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administration and 3-days withdrawal/week plus CDDP: 80mg/m²/day, q 3 weeks, and regimen B was 5'-DFUR: 1,400mg/m²/day, 4-days administration and 10-days withdrawal/every 2 weeks plus CDDP: 80mg/m² day, day 5, q 4 weeks.

The overall response rate for Regimen A was 40% (95% CI, 20.8–59.2%) and that for Regimen B was 36.4% (95% CI, 22.7–50.1%).

Quality of life evaluation

The quality of life (QOL) of patients undergoing chemotherapy is an important clinical endpoint. Changes of QOL with time in patients who had undergone abovementioned 5'-DFUR+CDDP for inoperable gastric cancers were investigated. The items studied included appetite, general feeling, sleep, fatigue, pain, family understanding and cooperation, association with friends and colleagues, anxiety concerning the disease, expectations of treatment and daily life activities. These 10 items were recorded by the patients for 2–4 weeks in five grades by a combination of the analog scale and category scale method. Moreover, the analog scale, 10 cm in length about “feeling” was also checked at the same time. By chance we could compare the change in the 10 items in the QOL questionnaires between Regimen A and Regimen B. A remarkable difference between Regimen A and Regimen B was recognized for appetite, general feeling, fatigue, expectations of treatment and the analog scale about “feeling” based on the followup data of the QOL questionnaire. As a result, from the point of QOL, Regimen B is considered to be much better than Regimen A.

In the near future, Leucovorin plus 5-FU and CPT-11 are expected to be used for advanced gastric cancers.

6. Angiotensin II-Induced Hypertension Chemotherapy (IHC) for Advanced Gastrointestinal, Pancreatic and Hepatobiliary Carcinoma

Masahiko Hoshi and Haruhiko Sato*

Key words: tumor microcirculation, induced hypertension chemotherapy (IHC), enhancement of drug delivery

Tumor blood flow was remarkably increased under an angiotensin II (All)-induced hypertension state and the increase in blood flow was selective in the tumor tissues when the mean arterial blood pressure did not exceed 150 mmHg. When blood flow in normal tissue such as the brain, bone marrow and liver did not increase, the blood flow of the kidney and subcutis conversely decreased (1).

Induced Hypertension Chemotherapy (IHC) is a drug delivery system based on this microcirculatory difference between the tumor and normal tissues. This clinical application has been carried out for various kinds of advanced malignancies since 1978.

Some experimental evidence has revealed that the increase of tumor blood flow was observed in all tumors arising from various organs and various types of histology (2, 3) and that the chemotherapeutic inhibitory effects on tumor growth in the liver and the peritoneum were enhanced under All hypertension (4, 5).

By comparison of Computed Tomography (CT) values in region of interests (ROIs) using dynamic CT, the enhancement of contrast media in the tumor area was clearly elevated under All hypertension (6).

The results of a cooperative, randomized, controlled trial for advanced gastric carcinoma showed a significant enhancement in the anti-cancer effects in the IHC-treated group compared with that of the non-IHC group which received ordinary iv treatment under normotension (7). The frequency and grade of the side effects of the anti-cancer drugs were not statistically different between the IHC and non-IHC groups. Moreover, pathohistological effects on the tumor tissues were evidently augmented in the gastrectomy-receiving patients of the IHC group. According to the criteria of the General Rules for the Stomach Cancer Study, one case of grade 3, 2 of grade 2, 3 of lb, and 2 of 1a were obtained in the IHC group, while one of 1b, 3 of 1a, and 2 of zero were obtained in the non-IHC group (8).

The procedure of IHC has been previously described elsewhere (9).

There were some accompanying symptoms such as a sense of chest oppression and headache when the blood pressure was only elevated, but they were not so severe that the IHC could not be performed in nearly all the cases. But, careful attention to control the blood pressure values must be paid to avoid excess...
Angiotensin II-Induced Hypertension Chemotherapy

Table 1. Clinical Summary of Induced Hypertension Chemotherapy for Non-Resectable Carcinoma Patients in Phase II Trial (1978-93)

<table>
<thead>
<tr>
<th>Primary organ</th>
<th>Evaluable/entered</th>
<th>CR</th>
<th>PR</th>
<th>NC (MR)</th>
<th>PD</th>
<th>Response rate (%)</th>
<th>Survival days mean±SD median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>10/12</td>
<td>4</td>
<td>3</td>
<td>(2)</td>
<td>3</td>
<td>40.0</td>
<td>166±125 164</td>
</tr>
<tr>
<td>Stomach</td>
<td>87/106</td>
<td>7</td>
<td>22</td>
<td>46 (13)</td>
<td>12</td>
<td>33.3</td>
<td>306±400 223</td>
</tr>
<tr>
<td>Pancreas</td>
<td>34/43</td>
<td>9</td>
<td>17</td>
<td>(7)</td>
<td>8</td>
<td>25.7</td>
<td>221±219 171</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>19/24</td>
<td>3</td>
<td>8</td>
<td>–</td>
<td>8</td>
<td>15.8</td>
<td>306±313 252</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>5/6</td>
<td>2</td>
<td>2</td>
<td>(1)</td>
<td>1</td>
<td>40.0</td>
<td>358±207 454</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>2/2</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>153</td>
</tr>
</tbody>
</table>


Moreover, an important technique in IHC is how to induce an elevated blood pressure level and to maintain it steadily. A good pattern of blood pressure elevation was a factor in producing a good clinical response.

This paper presents the results of Phase II of the IHC trial for non-resectable patients who had esophageal (ESP), gastric (STM), pancreatic (PNC), colorectal (COR), biliary tract (BT) cancer or hepatocellular carcinoma (HCC) and who were admitted to Tohoku University Institute Hospital and its related institution from 1978 to 1993.

The number of patients entered in Phase II was 193 [ESP 12, STM 106, PNC 43, COR 24, BT 6, and HCC 2]. A combination schedule of adriamycin (ADM), 5-fluorouracil (5-FU), mitomycin C (MMC) was used mainly for STM, PNC, BT, HCC and ESP, although MMC was changed cisplatin (CDDP) for ESP from 1984. MMC and 5-FU were selected for COR. According to the criteria of the Japan Society for Cancer Treatment, the cases receiving more than the first course of IHC were evaluated.

The response rate was 40.0% (4 Partial Response (PR)/10 evaluable) for ESP, 33.3% (7 Complete Response (CR) + 22PR/87) for STM, 25.7% (9PR/34) for PNC, 40.0% (2PR/5) for BT, 15.8% (3PR/19) for COR and 0% for HCC.

The mean (range, median) survival days after the start of IHC was 166 (44-387, 164: ESP), 306 (21-2,122, 223: STM), 221 (75-1,024, 171: PNC), 306 (71-1,520, 252: COR), 358 (225-651, 454: BT) and 153 (89, 214: HCC). The mean survival time of pathological DS 7 (53.8%) of 13 cases. The mean survival time (MST) of the patients who obtained a pathological DS was 1,040 days, and it was significantly longer than that of the non-pathological DS patients: 322 days (p<0.01).

Selective drug delivery is an essential factor for the enhancement of cancer chemotherapeutic effects, together with the selection of effective drugs against the tumor population.

In conclusion, IHC would be useful for any type of cancer and for any stage of disease, but its effectiveness should be confirmed according to clinical trials.

References