Clinical Appraisal of Hyperthermic Treatment Combined with Low Dose of Gemcitabine Hydrochlo Ride for the Unresectable Pancreas Cancer

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Abstract: Background: For the patients with unresectable pancreas cancer, improvement of quality of life (QOL) and prolongation of prognosis are most important proposition. The consecutive treatment with few side effects is required. For an unresectable pancreas cancer, we perform the hyperthermic therapy combined with low dose Gemcitabine Hydrochloride (GEM). In this study, we reviewed clinical significance of thermochemotherapy for unresectable pancreas cancer as tumor dormancy therapy.

Object and a method: For the 10 patients with unresectable pancreas cancer, we have performed thermochemotherapy. Hyperthermia was administered once a week and GEM was simultaneously given during hyperthermia. The effect of thermo-chemotherapy was evaluated from tumor contraction effect, variation of tumor marker value, and clinical benefit (assessed by pain relief and Karnofsky Performance status (KPS)). The prognosis of these patients compared with the 11 patients received best supportive with unresectable pancreas cancer (BSC group).

Results: The frequency of thermochemotherapy ranged from four sessions to 43 sessions (19.6 ± 12.1). As the antitumor effects, response rate was 10% and the decrease of a tumor marker was found in eight patients (80%). Responder in clinical benefit was recognized in six patients (60%). Median survival periods were 212 days of the patients in the TC group, and 140 days in the BSC group. The significant difference was accepted in both survival curves. Three out of 11 patients in the BSC and nine of 10 patients in the TC group could discharge from the hospital. Severe adverse reaction as grade 3 or 4 was not encountered.

Summary: The hyperthermic treatment combined with low dose GEM for the patients with unresectable pancreas cancer could be continued for a long term under the favor of few harmful toxicity, and which should bring about the favorable clinical benefit and the improvement of prognosis.

Key words: gemcitabine hydrochloride, pancreas cancer, thermo-chemotherapy

Introduction

For the patients with unresectable pancreas cancer who cannot expect a prolonged prognosis, the
Improvement of quality of life (QOL) and extension of life expectancy should be the most important problem. The treatment to the patients must have a little toxicity and be continued for long periods. There have been many reports on anti-tumor effects of combination therapy with hyperthermia and radiation. In recent reports, it has been indicated that hyperthermia associated with carcinostatic agents has been useful anti-tumor therapy.

Gemcitabine Hydrochloride (GEM) is an intranucleoside analog that has a broad spectrum of antitumor activity in solid tumor. The drug requires intracellular phosphorylation that results in accumulation of difluorodeoxycytidine triphosphate (dFdCTP). And this drug reduces intracellular deoxynucleoside triphosphate pools, presumably by inhibiting ribonucleotide reductase. Burrid et al. described that GEM was more effective than 5-FU in alleviation of some disease-related symptom in patients with advanced, symptomatic pancreas cancer, and conferred a modest survival advantage over treatment with 5-FU. Although GEM had the favorable results for the advanced pancreas cancer, toxicities as grade 3 or 4 myelosuppression was often found in regimen of high dose GEM.

We attempted to continue hyperthermic therapy with chemotherapy as long as the patient was tolerable. Therefore, a few drug-related toxicities would be desirable. In the present study, we estimated clinical validity of thermotherapy with low dose GEM to the patients with unresectable pancreas cancer.

Materials and Methods

Patients (Table I)

During the periods 1998-2003, 21 patients with unresectable pancreas cancer were treated at Higashiosaka City General Hospital. The ten patients after 2001 (TC group) were performed thermochemotherapy combined with low dose of GEM, and best supportive care was performed to 11 patients (BSC group) before 1999 when thermochemotherapy was not introduced. The age and gender was not different between the two groups. Among the 21 patients, five patients was performed

| Table I. Background of The 21 Patients with Unresectable Pancreas Cancer |
|-----------------------------|-----------------------------|
| Patients                    | TC group  | BSC group |
| Age (Mean±SD)               | 71±7       | 64±13     | N, S       |
| Gender (male/female)        | 7/3        | 6/5       | N, S       |
| Method of operations        |            |           |
| Choledochojejunostomy       | 2          |           |
| Gastrojejunostomy           | 2          |           |
| Cholecystojejunostomy       | 1          |           |
| Probelapatomy               | 1          |           |
| non-operation               | 8          | 7         |
| Reasons of unresection      |            |           |
| Vascular invasion           | 8          | 8         |
| Peritontial dissemination   | 1          |           |
| Liver metastasis            | 1          | 3         |

TC: thermochemotherapy, BSC: best supportive care
gastrointestinal or biliary tract bypass operation, and one patient (4.8%) was done exploratory surgery, and residual 15 patients (71.4%) have been done no operation. The reasons for unresection of the lesions were vessel invasion in 16 (76.2%), liver metastasis in four (19%) and peritoneal dissemination in one (4.8%).

Method of thermochemotherapy

Hyperthermia was induced once a week using radio-frequency (13.56 MHz) capacitive heating equipment (OMRON. Thermox 500, Tokyo). The duration of heating session was from 40 minutes to 60 minutes and the power output of heating was from 400 Watts to 500 Watts. The measurement of temperature of the deep sites had been performed through the biliary drainage tube in five patients. In all these 5 patients, maximum tumor temperature of 42°C or above was obtained over the course of treatments.

To the 10 patients (TC group), GEM (200mg/body) was simultaneously administered by dropping injection in 30 minutes during hyperthermia treatment for combine chemotherapy. In the 11 remaining patients (BCT), pain relief with medical treatment was performed.

Evaluation

Hyperthermic treatment was estimated from anti-tumor effects and clinical benefit. As anti-tumor effect, we estimate the shrinkage of the tumor from computed tomography, and the serum levels of tumor markers before and after the hyperthermic therapy. More than 50% shrinkage of the lesions was defined partial response (PR). Less than 50% regressions or less than 25% growing of tumor volume is defined no change (NC). Enlargement of tumor volume more than 25% is defined progressive disease (PD). Clinical benefit was estimated from the effect on pain relief (assessed by pain intensity and analgesic consumption) and functional impairment (assessed by Karnofsky Performance Status (KPS)). Each patient was classified as either positive, stable, or negative in both of clinical benefit measures, respectively. All the patients were categorized three groups as a responder, stable, and nonresponder by

Table II. Classifications and Assessment for Clinical Benefit

<table>
<thead>
<tr>
<th>Classifications for clinical benefit</th>
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<tr>
<td>Pain relief</td>
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<tr>
<td>positive: fall of pain intensity, or reduction of analgesic consumptions</td>
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<tr>
<td>negative: rise of pain intensity, or increase of analgesic consumptions</td>
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<tr>
<td>stable: any other results</td>
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<tr>
<th>Karnofsky Performance Status</th>
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<tr>
<td>positive: improvement of ≥ 10 points from baseline</td>
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<tr>
<td>negative: worsening of ≤ 10 points form baseline</td>
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<tr>
<td>stable: any other results</td>
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<th>Assessments for clinical benefit</th>
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<tr>
<td>Responder: improvement in both parameters, or stable in one parameter and improvement in the other parameter</td>
</tr>
<tr>
<td>Stable: stable in both parameters</td>
</tr>
<tr>
<td>Nonresponder: worsening in both parameters, or stable in one parameter and worsening in the other parameter</td>
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assessment of clinical benefits (Table II). Survival and the period of outpatients setting in TC group were compared with those in BSC group.

Ethical approval from the institution concerned from all patients. The statically significance of the differences between the group was evaluated by χ2 test and log-rank test.

Results

The frequency of thermochemotherapy of the all patients ranged four sessions to 43 sessions, and the mean was 19.6 sessions (Fig. 1). Eight patients have already died and two patients are continuing hyperthermic treatment. Table III lists the antitumor effects of TC group. Reduction of a neoplasm was obtained in one patient, and response rate was 10%. The decrease of a tumor marker was accepted in eight patients (80%), and three among these patients fell to 50% or less before the initiation of hyperthermic treatment. Both pain relief and KPS improved in five patients (50%), and one patient (10%) had an improvement in pain relief with stable in KPS. Therefore, six patients (60%) were classified as clinical benefit responder from their parameters. One patient had a worse in both of pain relief and KPS, and two patients had a worsening in KPS with stable in pain relief. Accordingly, three patients (30%) were classified as nonresponder. The one remaining patient was stable in both parameters (Table IV). Median survival periods were 212 days of the patients in the TC group, and 140 days in the BSC group. The
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The probability of surviving beyond 6 months and 12 months were 60% and 10% in the TC group, and 9.1% and 0% in BSC group, respectively (Fig. 2). The significant difference was accepted in both survival curves (log-rank test, p <0.05).

In BSC group, three out of 11 patients could not discharge from the hospital. The average of outpatient period of eight patients who could be discharged was only 45% of survival period (Fig. 3). On the other hand, nine patients out of 10 patients of the TC group could discharge from the hospital and the duration of outpatient was 70% or more of survival periods (Fig 4).

Toxicity was graded according to the WHO scale. Leucopenia of grade 1 occurred in one patient, nausea of grade 1 and 2 in one patient, respectively. Severe adverse reaction as grade 3 or 4 was not encountered. All ten patients who underwent hyperthermic treatment had no severe event as burn injury during heating.
Fig. 3. The periods of outpatient treatment during the survival periods of BSC group.

In BSC group, three out of 11 patients could not discharge from the hospital. The average of outpatient period of eight patients who could be discharged was only 45% of a survival period.

Fig. 4. The periods of outpatient treatment during the survival periods of TC group.

In TC group, outpatients treatment was performed in nine of 10 patients, and the periods of outpatient was 70% or more in the survival period.
Discussion

Pancreas cancer has the worst prognosis among gastrointestinal malignancy, and was the fifth most common cause of death in Japan. Of over all pancreas cancer, the median survival time (MST) and five years survival rate was 8.6 months and 9.7%, respectively. Although surgical resection is considered to be the only curative treatment, resection rate has been only 69.7%, and the stage IV cases have occupied absolute majority of all excised patients. In the excised cases, the MST was 11.7 months and five years survival rate was only 13.4%. Therefore, only the detection of the lesion in the early stage will contribute to improving the prognosis of pancreas cancer. Meanwhile, MST of unresectable pancreas cancer was only less than five months and the prognosis was extremely poor.

GEM is a deoxycytidine analogue with a broad spectrum of activity against transplantable solid tumors and xenografts in experimental animals and shows a greater therapeutic potential than another deoxycytidine analogue. Recently, some clinical studies have demonstrated the benefits of GEM for pancreas cancer, especially in term of disease stabilization, clinical benefit response (CBR), and survival. Burris et al defined clinical benefit as a composite assessment of pain, performance status, and weight and performed a randomized trial of GEM versus Fluorouracil (5-FU) in patients with advanced pancreas cancer. They concluded that GEM was more effective than 5-Fu in alleviation of some disease related symptoms and conferred a modest survival advantage over treatment with 5-FU.

Hyperthermia has been shown to increase the cytotoxic effects of some anticancer agents by the penetration of drug into tissue and can also cause thermal destruction of cancer cells. Hyperthermia combined with chemotherapy has been expected synergistic effect and which culminated in reduction of the dose of anti-cancer agent. GEM has recently been shown to be a potent hyperthermic sensitizer in preclinical studies. Haveman J. et al explained that the timing was extremely important in combination of GEM and hyperthermia. Simultaneous application led to decreased cytotoxicity, whereas an interval between the administration of GEM and hyperthermia of 20 or 24 hr led to an enhanced cell killing effects. Thus, a favorable clinical potential of hyperthermia combine with GEM was suggested.

In this study, despite of a modest response rate of only 10% in TC group, the decrease of tumor marker was determined in 80% and clinical benefit responder was found in 60%, respectively. We believe these discrete data indicate that the pancreas lesion and the around tissue after thermochemotherapy makes severe fibrotic changes and inflammation, and which usually compromise the definition of the border between the lesions and intact tissue. Therefore, the objective assessment by computed tomographic scans after ingathering therapy for advanced pancreas cancer might be too difficult. Most of the patients with advanced pancreas cancer experience tumor-related symptom as pain, nausea, appetite loss, weight loss, disability, and which mainly fluctuate according to the effect of the anti-tumor therapy. Clinical benefit composed with the transition of pain and KPS should have a great significance as a method to assess the effects of thermochemotherapy.

Since of administration of GEM in the standard dose of ≥1000mg/m² caused hematological toxicity, chemotherapy sometimes could not be continued. Significant GI toxicity was encountered with GEM delivered at weekly doses of > 400 mg/m², and most of the patients treated with > 400mg/m² required hospitalization for management of hematological and GI toxicities. Interruption of the therapy by
treatment-related toxicity would shorten the prognosis consequently. Symptomatic toxicity of hyperthermia combined with low dose GEM (200mg/body) has been quite a little, with a low incidence of nausea and appetite loss. In this study, nine patients (90%) out of TC group could discharge from the hospital and underwent continuously thermochemotherapy during 70% or more of the survival period. In contrast, eight patients (72%) of BSC group could leave the hospital, but the duration in the outpatients setting was only 45% of the survival periods. The survival advantage of the patients in TC group was highly statistically significant compared with patients in BSC group (7.1 vs. 4.7 months). For the patients with advanced pancreas cancer, alleviation of treatment related symptom results in maintains of high quality of life, and outpatient thermochemotherapy could be constantly continued. Data from more than 750 patients treated with GEM monotherapy in randomized trial have shown consistent results with a median survival of 5.4 to 6.1 months and a 1-year survival rate of 18% to 24% (19). In our study, a median survival and a 1-year survival rate of TC group was 7.1 months and 10%, respectively. This result was comparable to those of treatment with GEM alone in the standard dose of \( \geq 1000\, \text{mg/m}^2 \).

For the patients with advanced pancreas cancer, thermochemotherapy combined with low dose of GEM brought about improvements of tumor-related symptoms and contribute a clinical benefit in high frequency with low treatment-related toxicity. Therefore, thermochemotherapy could be repeated for a long time and associated with improved survival. We conclude that this treatment might be appreciably useful therapy for the patients with advanced pancreas cancer.

References


切除不能膵癌に対する低用量塩酸ゲムシタビンを
併用した温熱化学療法

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要 旨：【目的】非切除膵癌に対し低用量塩酸ゲムシタビン (GEM) を併用した温熱療法を施行した。【対象ならびに方法】非切除膵癌 10 例に対し、GEM200mg を併用した温熱療法 (13.56MHz 誘電加温) を週 1 回行った。抗腫瘍効果、症状緩和効果、予後を best supportive care を施行した非切除膵癌 11 例 (BSC 群) と比較した。【結果】抗腫瘍効果は奏効率 10%, 腫瘍マーカーの低下 6 例, 症状緩和効果有効 5 例であった。温熱開始後の生存期間は BSC 群に比し有意に長かった。有害事象は grade2 までの消化器症状であった。【まとめ】低用量 GEM 併用した温熱化学療法は長期間の病単治療が可能で意義ある治療法と思われた。