immunization (tumor vaccine) and adoptive immunotherapy (10) would be definitely required for utilization of adoptive immunotherapy for lung cancer.

References


4. Cytokine-Combined Chemotherapy for Advanced Cancer Patients Not-Indicated for Surgical Therapy

Yutaka KOHGO and YOSHIRO NITSU*

Key words: interleukin-2, chemoimmunotherapy, PSK, peripheral blood stem cell transplantation, granulocyte colony stimulating factor

Recent biotechnology advances have enabled us to use recombinant cytokines for cancer treatment. One approach is the use of anticancerous cytokines such as interleukin 2 (IL-2) and tumor necrosis factor (TNF) for immunotherapy. Another approach is the utilization of hematopoietic growth factors such as granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) for the recovery of bone marrow failure caused by aggressive chemotherapy. Both approaches can be used especially for the treatment of advanced or disseminated cancers which are not indicated for surgical therapy, as therapy of inoperable cancer requires new treatment strategies. Here, we present the fundamental and clinical results obtained using the above approaches.

1. Immunochemotherapy of advanced gastrointestinal cancers using interleukin 2 (IL-2), cyclophosphamide and biological response modifier (BRM).

To augment the effect of IL-2, we additionally used the anticancerous agents (cyclophosphamide) and BRM (PSK; Krestin®). Cyclophosphamide was used both for the improvement of the immunosuppressive condition of cancer bearers and for the accumulation of IL-2 activated anticancer effector cells such as natural killer cells and cytotoxic T-cells to tumor tissues. PSK, which has been known as an immunostimulating agent derived from the mycelium of Coriolus versicolor, was used for the neutralization of soluble immunosuppressive factors and for the induction of killer cells (1). It is assumed that the anticancerous immune network is further augmented by the combinations of these three agents.

Prior to the human study, animal experiments using Balb/c mice carrying B16 melanoma cells were conducted. B16 melanoma cells were subcutaneously transplanted into the hind limb and the number of pulmonary metastases and the survival rate were examined (2). Comparing the non-treated group and the IL-2 and cyclophosphamide-treated group, the latter showed good responses, i.e., a significant decrease of pulmonary metastases. Further studies on these three agents in mice are in progress.
Cytokine-Combined Chemoimmunotherapy

We then started the clinical pilot study using the three drug combination immunochemotherapy (3). All of the patients gave informed, written consent to the trial. Cyclophosphamide was intravenously administered at a dose of 600mg/m² every week and PSK (2g/day) was taken orally every day. IL-2 (TGP-3, 2,000 units/day) was administered through a central venous catheter for 4 weeks. This 4-week treatment cycle was repeated at least twice and the clinical effect was then evaluated. Table 1 shows patients characteristics and their treatment effect. All of the seven patients suffered from gastrointestinal malignancies which were not indicative for surgical treatment. A complete response (CR) was obtained in a patient with a metastatic liver tumor from gallbladder carcinoma (4), and two patients with colon carcinoma and hepatocellular carcinoma responded partially. A remarkable decrease in ascitic fluid was obtained in a patient with pancreatic carcinoma. A decrease in tumor markers such as α-fetoprotein (AFP) and carcinoembryonic proteins (CEA) were observed in two patients. Immunological improvements inducing the decrease of serum immunosuppressive factors (IAP; immunosuppressive acidic protein and IS; immunosuppressive substance) and an increase of killer cell activity were noted.

2. Recovery of chemotherapy-induced bone marrow failure by granulocyte colony stimulating factor and peripheral blood stem cell transplantation

Another approach of cytokine application for cancer chemotherapy is the use of hematopoietic growth factors and stem cells for the rapid recovery of bone marrow failure after high-dose anticancer chemotherapy. The diseases indicated for this treatment strategy are “chemotherapy-curable tumors” including leukemia, malignant lymphoma, germ cell tumors, breast cancer, and ovarian carcinomas. We presently are using G-CSF and peripheral blood stem cells (PBSC) for the recovery of chemotherapy-induced bone marrow failure (5). PBSC are efficiently mobilized into circulation after chemotherapy and/or G-CSF administration (6). When patients were treated with chemotherapy and then administered with G-CSF and PBSCs, which are confirmed by colony forming unit-granulocyte macrophage (CFU-GM) colony assay and by flow cytometry using anti-CD34 monoclonal antibody, are mobilized. The important issue to be resolved about PBSC is whether PBSC has a long standing hematopoietic ability as does bone marrow stem cells and whether the tissue distribution of PBSC is the same as bone marrow stem cells. CD34 positive mononuclear cells were prepared from the patient’s stem cells derived from both bone marrow and peripheral blood by using an Islolex 50 column and were transfected with neomycin-resistant (neo) gene-carrying retrovirus vector in the presence of interleukin-3 and interleukin-6. The CD34 positive cells marked with neo-gene were administered to severe combined immunodeficiency (SCID) mice through the tail vein, and the inserted neo-gene was then examined serially by the polymerase chain reaction (PCR) procedure. It was noted that the neogene was detected in the peripheral blood, as well as in the bone marrow, liver and spleen, even 24 weeks after PBSC inoculation, suggesting that PBSC has a long-lasting capability for hematopoiesis. In addition, the neo-gene of PBSC appeared in the circulation faster than that of bone marrow stem cells (6). These results confirm

Table 1. Characteristics and Clinical Effects of Patients Treated with IL-2, Cyclophosphamide, and PSK

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Clinical stage</th>
<th>Prior treatment</th>
<th>Clinical effects</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>YS</td>
<td>72</td>
<td>M</td>
<td>Colon ca</td>
<td>III</td>
<td>None</td>
<td>Regression of main tumor</td>
<td>Fever</td>
</tr>
<tr>
<td>SY</td>
<td>60</td>
<td>M</td>
<td>Rectal ca liver metastasis</td>
<td>IV</td>
<td>5FU</td>
<td>Decrease of serum CEA</td>
<td>None</td>
</tr>
<tr>
<td>KK</td>
<td>68</td>
<td>M</td>
<td>Pancreas ca peritonitis carcinomatosa</td>
<td>IV</td>
<td>Surgery</td>
<td>Reduction of ascites</td>
<td>Nausea vomiting</td>
</tr>
<tr>
<td>SS</td>
<td>58</td>
<td>M</td>
<td>Gallbladder ca liver metastasis</td>
<td>IV</td>
<td>Surgery MMC, 5FU</td>
<td>CR</td>
<td>Fever</td>
</tr>
<tr>
<td>NH</td>
<td>85</td>
<td>F</td>
<td>Gastric ca</td>
<td>III</td>
<td>None</td>
<td>NC</td>
<td>Fever</td>
</tr>
<tr>
<td>YK</td>
<td>51</td>
<td>F</td>
<td>Rectal ca bone metastasis</td>
<td>IV</td>
<td>Surgery ADR</td>
<td>NC</td>
<td>None</td>
</tr>
<tr>
<td>SS</td>
<td>67</td>
<td>F</td>
<td>Hepatocellular ca</td>
<td>IV</td>
<td>TAE</td>
<td>Disappearance of new lesion decrease of AFP</td>
<td>Nausea fever</td>
</tr>
</tbody>
</table>

Table 2. Effects of High-Dose Chemotherapy Supplemented with G-CSF and Peripheral Blood Stem Cell Transplantation in Patients with High Risk Germ Cell Tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Histology</th>
<th>Stage</th>
<th>Response to prior therapy</th>
<th>Response to high dose therapy</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH</td>
<td>18</td>
<td>M</td>
<td>Mixed</td>
<td>III B1</td>
<td>PR</td>
<td>CR</td>
<td>17 (alive, NED)</td>
</tr>
<tr>
<td>TK</td>
<td>40</td>
<td>M</td>
<td>Mixed</td>
<td>III B2</td>
<td>NC</td>
<td>PR</td>
<td>18 (alive)</td>
</tr>
<tr>
<td>MK</td>
<td>24</td>
<td>M</td>
<td>Mixed</td>
<td>III C</td>
<td>PD</td>
<td>PR</td>
<td>6 (dead)</td>
</tr>
<tr>
<td>NR</td>
<td>26</td>
<td>M</td>
<td>Chorio</td>
<td>III B1</td>
<td>PR</td>
<td>CR</td>
<td>35 (alive, NED)</td>
</tr>
<tr>
<td>HM</td>
<td>42</td>
<td>M</td>
<td>Chorio</td>
<td>III C</td>
<td>PD</td>
<td>PR</td>
<td>15 (dead)</td>
</tr>
</tbody>
</table>


the evidence that PBSC is an appropriate candidate to substitute the bone marrow stem cells.

To date, we have conducted high-dose chemotherapy using hematopoietic stem cell transplantation in 15 patients (malignant lymphoma, germ cell tumor, breast cancer, etc.) who were not indicated for surgical treatment. Among them, 9 complete responses (CRs) and 6 partial responses (PRs) were obtained, which were very favorable results. In collaboration with the Urology Department of the Sapporo Medical University School of Medicine, we treated five poor risk patients with germ cell tumor (according to National Cancer Institute risk criteria) with a high dose chemotherapy protocol using carboplatin (400 mg/m²/day -5 to -3), VP 16 (400 mg/m²/day -5 to -3), ifosphamide (2.5 g/m²/day -5 to -3), PBSC transplantation (day 0) and G-CSF administration (from days 0 to 14). It is known that these patients usually die within 24 months if the conventional (regular-dose) chemotherapy is undertaken. The clinical effect of this therapy revealed 2 CRs and 3 PRs (Table 2) and the 40-months survival was 60% by Kaplan-Meier analysis, which was very effective. Further application of this treatment is promising if more treatment regimens for curing other cancers are established.

References

5. Recent Advances in Inoperable Gastric Cancer Chemotherapy

Minoru KURIHARA and Masaaki MATSUKAWA

Key words: gastric cancer, chemotherapy evaluation criteria, 5'-DFUR, CDDP

1. Response criteria of gastric cancer chemotherapy by the Japanese Research for Gastric Cancer

It is extremely difficult to accurately measure the size of the primary foci in the majority of patients. The Japanese Research for Gastric Cancer have developed a system of evaluating the response to chemotherapy that is widely used in Japan. The system is based on the regression of the primary gastric tumor size, and it is referred to as the Japanese Research for Gastric Cancer (JRG) criteria. The JRG criteria categorize the response to chemotherapy into four categories: complete response (CR), partial response (PR), no change (NC), and progressive disease (PD).

- **Complete Response (CR):** The primary gastric tumor and all metastatic lesions disappear and do not recur within 24 months.
- **Partial Response (PR):** The primary gastric tumor and all metastatic lesions have shrunk by more than 50%.
- **No Change (NC):** The primary gastric tumor and all metastatic lesions have not changed within 24 months.
- **Progressive Disease (PD):** The primary gastric tumor and all metastatic lesions have increased by more than 25%.

The JRG criteria are based on the regression of the tumor size and are considered more objective than subjective assessments. This system has been widely adopted in Japan and is now being used in many other countries as well. The JRG criteria have also been used to evaluate the effectiveness of new drugs and treatment regimens in clinical trials. The use of the JRG criteria has improved the accuracy of evaluating the response to chemotherapy and has provided a standardized method for comparing the results of different treatment regimens.