal levels of immunosuppressive acidic protein (IAP) who underwent total or proximal gastrectomy plus splenectomy responded well to postoperative immunotherapy²¹⁾. We suggest that preoperative serum APR values are also correlated with a better response to PSK in both esophageal and gastric cancer. On the other hand, patients with abnormal SA levels did not show a good response to OK-432 in the present study, but those with a negative SUPS skin test showed a good response

to OK-432. From the results of the present study and the above mentioned reports, it appears that there may be different predictors for the immunopotentiators PSK and OK-432.

It has been reported that patients with a positive SUPS reaction have a good prognosis and that those who change from a negative to a positive SUPS reaction have a good response to OK-432 treatment^{22,23)}. However, the relationship between the preoperative SUPS reaction and the effectiveness of OK-432 has been unclear. A negative SUPS skin reaction means that the patient have not had streptococcal infection. The present study suggests that the effectiveness of OK-432 depends on the lack of streptococcal infection before treatment.

We conclude that preoperative assessment of the SUPS skin reaction can help clinicians to decide on OK-432 treatment for gastric cancer with peritonitis carcinomatosis. However, as this trial employed a small number of patients, further evaluation of the association between the SUPS skin reaction and OK-432 should be undertaken in the future. Nevertheless, the studies performed to date have led to the conclusion that prolongation of survival is observed when immunochemotherapy using OK-432 is given to patients with a negative SUPS reaction and chemotherapy is given to those with a positive SUPS reaction.

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Appendix

The Kanagawa cooperative study group for gastric cancer with peritonitis carcinomatosis includes the following members : Yasumasa Kondoh, Second Department of Surgery, Tokai University, Isehara ; Motonori Sairenji Department of Surgery, Kanagawa Cancer Center Hospital, Yokohama ; Kiyoshi Nishiyama, Togou Shinji, Second Department of Surgery, Yokohama City University, Yokohama ; Shuuhei Suzuki, Hiroshi Suwa, Yokosuka Kyosai Hospital, Yokosuka ; Hiroshi Takemura, Hideki Kikuchi, Takashi Nagashima, Department of 1st. Surgery, St. Marianna University ; Akio Nakayoshi, Kimio Namatame, Tadaaki Ikeda, Department of Surgery, Fujigaoka Hospital, Showa University ; Kanki Mieno, Department of Surgery, Kitasato University ; Katsuaki Kataba, Toyota Yamanaka, Department of 2nd. Surgery, St. Marianna University ; Tomishige Amano, Toshio Imada, First Department of Surgery, Yokohama City University, Yokohama ; Kazuhiro Horikuchi, Kunihiro Masukawa, Ashigarakami Prefectural Hospital ; Hiroshi Takemura, Hidetarou Yokoyama, Saiseikai Yokohamashi-Nambu Hospital ; Tishiki Takahashi, Hirohiko Minoura, Yohei Yasogawa, Department of Surgery, Sagami National Hospital, Sagami-hara ; Hiroyoshi Koizumi, Yoshikazu Fujimoto, Department of Surgery, Hiratsuka Kyosai Hospital, Hiratsuka, Hitoshi Kaneko, Nariko Yoshimura, Department of Surgery, Teikyo University Hospital at Mizonokuchi ; Takao Jyujima, Hatano Red Cross Hospital, Hatano ; Mitsuhiro Kubota, Hitoshi Hanaue, Department of Surgery, Ooiso Hospital, Tokai University ; Kanagawa, Japan.

Dr. K. Suzuki and Dr. H. Hanaue are now deceased.

A clinical study of CEA doubling time in recurrent lung adenocarcinoma p27~29

Yutaka Takahashi et al.

CEA高値を呈した肺腺癌再発症例46例を対象に、無治療時のCEAダブリングタイムを求めるとともに、それに関わる因子を臨床病理学的諸因子から検討した。

その結果、CEAダブリングタイムは、13~168日と広い範囲に分布し、平均 64.8 ± 47.1 (SD) 日、中央値47日であった。CEAダブリングタイムを左右する因子の検討では、性別で差はみられなかったのに対し、年齢では、60歳以下の19例では15~62日、平均 34.9 ± 15.5 日、60歳以上の27例では13~168日、平均 80.6 ± 49.1 日であり、両者のあいだに有意差が認められた。組織分化度では、低分化型腺癌9例で13~58日、平均 27.8 ± 15.8 日、高分化型腺癌18例が22~153日、平均 72.1 ± 48.3 日、中分化型腺癌19例が23~168日、平均 71.5 ± 50.1 日であるのにくらべると、有意に小さい値であった。さらに、再発部位では、脳の12例で15~76日、平均 33.2 ± 18.5 日、骨の10例で28~156日、平均 81.8 ± 48.8 日、頸部リンパ節の11例で13~156日、平均 74.8 ± 47.4 日、肺の10例で22~168日、平均 94.2 ± 63.8 日であり、脳と他の部位で有意の差が認められた。

以上より、肺腺癌のCEAダブリングタイムからみた発育速度に影響する因子は、年齢では若い症例、組織分化度では低い症例で発育速度が速いことが示された。また、再発部位では、脳が他の部位に比し有意に発育速度が速い成績が得られたが、これは肺腺癌の再発の中で、脳再発が最も早い時期に発生する臨床的所見と一致するものと考えられた。

Locally recurrent gastric adenocarcinoma responsive to cisplatin, 5-fluorouracil and leucovorin p31~34

Yasushi Rino et al.

当科では胃癌術後再発に対し、CDDP、5FU、ロイコボリンを併用したFLP療法を施行している。CRの症例を経験したので報告する。

FLP療法 (CDDP、5FU、ロイコボリン) で病理学的にCRを得た1例を報告する。

症例は68歳、女性、stage II (N₁ S₁ P₀ H₀) の胃癌で平成2年3月8日、胃全摘、ROUX-Y再建を施行、絶対治癒切除であった。

術後、5-FU (150mg/day) の経口投与で外来通院していた。平成4年5月よりつかえ感出現し、6月29日内視鏡検査にて吻合部小腸側に潰瘍形成、吻合部狭窄を認めた。生検にてgroup V、局所再発の診断を得た。食餌摂取困難のため8月11日入院、IVH管理し、全身状態改善し、9月7日、9月30日よりFLP療法 (経静脈的投与) を2回施行した。副作用は一過性の食思不振、下痢のみであった。FLP療法後、2回内視鏡的生検施行し、group I、IIであったが、狭窄症状改善せず、11月13日狭窄部切除術施行。病理学的検索で切除標本に癌細胞は認められず、CRを得たと考えた。術後再発の徴候はなく、現在、外来通院中。

A randomized trial of immunotherapy in combination with chemotherapy for gastric cancer with peritonitis carcinomatosa p35~39

Toshio Mitomi et al.

胃癌の癌性腹膜炎患者は、肝転移患者同様に非常に予後不良である。鳥巣らは、癌性腹水に対しOK-432を腹腔内に投与し、良好な成績を報告している⁶⁾。本稿では、癌性腹膜炎患者に対するOK-432の有用性を検討するために神奈川県下で行われた比較対照試験の結果を報告する。

[対象と方法] 対象は癌性腹膜炎を有する胃癌患者である。1986年10月より88年12月までに67例が登録された。67例の内6例 (8.9%) が治療後30日以内死亡例で、2例が消息不明例となった。化学療法は35例 (胃切除例18例、非切除例12例、再発、非手術例5例)、化学療法+OK-432療法は32例 (胃切除例11例、非切除例14例、再発、非手術例7例) に施行された。一部の患者には、術前にACT、シアル酸、IAP、ASP、およびSUPS皮膚皮内反応を測定した。

[結果] ① OK-432投与の有無では生存率に差を認めなかった (Fig.1)。

② 胃切除例では、OK-432投与例が予後良好であったが、有意の差は認められなかった (Fig.2)。

③ SUPS皮膚皮内反応陽性例では、OK-432投与の有無で差は見られなかったが、SUPS皮膚皮内反応陰性例では、OK-432投与例が有意に予後良好であった (Fig.3)。

④ Coxの比例ハザードモデルでの解析では、SUPS皮膚皮内反応陽性例では化学療法が、SUPS皮膚皮内反応陰性例ではOK-432投与が有意な予後因子であった (Table 2)。

[考察] OK-432には腹水中の癌細胞に対する直接殺細胞効果があること、フッ化ピリミジン剤の中では、HCFUの腹水中の濃度が高値であるとの理由で¹⁶⁻¹⁸⁾、OK-432とHCFUの併用は、癌性腹膜炎に有用であると考えられた。癌性腹膜炎に対するstrategyとして上記の薬剤併用がもっともよい組み合わせであると考えられた。しかし、結果としてはOK-432の効果は認められなかった。このことは癌集学的治療財団の特定研究8“胃がん腹膜播腫例に対するOK-432投与の有用性に関する研究”の研究報告書でも同様であった¹⁹⁾。

本研究では、症例数も少なく断定的なことは将来の問題としても、治療前にSUPS皮膚皮内反応陰性例ではOK-432の有用性が期待でき、有意義であると考えられた。