Randomly Controlled Study of Chemotherapy versus Chemoimmunotherapy in Postoperative Gastric Cancer Patients

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ABSTRACT

From September 1979 through March 1981, a total of 302 patients with gastric cancer and undergoing gastrectomy at the Department of Surgery at Chiba University Hospital and its 14 affiliated hospitals was studied for clinical effectiveness of immunotherapy with Nocardia rubra cell wall skeleton. The patients were stratified by gross stage of cancer and degree of operative curability. They were then assigned randomly to either chemotherapy or chemotherapy plus immunotherapy group. Immunotherapy used was intradermal injection of 400 μg of N. rubra cell wall skeleton which was given weekly for the first month and monthly thereafter. After the specimen was examined microscopically, the patients were classified by histological stage of cancer and radicality of surgical intervention into curative or noncurative groups. The patients were surveyed for survival period in December 1981. The postoperative survival rate was compared in patients of histologically curative or noncurative resection cases between the two treatment groups. No statistical difference was detected between the groups in age, sex, or operative procedures that might influence the patient’s survival. As a result, statistical intergroup difference in survival rates was not seen in patients of the curative group, probably due to a short observation period. However, the intergroup difference in survival rates was statistically significant in patients of the noncurative group (p < 0.01). These results indicate the adjunctive effect of N. rubra cell wall skeleton as an immunotherapeutic agent in patients undergoing gastrectomy for gastric cancer.

INTRODUCTION

Since the reports of the effectiveness of BCG in the treatment of leukemia and malignant melanoma by Mathé et al. (12) and Morton et al. (13), immunotherapy was attended with great hopes as a new treatment modality for cancer in the 1970s. Malignant tumors subjected to the study of immunotherapy in Europe and the United States have been mainly leukemia, malignant melanoma, or lung cancer (4, 6, 19). Since there is a high incidence of gastric cancer and unsatisfactory survival rates after surgery in Japan, there is a great hope for the introduction of new therapy supplementary to surgical treatment of gastric cancer, especially immunotherapy. In the initial stage of investigations, clinical effectiveness was mainly based on comparative studies with historical controls. As a result of the studies made over the past decade, it has been clarified that the clinical evaluation of immunotherapy or immunotherapeutic agents should be conducted by a well-designed, randomized, controlled study in which the survival or the remission period is compared without reference to historical controls. However, the effectiveness of nonspecific immunotherapy is still controversial (20). In order to evaluate the efficacy of immunotherapy on gastric cancer, we conducted 2 randomized clinical trials. The first trial of nonspecific immunotherapy with BCG-CWS was conducted in patients operated on for gastric cancer at our institution during 3 years from January 1976 through December 1978, and the results demonstrated the efficacy of this agent (15). The clinical effectiveness of BCG-CWS was also demonstrated in patients with lung cancer (22). Azuma et al. (2, 3) showed that N-CWS had more profound immunopotentiating activity and antitumor activity against syngeneic transplantable tumors in mice than did BCG-CWS. They instituted the clinical application of N-CWS in a Phase I study in patients with lung cancer, leukemia, and malignant melanoma (21). Subsequently, we carried out the present randomized controlled trial of N-CWS to evaluate its effectiveness in patients gastrectomized for gastric cancer. The study was undertaken as strictly as possible to obtain a real effect of nonspecific immunotherapy under a supervision of a biostatistician as a controller. According to a randomization of treatments using sealed envelopes containing key codes, it was determined under the strict direction of an independent controller to which therapy group the subjects were assigned: a chemotherapy group or a group receiving chemotherapy plus N-CWS (chemoimmunotherapy group). The subjects were patients with gastric cancer who underwent gastrectomy by the surgeons trained in these operative procedures at the Second Department of Chiba University Hospital. These patients were registered from September 1979 to March 1981, and their survival was surveyed as of December 31, 1981, to compare the survival rate curves between the 2 treatment groups. The present paper deals with the study results.

MATERIALS AND METHODS

Organization. The present clinical trial was carried out at the Second Department of Surgery at the Chiba University School of Medicine and the surgical departments of its 14 affiliated hospitals. The study was directed by an independent controller (T. T.). He was responsible for random allocation of therapy regimens, sealing of the randomly allocated key codes in envelopes, preservation of the key codes and integrity in determining patient eligibility for inclusion in the analysis of data, and treatment of data. For this investigation, a secretariat headed by Ochiai was organized at the Second Department of Surgery, Chiba University School of Medicine, to play a specific role for distribution of the sealed

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envelopes to the participating institutions and for reception of patient registration from these institutions after opening of the sealed envelopes. The secretariat, furthermore, reviewed the operative procedures and histopathological findings in all enrolled cases based on the case report forms submitted from the participating institutions. Histological evaluation was made on all cases at each participating institution; however, the final determination as to the histological staging and degree of surgical curability of each individual was made by the secretariat. Whenever the description of histological findings of the case report form was not clear, the actual histological slides were reviewed by the secretariat. They also handled all inquiries concerning immunotherapy or chemotherapy, such as side effects that might require clarification.

A subcommittee consisting of the controller and senior investigators was set up to evaluate inclusive cases for the analysis of data. The subcommittee prepared in advance the criteria for treatment of subjects enrolled and determined inclusive cases for analysis under binding of the key codes for therapy regimens.

Subjects. The subjects were selected from consecutive patients with gastric carcinoma undergoing gastrectomy at the participating institutions during the 19-month period from September 1, 1979, until March 31, 1981, provided that: (a) the subjects had not received any anticancer treatment; (b) the subjects were younger than 75 years old; and (c) the subjects were free of serious cardiac, renal, or pulmonary complications and were in seemingly adequate systemic condition to tolerate the surgical procedures. The subjects were free of serious cardiac, renal, or pulmonary complications and were in seemingly adequate systemic condition to tolerate the operative procedures. Immediately after completion of the MFC therapy, p.o. Tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] was instituted in a daily dose of 600 mg (<50 kg body weight) i.v. of MMC during surgery and 10 mg MMC on the following day. The patient was then given weekly an i.v. injection of 2 mg of MMC, 250 mg of 5-FUra, and 20 mg of 1-β-D-arabinofuranosylcytosine designated as MFC chemotherapy for 10 weeks beginning 1 month after operation. Additionally after completion of the MFC therapy, a combination of MMC, 5-FUra, and 1-β-d-arabinofuranosylcytosine was administered as MFC chemotherapy to be effective (10).

The dosage regimens used in this study are illustrated in Chart 1. The patient received either 20 mg (in the case of ≥50 kg body weight) or 10 mg (<50 kg body weight) i.v. of MMC during surgery and 10 mg MMC on the following day. The patient was then given weekly an i.v. injection of 2 mg of MMC, 250 mg of 5-FUra, and 20 mg of 1-β-d-arabinofuranosylcytosine as MFC chemotherapy for 10 weeks beginning 1 month after operation. Immediately after completion of the MFC therapy, p.o. Tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] was administered in a daily dose of 600 mg. A single i.v. injection of 10 mg of MMC was combined with Tegafur therapy triweekly during the first year and at 6-month intervals thereafter.

The dosage schedule of chemotherapy was modified on the basis of laboratory findings, e.g., WBC, platelet count, serum protein and albumin concentrations, liver and renal function, postoperative complications, and systemic condition.

Criteria for Treatment of Subjects. The criteria for treatment of the enrolled subjects were determined in advance by the subcommittee.
The patients receiving N-CWS even once were to be included in the analysis. However, the patients receiving no MMC injection at the time of operation and less than 3 episodes of MFC therapy were to be treated as exclusions. After histological examination, the patients with early gastric cancer, which is confined to the mucosa without lymph node involvement, were excluded from the study. The reason of exclusion was that their 5-year survival rate was reported to be 95% and that postoperative adjuvant chemotherapy was not beneficial for them (23).

Evaluation of Therapeutic Response. All patients enrolled in the study were surveyed for survival as of December 31, 1981, and the effectiveness of the immunotherapy was appraised by comparing chemoimmunotherapy and chemotherapy groups for the survival rate curves from the day of operation to the day of death. The retrospective yearly survival rates of gastrectomized patients were assessed based on histological findings rather than on macroscopic findings at surgery. Definition of histological stage of cancer and surgical curability used in the study was described elsewhere (7). The method of Kaplan and Meier (8) was used for calculating survival rates, and the generalized Wilcoxon test of Gehan (5) was used for the statistical testing difference in survival.

RESULTS

Breakdown of Patients

A total of 302 patients was registered to the secretariat: 143 for the chemotherapy group and 159 for the chemoimmunotherapy group. Of these, the 258 analyzed subjects consisted of 118 for the chemotherapy group and 140 for the chemoimmunotherapy group. There were 44 exclusions with 25 from the chemotherapy group and 19 from the immunotherapy group. Of the 9 drop outs excluded from analysis, 3 were from the chemotherapy group, and 6 were from the immunotherapy group.

The most common reason for exclusions was early stage of gastric cancer, diagnosed by histological examination of the specimen, which was found in 20 patients (Table 3). Other than 2 patients who died within 30 days after operation, there were 2 exclusions due to the postoperative complications. No patients failed to receive MMC chemotherapy at the time of operation and fewer than 3 episodes of MFC chemotherapy on the following day. As for immunotherapy, all patients received at least one dose of N-CWS and were included in the statistical analysis except for one patient who never received even a single dose. This case was treated as an infringement. Of 258 analyzed subjects, 9 patients fell into the category of dropouts with 3 from the chemotherapy group and 6 from the immunotherapy group. Of these, 7 patients received other immunotherapeutic agents, and 2 patients succumbed to other diseases, heart failure and pulmonary infection, respectively.

Surgical Curability after Histological Assessment

After the specimen was examined microscopically, the patients were classified by histological stage of cancer and radicality of surgical intervention into curative or noncurative groups. Histological curative resection was conducted in 90 patients of the chemotherapy group and in 97 patients of the chemoimmunotherapy group, and noncurative resection was conducted in 28 and 43 patients, respectively. The noncurative resection cases were much more widely distributed in the chemoimmunotherapy group, since the operative curability was determined on the basis of the histological findings as follows. (a) The change from macroscopically curative resection to histologically noncurative resection was made in all the cases of the immunotherapy group. (b) On the contrary, the change from macroscopically noncurative resection to histologically curative resection was more frequent in the chemotherapy group than in the immunotherapy group.

Patient Background Factors

The curative and noncurative resection cases in both groups were analyzed with respect to various background factors to test statistically intergroup differences. Tables 4 and 5 show that no significant difference was noted between the chemotherapy and chemoimmunotherapy groups in distribution of noncurative resection cases with respect to sex, age, extent of gastrectomy, presence or absence of multivisceral resection, radicality in regional lymphadenectomy, grade of liver metastasis or disseminating peritoneal metastasis, histological grade of regional lymph node metastasis, depth of cancerous invasion, cancer infiltration at the resection margin, infiltrative growth pattern of carcinoma, or histological type of carcinoma.

Immunotherapy

The frequency of N-CWS injections was distributed from 2 to 35 times in 140 patients of the immunotherapy group. The mean frequency was 16.5.

Chemotherapy

Table 6 shows the actual practice of anticancer chemotherapy

<table>
<thead>
<tr>
<th>Criteria for treatment of enrolled subjects</th>
<th>Chemoimmunotherapy</th>
<th>Immunotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infringement against allocation of therapy regimen</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Early stage of gastric cancer</td>
<td>13</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Cancers other than gastric cancer</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No surgical resection</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Simultaneous multicarcinogenesis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Died within 30 days after operation</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Serious complications existing prior to operation</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Study treatment impracticable due to postoperative complications</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Over 76 yr of age at operation</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Histologically unevaluable</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma other than common type of adenocarcinoma</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>19</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drop outs</th>
<th>Chemoimmunotherapy</th>
<th>Immunotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usage of other immunotherapy before completion of study treatment</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Died of other disease (cardiac failure or pneumonia)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>
### Table 4

**Homogeneity of patients due to background factors**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Extent of resection</th>
<th>Concomitant resection</th>
<th>Grade of lymph node removal</th>
<th>Grade of liver metastasis</th>
<th>Grade of disseminating peritoneal metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>&lt;40</td>
<td>40-54</td>
<td>55-64</td>
<td>65-75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Distal gastrectomy</td>
<td>Proximal gastrectomy</td>
<td>Yes</td>
</tr>
<tr>
<td>Curative resection cases</td>
<td>66</td>
<td>24</td>
<td>8</td>
<td>31</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Chemotherapy (90 cases)</td>
<td>55</td>
<td>42</td>
<td>8</td>
<td>30</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Immunotherapy (97 cases)</td>
<td>21</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Noncurative resection cases</td>
<td>19</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Chemotherapy (28 cases)</td>
<td>29</td>
<td>14</td>
<td>2</td>
<td>16</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Immunotherapy (43 cases)</td>
<td>20</td>
<td>10</td>
<td>3</td>
<td>17</td>
<td>10</td>
<td>21</td>
</tr>
</tbody>
</table>

Statistical test

- NS (χ² = 0.05)
- NS (χ² = 3.65)
- NS (χ² = 4.06)
- NS (p₀ = 0.16)
- NS (χ² = 1.00)
- NS (χ² = 0.31)
- NS (χ² = 1.42)

*a* Incomplete removal of Group 1 lymph nodes; R₁, complete removal of Group 1 lymph nodes; R₂, complete removal of Group 1 and 2 lymph nodes; R₈, complete removal of Group 1, 2, and 3 lymph nodes.

These are defined by the General Rules for Gastric Cancer Study (7); H₂, no liver metastasis; H₈, metastasis limited to one of the lobes; H₈, few scattered metastases to both lobes; H₂, numerous scattered metastases to both lobes. These are defined by the General Rules for Gastric Cancer Study (7); P₀, no disseminating metastases; P₁, disseminating metastasis to the adjacent peritoneum; P₂, a few scattered metastases to the distant peritoneum; P₃, numerous metastases to the distant peritoneum [These are defined by the General Rules for Gastric Cancer Study (7)]; NS, not significant; χ², χ² test; χ², Fisher's exact probability test.

### Table 5

**Homogeneity of patients due to background factors and histological examination**

<table>
<thead>
<tr>
<th>Grade of lymph node metastasis</th>
<th>Depth of cancerous invasion in stomach wall</th>
<th>Cancer infiltration at the resection margin</th>
<th>Growth pattern of cancer</th>
<th>Unassessable</th>
<th>Histological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>n(⁻)</td>
<td>n(+)</td>
<td>m</td>
<td>sm</td>
<td>ss a b</td>
<td>ss b</td>
</tr>
<tr>
<td>Curative resection cases</td>
<td>42</td>
<td>26</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy group (90 cases)</td>
<td>42</td>
<td>26</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Immunotherapy group (97 cases)</td>
<td>48</td>
<td>30</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Noncurative resection cases</td>
<td>3</td>
<td>7</td>
<td>16</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chemotherapy group (28 cases)</td>
<td>3</td>
<td>7</td>
<td>16</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Immunotherapy group (43 cases)</td>
<td>3</td>
<td>12</td>
<td>20</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Statistical test

- NS (χ² = 4.81)
- NS (χ² = 7.87)
- NS (p₀ = 0.12)
- NS (p₀ = 0.104)
- NS (χ² = 0.49)
- NS (χ² = 8.38)

*a* n(⁻), no suspected lymph node metastasis by the histological examination; n(+) metastasis to Group 1 lymph nodes; n(+) metastasis to Group 2 lymph nodes; n(+) metastasis to Group 3 lymph nodes; n(+) metastasis to lymph nodes located beyond Group 3; m, tunica mucosa; sm, tela submucosa; pm, tela muscularis propria; ss, tela subserosa; s, tunica serosa; se, cancer cells present on the serosal surface and exposed to the peritoneal cavity; si, cancer cells infiltrating the neighboring tissue; ow(+), cancer cells present within 5 mm of the cut edge of the p. m.; aw(+), cancer cells present within 5 mm of the cut edge of the anal margin; INF α or α, cancerous invasion with a distinct border from the surrounding tissue; INF β or β, cancerous invasion intermediate between α and γ; INF γ or γ, cancerous invasion with an ill-defined border; pap, papillary adenocarcinoma; tub 1, tubular adenocarcinoma, well-differentiated type; tub 2, tubular adenocarcinoma, moderately differentiated type; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma; NS, not significant; χ², χ² test; χ², Fisher's exact probability test.

*b* For α, β, and γ, see definitions for INF in Footnote a.
classified by patients with curative resection and those with noncurative resection.

**MMC Therapy at the Time of Operation.** Among the patients receiving noncurative resection, MMC was given on the day of operation to 28 (100%) of the 28 patients in the chemotherapy group and to 40 (93.0%) of the 43 patients in the immunotherapy group and, on the following day, to 26 (92.0%) patients in the chemotherapy group and to 39 patients (90.7%) in the immunotherapy group. There were no significant differences in the frequency of MMC medication between the 2 treatment groups.

**MFC Therapy.** The protocol required a course of MFC therapy given 10 times for 10 weeks beginning 1 month after operation. Among the patients receiving noncurative resection, 19 (67.9%) of the 28 patients in the chemotherapy group and 33 (76.7%) of the 43 patients in the immunotherapy group completed the full course of therapy. There were 3 (10.7%) and 4 patients (9.3%) in these groups, respectively, who received MFC only once or twice during the observation period. No significant difference was observed between the chemotherapy and immunotherapy groups as to the actual practice of MFC therapy.

**Tegafur.** Twenty-two (78.6%) of the 28 patients in the chemotherapy group and, on the following day, to 26 (92.0%) patients in the chemotherapy group and to 39 patients (90.7%) in the immunotherapy group. There were no significant differences in the frequency of MMC medication between the 2 treatment groups.

**Ambulatory MMC Therapy.** No significant difference was seen between the chemotherapy and the immunotherapy groups of noncurative resection cases as to the frequency of i.v. injections of MMC for an ambulatory treatment.

**Duration of Observation**

The mean duration of observation from the day of operation until the time of the survival survey, December 31, 1981, was 593 days in the total of 258 patients included for analysis. The mean duration of observation was 588 days in the 28 noncurative resection cases receiving chemotherapy and 613 days in the 43 cases receiving immunotherapy.

**Comparison of Survival Rate Curves**

Since the patient background factors were homogeneous in the 2 treatment groups including actual practice of chemotherapy, the curative and noncurative patients in these 2 groups were compared for survival rate curves (Chart 2). In the curative resection cases, both treatment groups showed a survival rate of better than 80% by the time of the survival survey. No significant intergroup difference was noted.

In the noncurative resection cases, the 1-year survival rate was 26.9% for the chemotherapy group and 65.3% for the immunotherapy group. The 50% survival period was 458 days in the immunotherapy group, whereas it was 281 days in the chemotherapy group. There was a significant difference in the survival rate curves between the 2 treatment groups ($p < 0.01$).

These findings indicate that postoperative immunotherapy with N-CWS was effective in the patients with noncurative resection for gastric carcinoma.

**Side Effects**

A total of 151 patients treated with N-CWS, comprising 140 inclusions and 11 exclusions, was analyzed for side effects of N-CWS (Table 7). The side effects associated with N-CWS medication were local reactions at the i.d. injection site or systemic reactions. Local manifestations encountered included redness in 11 cases, induration in 2 cases, vesicle in one case, swelling in 4 cases, abscess in 7 cases, ulceration in 18 cases, and pain in 5 cases. Systemic symptoms were seen in 8 patients who had fever of 38-39° following injection. One patient complained of feverish feeling for 1 to 2 days after injection, and another patient developed eruption on the extremities.
These local and systemic adverse reactions were a total of 58 episodes encountered in 48 (31.8%) of the 151 patients. Of the 48 patients, the side effects did not prevent continuation of the N-CWS therapy in 32 cases (66.7%) and led to a temporary discontinuation of therapy in 7 cases (14.6%). In the remaining 9 cases (18.7%), the side effects led to withdrawal of N-CWS therapy, including 3 cases refusing to receive medication. These local reactions associated mainly with ulcer were cured with no special treatment in most cases or were cured usually within 1 month by treatment with conventional ointments in other cases. Fever subsided within 1 to 3 days without any special treatment. No fatal or serious adverse reactions developed.

Table 8 shows the incidence of and reasons for temporary discontinuation or withdrawal of the chemotherapeutic medication. MFC therapy was temporarily discontinued or withdrawn in 26.3% of the patients in the chemotherapy group and in 27.1% of those in the immunotherapy group. The corresponding rates during Tegafur therapy were 45.2 and 52.5%, respectively. Statistical analysis revealed no significant intergroup difference in the incidence of temporary discontinuation or withdrawal due to side effects associated with chemotherapy or other reasons.

**DISCUSSION**

Since the report of a protracted remission of leukemia in patients receiving BCG by Mathé et al. (12) and that of regression of malignant melanoma after i.l. injections of BCG by Morton et al. (13), the 1970s represented an era when great hopes were entertained for anticancer immunotherapy. Several clinical studies for lung cancer as well as for leukemia and malignant melanoma demonstrated the clinical effectiveness of immunotherapy (4, 6, 19).

In the initial stage of clinical investigations of anticancer immunotherapy, many papers purported its effectiveness as compared with that of historical controls. The accumulation of studies has led to a conclusion that objective assessments by a well-designed, randomized, and controlled clinical study are essential for evaluation of the efficacy of immunotherapy. The present clinical investigation of N-CWS was conducted under a protocol designed for multicenter randomized study especially directed by an independent controller. The observation period averaged 593 days. During such a short observation period, the curative resection cases showed a survival rate of better than 80%, and there was no significant difference between chemotherapy and chemoinmunotherapy groups in the survival rate curves. The noncurative resection cases seemed to show a poorer prognosis; on the other hand, the chemotherapy group showed a 1-year survival rate of 26.9%, and the chemoinmunotherapy group showed a 1-year survival rate of 65.3%. Statistical analysis of the intergroup difference in survival rate curves revealed a significant prolongation of survival in favor of treatment with N-CWS (p < 0.01). The prolongation of survival observed in the chemoinmunotherapy group was not presented due to a poor therapeutic outcome in the control (chemotherapy) group because the 50% survival period for the noncurative resection cases in the chemotherapy group was 281 days (9.3 months) as compared to that (8 months) in that noncurative resection cases of gastric cancer treated as well at the Cancer Research Institute Hospital in Japan (11). In view of our previous randomized study of BCG-CWS conducted over 3 to 6 years (15), the result of curative resection cases in the present study with a short observation period is preliminary, and it should be possible to delineate the effectiveness of N-CWS after further observation.

Although our results of randomized controlled trials with BCG-CWS and N-CWS were positive, the effectiveness of nonspecific immunotherapy is still controversial. Many negative results were presented at the International Conference of Immunotherapy held at Bethesda, Md., in 1980 (20). It is difficult to give a reasonable explanation of discrepancy between our positive and their negative results. To avoid a bias to immunotherapy and to get an objective result, the present study was undertaken as strictly as possible under the supervision of a biostatistician as a controller. Several possible explanations may be raised for our positive results. Gastric cancer might be a good choice for the
study to evaluate nonspecific immunotherapy. Since clinicopathological features of the disease were well defined by the Japanese Gastric Cancer Research Society, clinical evaluation can be made on the basis of similar background factors between the control and immunotherapy groups. A choice of an immunotherapeutic agent, N-CWS, was also an important factor for our results.

N-CWS is a constituent of the cell wall skeleton subfractionated from N. rubra which is taxonomically related to BCG. It has been shown to consist of a bound lipid (nocardomycolic acids), neutral polysaccharides (composed of β-arabinose and D-galactose), and mucopolysaccharides moieties (1). N-CWS has been demonstrated to possess more profound immunopotentiator activity and to be endowed with more pronounced, host-mediated antitumor activity than has BCG-CWS (2, 17). As one of the mechanisms on the suppression of syngeneic tumor growth by N-CWS, Kawase et al. (9) reported that N-CWS enhanced T-cell-mediated cytotoxicity in mice, while Ogura et al. (16) and Sone et al. (18) pointed out the participation of macrophages in the antitumor effect of N-CWS. It is difficult to clinically grasp each site of immunological reaction against autochthonous tumor cells in individual patients with malignant tumors. The mechanism of action underlying the effectiveness of N-CWS observed in the present study is obscure. Nevertheless, there were the facts that an antitumor effect of N-CWS was evident in the host's immunological system of the experimental model, and N-CWS was effective in the treatment of patients with gastric cancer. These 2 facts suggest a possibility that N-CWS exerts its antitumor effect against autochthonous tumors through the immunological system in humans as well.

The side effects of N-CWS, such as fever or ulcer at the injection site, may be the inevitable consequence of the delayed immune responses evoked by this agent. They were fully tolerable from the viewpoint of therapy for malignant tumors.

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