The Concept of Immunochemosurgery in Gastric Cancer

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To evaluate the effectiveness of adjuvant immunochemotherapy in advanced adenocarcinoma of the stomach, patients who had undergone radical subtotal gastrectomy for stage III gastric carcinoma were randomized to receive immunochemotherapy or not. For immunotherapy, Streptococcus pyogenes preparation (pilbanil) was given intramuscularly every week, and for chemotherapy, either MFC (mitomycin C, 5-fluorouracil, and cytosine arabinoside) regimen or FME (5-fluorouracil and methyl-CCNU) regimen was given. Immunochemotherapy was started at the fourth or fifth postoperative day and chemotherapy was started at the eighth to tenth postoperative day.

To evaluate the immune status of patients, various immune parameters such as 1-chloro-2, 4-dinitrobenzene (DNCB) test, T-lymphocyte count, PHA- and concanavalin-A-stimulated lymphoblastogenesis, and antibody-dependent cellular cytotoxicity (ADCC) activity were checked before surgery and 3-4 months postoperatively.

One hundred and thirty-eight patients were chosen for study during a 5-year period. Seventy-four patients received postoperative immunochemotherapy and 64 patients received no further anticancer therapy following their operation. All patients had been followed for at least 5 years since they underwent surgery. Survival rate and immune status were compared between the 2 groups. Patient characteristics and preoperative values for the immune status of the 2 groups were similar to each other.

The 5-year survival rate of the postoperative immunochemotherapy group was 44.6%, whereas that of the surgery alone group was 23.4%. The difference is statistically significant (p < 0.05). All the postoperative values of immune parameters showed more favorable data in the postoperative immunochemotherapy group.

Postoperative immunochemotherapy is no longer adjuvant, but is an essential systemic therapy to prolong patient survival and cure disease. This author proposes to use the term "immunochemosurgery" instead of "surgery and adjuvant immunochemotherapy" for gastric cancer.

Even when thorough and extensive radical operations have been performed for patients with stage III gastric cancer, recurrent diseases are found in a number of patients within 1-2 years after their operation and the reported 5-year survival rate varies from only 6% to 33.2% [5-10]. Survival curves of 957 patients who underwent surgery for gastric cancer at the Seoul National University Hospital during a 7-year period are shown in Fig. 1.

Since the concept of multimodality therapy was established, chemotherapy as an adjuvant to surgical treatment has been used in patients with advanced disease to eradicate the remaining cancer cells or micrometastasis and to cure the disease. Although many trials have failed to demonstrate any benefit with the use of adjuvant therapy, there have been some encouraging reports of prolonged survival and disease-free interval. Taguchi et al. [11] reported improved survival in patients with stage III gastric carcinoma who received mitomycin C and 5-fluorouracil (5-FU) after surgery. Livstone and Stablein [12] reported a prolonged disease-free interval and survival following curative resection for gastric carcinoma using 5-FU and methyl-CCNU. Although the results of primary chemotherapy in advanced cases are generally poor, a combined administration of mitomycin C, 5-FU, cytosine arabinoside (MFC), or 5-FU and methyl-CCNU (FME) was documented to be efficacious [13, 14].

In the late 1960's, Mathé et al. [15] reported an immunotherapeutic effect of bacillus Calmette-Guerin (BCG) and allogenic tumor cell vaccine with an increase in remission duration and survival in a child with leukemia and Morton et al. [16] reported an immunotherapeutic efficacy of intradermal BCG inoculation on metastatic cutaneous malignant melanoma. Since then the interest in immunotherapy has greatly increased. Many clinical studies have shown that immunotherapy can be effective against certain malignancies including gastric cancer [5, 15-27]. Immunotherapy alone is rarely effective against clinically measurable cancer. It would be an important therapy, however, to attack cancer cells and to improve host immune status in the case of conjunction with the other treatment modalities.

This author's previous studies [28, 29] have shown that both cell-mediated immunity, measured by T-lymphocyte quantitations, and the positivity of 1-chloro-2, 4-dinitrobenzene (DNCB)-
Table 1. Distribution of TNM stage in gastric adenocarcinoma (SNUH, 1971–1985).

<table>
<thead>
<tr>
<th>Period</th>
<th>I (no. &amp; %)</th>
<th>II (no. &amp; %)</th>
<th>III (no. &amp; %)</th>
<th>IV (no. &amp; %)</th>
<th>Total (no. &amp; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971–1975</td>
<td>12 (2.5)</td>
<td>45 (9.3)</td>
<td>225 (46.6)</td>
<td>201 (41.6)</td>
<td>483</td>
</tr>
<tr>
<td>1976–1980</td>
<td>45 (4.9)</td>
<td>133 (14.4)</td>
<td>428 (46.3)</td>
<td>318 (34.4)</td>
<td>924</td>
</tr>
<tr>
<td>1981–1985</td>
<td>210 (10.3)</td>
<td>210 (10.3)</td>
<td>1,001 (49.3)</td>
<td>611 (30.1)</td>
<td>2,032</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>267 (7.8)</td>
<td>388 (11.3)</td>
<td>1,654 (48.1)</td>
<td>1,130 (32.9)</td>
<td>3,439</td>
</tr>
</tbody>
</table>

Fig. 1. Survival curves of patients with resectable gastric cancer according to TNM stage (SNUH, 1974–1980). Number of follow-up cases/total: 957/1,137 (84.2%).

delayed cutaneous hypersensitivity in patients with malignancy are decreased significantly and the level of immunosuppressive acid protein (IAP) is significantly higher than that of normal individual. The further the clinical stage of gastric cancer is progressed, the more depressed is the cell-mediated immunity of the host (Fig. 2) [29, 30]. In view of this finding, enhancement of the depressed immune status of the host is thought to be an important aspect in the treatment of cancer patients.

The purpose of this study is to evaluate the therapeutic effectiveness of postoperative immunochemotherapy in advanced, but resectable, adenocarcinoma of the stomach. Survival rate and immune status of patients with stage III gastric carcinoma who received postoperative immunochemotherapy were compared with those of patients who received surgery with no adjuvant therapy.

Material and Methods

During the 5-year period from 1975 to 1980, we enrolled in this study 138 patients who had undergone radical subtotal gastrectomy for stage III gastric cancer at the Department of Surgery, Seoul National University Hospital. Prior to surgery all patients with stomach cancer underwent a complete history and physical examination with measurements of disease, immune parameters as mentioned below, performance status, routine laboratory tests, and liver scan. If the history or physical examination suggested distant metastases, special studies such as a bone scan and brain scan were performed. Following surgery, patients, specifically chosen with histologically confirmed lymph node-positive stage III adenocarcinoma of the stomach, were randomized to receive postoperative immunochemotherapy or not (Table 2) after the routine examination including hemogram, liver function test, and renal function test showed the normal range values. Patients were ineligible for study if they had previous history of chemotherapy or radiation therapy or if their age was over 75. Initial performance status was within the range of the Eastern Cooperative Oncology Group (ECOG):0–2 in all patients.

Surgery

Curative surgery for gastric cancer performed in this center includes subtotal gastric resection, complete dissection, so-called skeletonization, of regional lymph nodes along the celiac axis, hepatic artery, splenic artery, portal vein, and retropancreatic lymph node as well as perigastric lymph nodes and removal of omentum with adjacent tissues. All the tissues were removed in en bloc fashion. Frozen biopsy of both resection margins was done in all cases.