Review

Improvement of Cancer Cachexia with Chemothermotherapy in a Patient with Advanced Pancreatic Cancer

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Abstract: The ultimate goal of cancer treatment is to achieve a complete eradication of the cancer. However, patients with terminal cancer are also treated to obtain an improvement in their quality of life (QOL).

In this report, we describe the dramatic response of an end-stage pancreatic cancer patient with cachexia to a combination of hyperthermia (HT) and chemotherapy (CH). The patient was treated with a combination of intermittent 5-FU/cisplatin (CDDP) therapy and HT. Three months later, the local recurrent cancer had disappeared, the liver metastases were reduced by 80%, the lung metastatic lesion was markedly reduced, tumor markers had returned to normal, and the cachexia had been almost reversed. Performance status (PS) improved from 4 to 1, QOL improved, and the patient survived until his 258th hospital day.

In this patient, the combination of CH and HT was useful not only for improvement of cachexia, but also for tumor reduction. A possible mechanism leading to this effect is discussed.

Key Words: advanced pancreatic cancer, chemothermotherapy, cancer cachexia, cytokines

Introduction

The response rate (complete response (CR)+partial response (PR)) in response to CH for pancreatic cancer has generally been very low[1]. The response rate of pancreatic cancer to MMC/5-FU has been reported to be as low as 7% (2/27)[2]. The response rate of pancreatic cancer to even standard gemicitabine (GEM) CH was 8.2-18%[3,4]. However, chemothermotherapy (CHT) has been reported to produce better results than CH alone. A multi-institutional study on the effect of MMC-5FU in combination with HT against pancreatic cancer showed a response rate of 36.4% (8/22, with CR in 3)[5]. Another multi-institutional study conducted by research teams of the Japanese Society for Thermal

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Medicine reported a response rate of 30% (8/27, with CR in 3) for CHT in 1992[2]. Kakehi et al.[6] reported a response rate of 60% (6/10) for CHT in 1993.

Advanced and end-stage cancers are generally associated with an impaired general condition. CHT has been reported to improve PS in pancreatic cancer patients by 43% (39/90)[2], 45.2% (14/34)[5], and 60% (6/10)[6]. Ohno et al.[2] reported that the pain improvement rate produced by CHT was as high as 75% (40/53). Miyazaki et al.[7] reported that the clinical benefit rate of a combination of low-dose GEM and HT was high at 60% (6/10), while Burris et al.[8] reported that the clinical benefit rate of GEM monotherapy was as low as 23.8% (15/63). Ohno et al.[2] reported that CHT significantly increased the survival in pancreatic cancer patients : the 50% survival time was 7 and 2 months in patients treated by CHT or CH, respectively. Theses studies clearly demonstrated that CHT is useful not only for life-prolongation but also for improving the QOL through an improving PS and reduced pain in the patients. Advanced and end-stage cancers are often associated with cachexia, which impairs the QOL and prevents survival enhancement, making the treatment of cachexia important. Although the effect of CHT on PS, pain, and survival have been reported as described above, little is known about effect of CHT on cachexia itself in pancreatic cancer patients. As described later, the mechanism of development of cachexia has been slowly elucidated in recent years. The treatment of cachexia has been mainly a symptomatic treatment[9,10], although therapy with the immunotherapeutic agent lentinan has been proposed[11].

In this report, we describe a case study of a patient with cachexia in end-stage pancreatic cancer, and whose cachexia was virtually reversed by CHT. We further discuss a hypothesis to explain how CHT may have improved the cachexia in the patient, and review relevant literature on this mechanism.

Table I. Laboratory findings.

Complete blood contents		on admission	120days after ad.	240days after ad.
WBC	(/μl)	8,900	4,200	5,500
RBC	($\times 10^4/\mu$l)	223	209	228
Hb	(g/dl)	8	8.5	8.8
Ht	(%)	22.4	23.5	24.8
PLT	($\times 10^4/\mu$l)	41.4	40	29.3
Blood chemistry				
TP	(g/dl)	5.5	5.7	5.5
Alb	(g/dl)	2.4	3.6	3.2
TB	(mg/dl)	0.4	0.5	0.4
AST	(IU/l)	175	15	44
ALT	(IU/l)	109	18	13
ALP	(IU/l)	929	456	344
LDH	(IU/l)	853	180	625
LAP	(IU/l)	123	71	71
γ-GTP	(IU/l)	262	131	96
Gluc	(mg/dl)	119	148	85
TC	(mg/dl)	63	66	84
TG	(mg/dl)	49	97	93
BUN	(mg/dl)	23.1	7.2	10.3
Cr	(mg/dl)	0.9	0.5	0.47
Tumor markers				
CEA	(ng/dl)	207.8	5	81.8
CA19-9	(ng/dl)	506	30	818
Supan-1	(u/ml)	207	28	263
Others				
Ferritin	(ng/ml)	909	1,025	663

Case Report

A 56-year-old man noticed jaundice on July 2003, and visited a local clinic. He was diagnosed with pancreatic cancer, referred to a hospital specializing in cancer treatment, and admitted there on August 25. He underwent pancreatic-oduodenectomy on September 8, and

was discharged on September 27. In March of the next year, he was found to have liver metastases, readmitted to the same hospital on March 22, and received GEM treatment. CT imaging revealed a local recurrence and multiple metastases in the liver, periaortic lymph node, and right lung. The administration of three courses of GEM was ineffective, and resulted in progressive disease (PD). After the attending physician informed him that he was in a terminal stage, he left the hospital on June 1 and

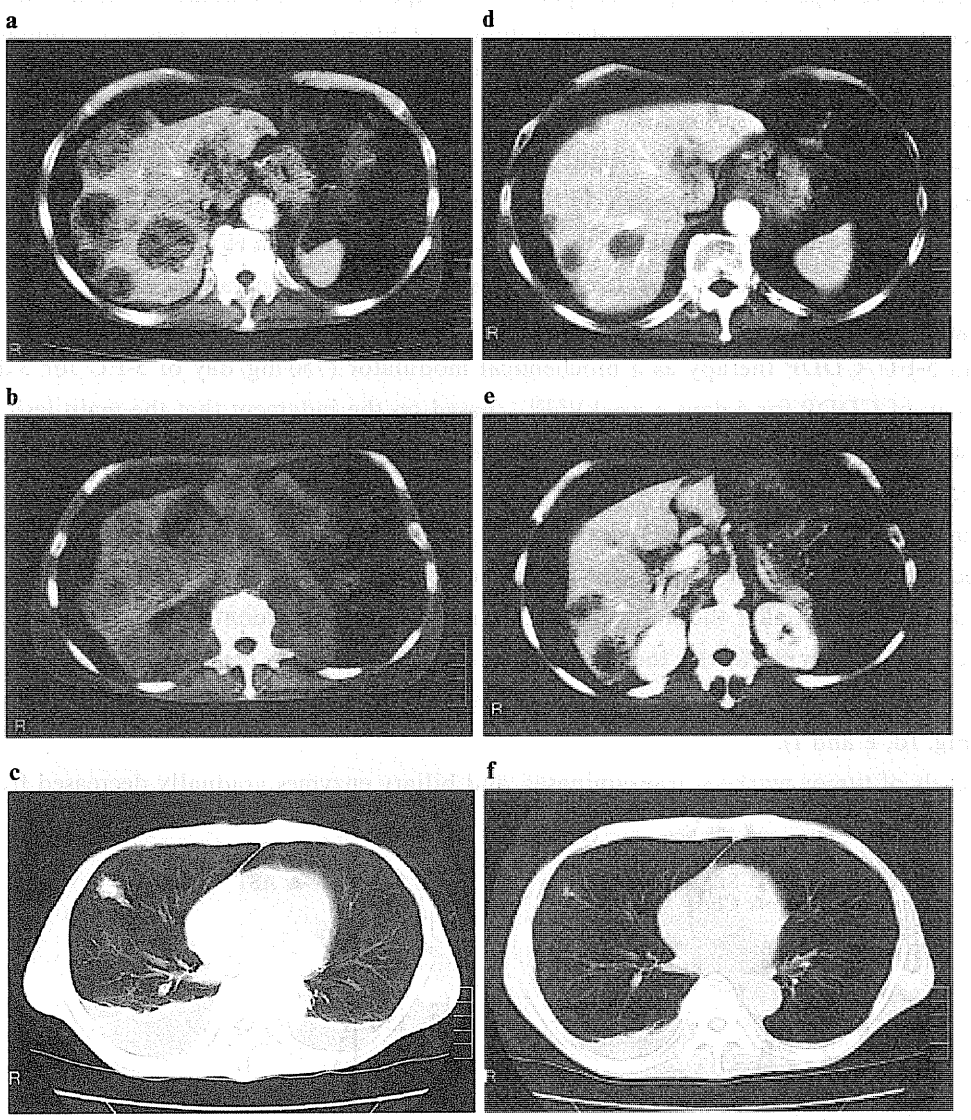

Fig. 1. CT findings on admission (a, b and c) and 3 months after treatment (d, e and f).

a : There were multiple tumors with central degeneration and necrosis in both hepatic lobes.
b : There were local tumor recurrences in the pancreatic head and the origin of the celiac artery.
c : There was a 15-mm tumor in the right middle lobe of the lung with bilateral pleural effusion.
d : The liver metastatic lesions were reduced in size by 80%.
e : The local recurrent tumor had disappeared, and the volume of ascitic fluid was reduced.
f : The tumor in the right middle lobe of the lung had markedly regressed, and the volume of the pleural effusion was reduced.

he requested HT, at our hospital on July 5. On admission, he was thin, measuring 159 cm in height and weighing 49 kg and complained of anorexia, general fatigue, and diarrhea, and he could not roll over by himself. His PS was listed as 4 ; blood pressure was 156/60 mmHg ; and pulse rate was 76/min. His skin was pale but not jaundiced. The bulbar conjunctivae were anemic. He had a thin subcutaneous fat layer, with muscular atrophy and generalized edema. Physical examination of the chest revealed no abnormalities. No superficial lymphadenopathy was palpable. The abdomen with an old surgical scar was markedly distended with ascites. Hematology and blood chemistry tests on admission showed anemia, mild thrombocytosis, hypoproteinemia, hypoalbuminemia, and hypocholesterolemia, with elevated levels of transaminases, biliary enzymes, ferritin, and tumor markers (Table I).

CT scans showed massive ascites, multiple tumors with central degeneration and necrosis in both lobes of the liver, local tumor recurrence in the pancreatic head and the origin of the celiac artery, and a 15mm tumor in the right middle lobe of the lung with pleural effusion (Fig. 1a, b and c). The findings from these tests, along with weight loss, anemia, general fatigue, and generalized edema, led to a diagnosis of end-stage pancreatic cancer with cachexia. The patient underwent CHT, that is, a combination of intermittent 5-FU/CDDP therapy as a biochemical modulator (750 mg/day of 5-FU for 3 days a week and 3 mg/day of CDDP for 5 days a week)[12,13]. Based on the judgment that the main lesions were the liver metastases and a local recurrence, HT was confined to the upper abdomen, excluding the chest. HT (1285 W, 45 min/session), was applied three times a week using a deep heating device, the Thermotoron RF-8 (Yamamoto Vinita Co., Ltd., Osaka). Total parenteral nutrition (TPN) was administered to the patient because of his loss of eating ability due to anorexia. The liver metastases began to regress gradually about 1 month after the start of CHT. On CT images at 3 months, the liver metastatic lesions were reduced in size by 80%, the local recurrence and lymph node metastases disappeared, the lung metastatic lesion outside the heating site markedly regressed, and the volume of pleural effusion was reduced (Fig. 1d, e and f).

The levels of tumor markers, transaminases, and biliary enzymes gradually decreased from 1 month

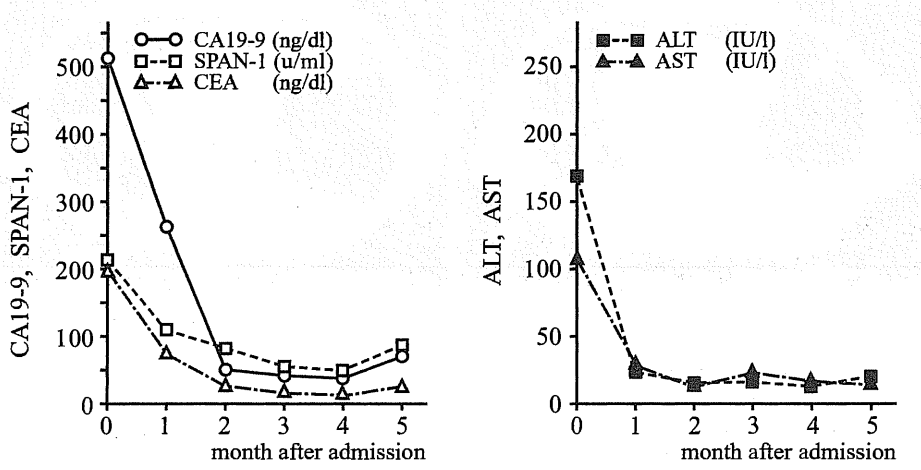

Fig. 2. The time-course of changes in tumor markers and transaminases.
Levels of tumor markers gradually decreased from 1 month after the start of CHT and returned to normal at 3 months. Levels of transaminases returned to normal at 1 month after the start of CHT.

after the start of CHT, and returned to normal in 3 months (Fig. 2). The anorexia, general fatigue, and generalized edema, noted at the time of admission, were markedly improved at 1 month after the start of CHT, and the diarrhea subsided in 2 months, so that the patient was able to walk in his room, and to stay out overnight. However, it took 5 months to terminate TPN. On admission, he had severe anemia, for which MAP blood transfusions (400 ml) were performed three times ; however, the anemia gradually improved from the 4th month to an Ht of 30%. Since he also had hypoproteinemia, he was given albumin transfusions. The hypocholesterolemia also improved but was not cured completely.

The patient was in good condition for almost 4 months, and the cachexia and QOL improved ; however, after the 180th hospital day, the tumors began to enlarge, the levels of tumor markers rose, and he died on the 258th hospital day (Fig. 3).

Discussion

Antitumor effect

The results observed in the present study are in accordance with previous reports that CHT produced a higher response rate than CH alone in patients with advanced pancreatic cancer. To achieve an optimal therapeutic effect with HT, heating conditions (such as the intratumor temperature, heating time, number of heat treatments, and interval between heat treatments) are important[14,15]. In general, effective HT conditions are considered to occur when the tumor can be heated to 42.5°C or higher, for 40-60 min, once or twice a week[15]. Although the tumor temperature was not measured directly in the present study, the RF output was maintained at 1285 W.

Imada et al.[16] reported that the esophageal temperature was about 43°C when lung cancers were heated with a RF output of 1200 W. Therefore, it would be reasonable to assume that the temperature of the abdominal tumor in the present patient would rise to about 43°C. In a study with femoral subcutaneous tumors in mice, Miyata et al.[17] found that daily heating produced a stronger antitumor effect, and concluded that the problem of thermotolerance could be ignored.

In the present study, HT was applied three times a week. Based on the results of Miyata et al.[17], it was assumed that thermotolerance was not a major problem in the treatment of pancreatic cancer in this patient. HT is usually applied 1-12 times[14] in the treatment of various human cancers, but the number of heat treatments in the present study was not restricted.

It is thought that the anticancer drugs 5-FU and CDDP used in the present study not only caused cancer cell death (probably through apoptosis), but also increased the thermosensitivity of tumor cells. It is also thought that biochemical modulation therapy (intermittent FP therapy)[12,13] had a further additive effect in combination with HT.

Although HT was not performed for the lung metastatic lesion in this patient, a marked regression of the lesion in the lung and a reduction in the volume of the pleural effusion was observed. It has been reported in recent years that HT increases anti-cancer immunity. Miyata et al.[17] observed a significant activation of immune competence after the heating of tumors at temperatures below 42.5°C. Terunuma et al.[18] reported that NK cells were activated by mild HT. It is thought that HT applied to the abdomen not only had an antitumor effect on the liver metastatic and local recurrent lesions, but also induced an immune reaction against the lung metastasis. It is further thought that HT inhibited TGF-β and Th2

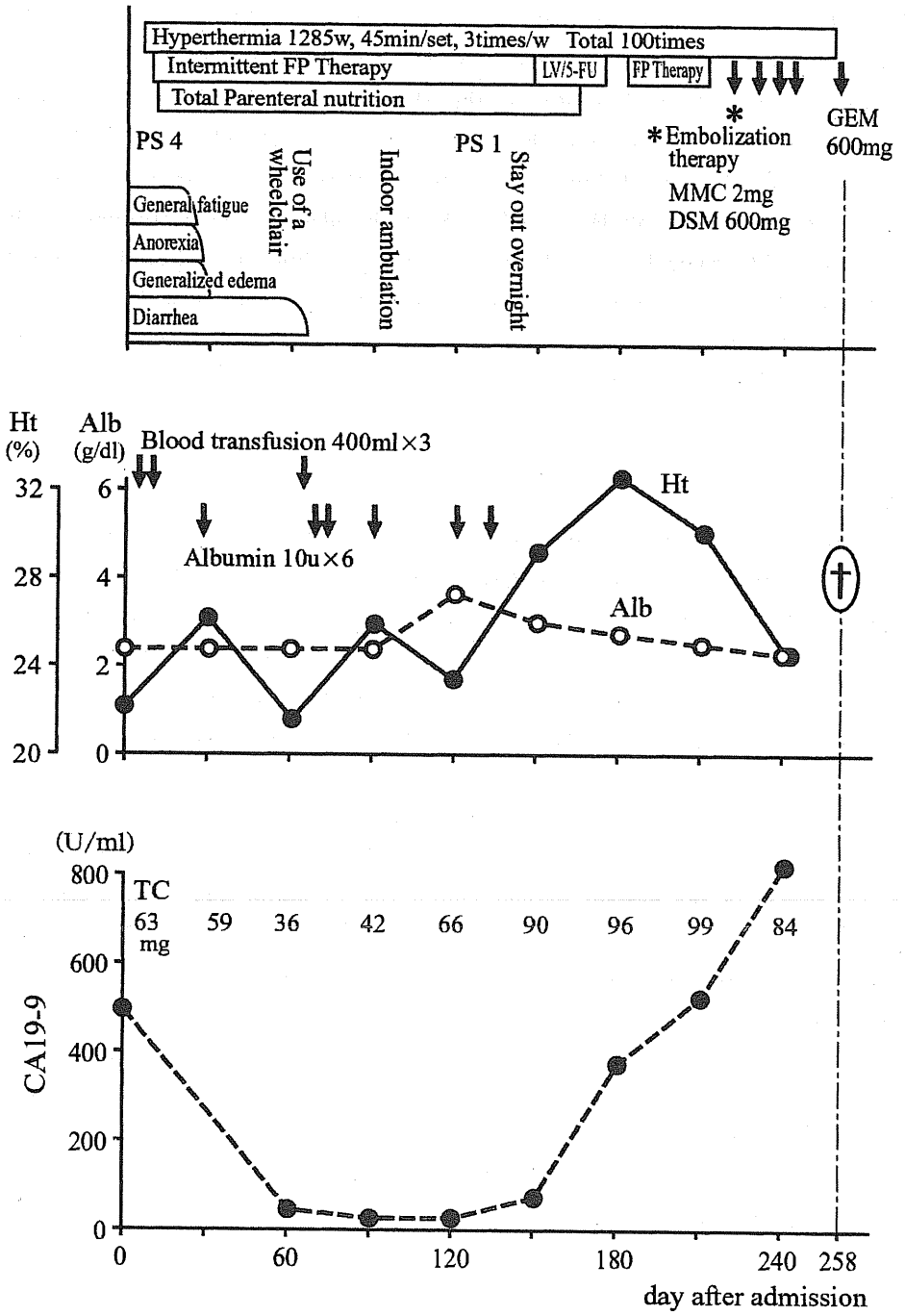

Fig. 3. Clinical course.
General fatigue, anorexia and generalized edema subsided after 1 month, diarrhea after 2 months, following start of CHT, and PS improved from 4 to 1. The condition of patient remained stable for an additional 4 months, but subsequently became refractory to therapy, and the patient died on the 258th hospital day.

cytokine production, enhanced Th1 cytokine production in these sites, and caused the activation of cellular immunity. These anti-tumor immune reactions together with intermittent FP therapy[12,13] may have worked cooperatively, resulting in the regression of the lung metastasis and reduction in the pleural effusion volume.

Although CH is usually administered to patients with a PS of 1 or 2[1], Ohno et al.[2] reported that, of the 99 advanced pancreatic cancer patients who underwent CHT, 19 had a PS of 4, as did the present patient. It seems likely that CHT is effective, even in patients with an extremely poor QOL, with a PS of 3 or 4. In addition, when used with local or regional HT, the dose of anticancer drugs may be reduced, thereby, reducing serious drug side effects.

As described above, the patient treated in the present study showed a near-complete response for about 4 months, but became resistant to CHT, and died on the 258th hospital day. Thus, even though the response was transient, a clear tumor-reducing effect, a goal of cancer therapy, was confirmed.

Pathological conditions of cachexia

The word "cachexia" is derived from the Greek words "kakos" meaning "bad" and "hexis" meaning "condition"[9,10]. It has been reported that about 50% of end-stage cancer patients lapse into this unusual pathological condition of cachexia[19], have an impaired QOL, and become weak.

Cachexia refers to an extremely poor general condition, characterized by weight loss, anorexia, fatigue, anemia, and weakness[10,19]. There are also various pathological conditions associated with metabolism, nerve function, endocrine secretion, and immunity[20]. The weight loss, which is observed in 83% (92/111)[19] of pancreatic cancer patients at diagnosis, has been reported to be due to deprivation of nutrition by rapidly growing cancer tissue, impaired absorption from the atrophied gastrointestinal mucosa, accelerated degradation and catabolism and reduced synthesis in skeletal muscles and body fat[19–21]. Langstein et al.[19] and Vigano et al.[22] described cachexia-associated metabolic abnormalities in detail (Table II). Although the metabolic abnormalities in the patient treated in the present study were in accordance with those shown in Table II, the TG level of our patient was not high. This is presumably related to the liver metastases and impaired digestion and absorption.

Table II. Some metabolic abnormalities seen in cancer cachexia.

Parameter	cachexia
Anorexia	yes
Weight loss	yes
Anemia	yes
Skeletal muscle	
body muscle mass	↓
catabolism	↑
synthesis	↓
Hepatic Protein	
synthesis	↑
gluconeogenesis	↑
Lipid	
body lipid mass	↓
liproprotein lipase activity	↓
fat synthesis	↓
serum lipid/triglyceride	↑
body glycogen mass	↑
glucoose production	↑
insulin effects	blunted
Total body water	↑

Cited from Langstein et al.[19] and Vigano et al.[22]

Cachexia and cytokines

The toxohormone theory of Nakahara et al.[23]

had long dominated the field of cachexia pathogenesis until 1986, when Mosmann et al.[24] broadly classified helper T cells into type 1 helper T cells (Th1) and type 2 helper T cells (Th2), and reported their involvement in the development of cachexia. Since then, a number of studies using animals, have studied the role of cytokines in the induction of cachexia[25–27].

Advanced cancer represents a state resembling a systemic inflammatory response syndrome, in which cytokines are produced, leaving the host in a state of hypercytokinemia[28].

Shibata et al.[20] found that the blood levels of the Th2 cytokines IL-6 and IL-10 were significantly higher (Fig. 4), and the blood level of the Th1 cytokines IL-12 and IFN-γ were significantly lower in patients with cancer cachexia than in normal subjects or in patients with non-advanced cancer. These observations indicated that cytokines are closely related to cachexia. In addition, Inui[29] reported that the pathological state of cachexia may be caused by a cytokine-induced, relative excess of leptin signals.

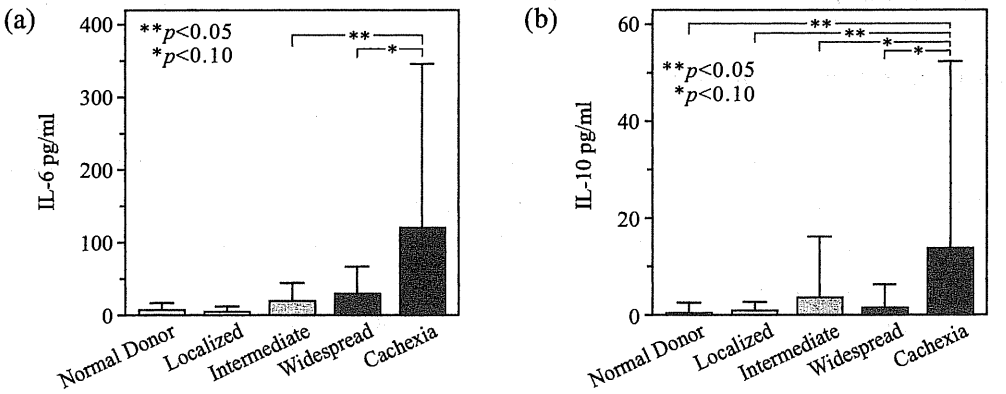

Fig. 4. Blood Th2 cytokine levels in cancer patients (Reproduced from Shibata et al.[24] with permission).
The levels of IL-6 and IL-10 in the peripheral blood of patients with gastric and colorectal cancers were measured by ELISA. Their levels were high in patients with advanced end-stage cancer (cachexia). Normal donor: Healthy adults; Localized: Lymph node metastasis (−), Intermediate: Regional lymph node metastasis (+), Widespread: Distant metastasis (+).

Pathogenesis of cachexia

An increasing number of studies with animals have demonstrated that the main cause of cachexia is TNF[19,21]. This conclusion was subsequently supported by Laviano et al.[30]. However, Tisdale[9] criticized the cytokine-mediated cachexia theory mentioned previously because a number of clinical and laboratory studies suggested that the action of cytokines alone was unable to explain the complex mechanism of wasting in cancer cachexia.

In contrast, Hamuro et al.[31] in 1996 used the Th1/Th2 balance theory[32] to explain a mechanism leading to cachexia based on experimental results. They broadly classified macrophages into two classes of macrophages i.e., reductive macrophages with a high content of glutathione, and oxidative macrophages with a reduced content.

According to their theory, the core of a tumor undergoes necrosis which induces a strong, local inflammatory reaction. The tumor becomes acidic, and the macrophages infiltrating the tumor tissue are oxidative macrophages

The production of PGE2 and Th2 cytokines (TNF, IL-1, IL-4, IL-6, and IL-10) by tumor tissues and oxidative macrophages increases, whereas a decline in reductive macrophages occurs, and results in a decreased production of Th1 cytokines (INF-γ, IL-2, and IL-12). In short an oxidative shift of the intracellular redox status results in a shift of the Th1/Th2 balance toward Th2 dominance, leading to cachexia with suppressed cellular immunity, impairing the QOL and survival. The mechanism of macrophage-mediated immune suppression and cachexia is schematically shown in Fig. 5.

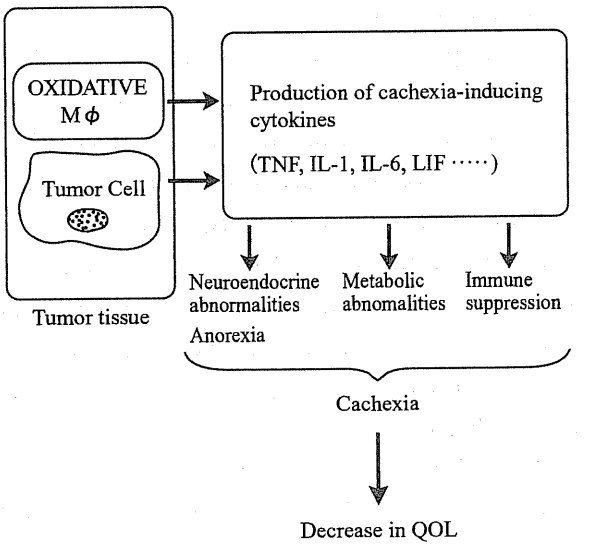

Fig. 5. Proposed mechanism for cancer cachexia (Reproduced from Hamuro et al.[31] with permission).
With the progression of cancer, a progressive increase in oxidative macrophages occurs, resulting in a shift of the Th1/Th2 balance toward Th2 dominance, leading to immunosuppression and metabolic and neuroendocrine abnormalities, causing cachexia.

Mechanism of improvement of cachexia with CHT

The dramatic improvement of cachexia in our patient treated with CHT may be explained by the theory proposed by Hamuro et al.[31].

Firstly, CHT induces tumor tissue coagulation necrosis[14] and apoptosis[33], suppresses inflammatory reactions, and inhibits Th2 cytokine production in the tumor. Next, suppression of the inflammatory reaction reduces oxidative macrophages, thereby reducing Th2 cytokine production, while activating reductive macrophages and resulting in increased Th1 cytokine production. A reductive shift of the intracellular redox status results in an alteration of the Th1/Th2 balance toward Th1 dominance. As a result, the production of PGE2 and Th2 cytokines decreases, restoring cellular immunity, improving cachexia and the QOL, thereby prolonging survival (Fig. 6).

In many cases, the goal of treatment of cachexia in the presence of an incurable cancer is to stimulate appetite, prevent decreases in body fat and skeletal muscle mass, improve the QOL, increase the tolerance to various treatments, and to improve the patient's prognosis.

Therefore, the clinical management of cachexia has included nutrition management and the administration of appetite stimulants, analgesics, etc.[10,22,30]. Recently, RC-1291, a new low-molecular-weight ghrelin-like drug, was developed to treat cachexia, and is reportedly being tested in a phase II clinical trial in patients with cancer cachexia in the United States[34]. Hamuro et al.[11] proposed that the immunotherapeutic agent lentinan improved cachexia by inducing the conversion of oxidative to reductive macrophages. This observation lead Fearron et al.[10] to conclude that the best treatment for cancer cachexia was the treatment of the cancer itself.

In the patient described in the present study, CHT improved the gastrointestinal symptoms of cachexia early, and later anemia, but did not restore body weight, suggesting that this restoration can take a long time.

Prospects for CHT

The patient in the present study initially experienced beneficial effects of CHT, but developed resistance to the treatment later. This is probably because cancer cells remaining around necrotic and apoptotic areas acquired resistance to CHT and proliferated. The CHT resistance that developed in this patient will be an important subject of further studies. In the present case, the major objectives (or endpoints) of cancer CHT were achieved: a QOL improvement and life prolongation through the improvement of cachexia,. It is clear that the combined use of HT and low-dose 5-FU/CDDP was ideal because of their interactive effect and the absence of side effects. The clinical effects of CHT are summarized in Table III. In 2005, Sugahara et al.[35] suggested considering (as a new field of study) potential QOL improvements and life prolongation for refractory (end-stage) cancer patients.

In this study, the clinically important problem of improving cachexia with CHT was examined; however, in the absence of pertinent literature on the improvement of cachexia with CHT, progress in treating this problem is difficult. The results from this patient have been summarized, and hopefully will be of value to make generalizations for future treatments. It is hoped that this present report will provide an initial effort to stimulate future reports and progress in this field.

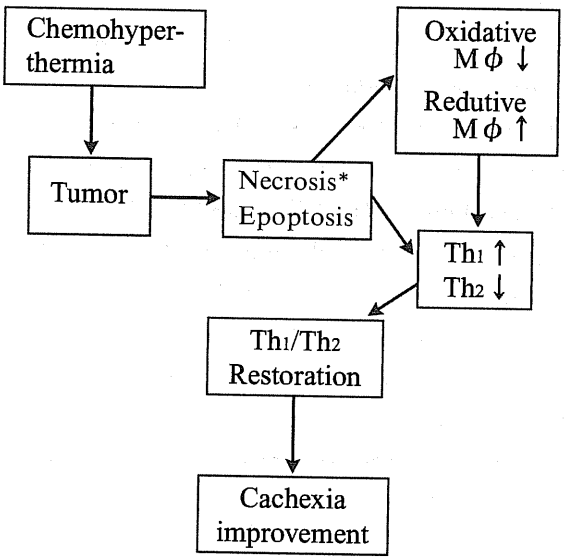

Fig. 6. A proposed mechanism for cachexia improvement. CHT induces cancer coagulation necrosis and apoptosis, causing a decrease in oxidative macrophages and an increase in reductive macrophages, with the resultant restoration of the Th1/Th2 balance with dominant Th1, cells leading to improvement of cachexia.

Table III. Clinical effects of CHT*.

1. Tumor reduction
2. Immune activation
3. Improvement of cachexia
4. Improvement of QOL
5. Life prolongation

*Proposed by Minoru Takara

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Abstract in Japanese

温熱化学療法が有効であった癌悪液質を伴った末期膵癌の一例

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要　　旨：末期癌に対しては，積極的治療が行われていないのが現状である．我々は膵癌術後局所再発，多発性肝転移および右肺転移を来し，癌悪液質を伴った末期膵癌患者に温熱化学療法 (CHT) を行った．その結果，局所再発の消失，肺転移巣の著明縮小および肝転移巣の約 80%縮小と共に腫瘍マーカーも正常となる抗腫瘍効果と，癌悪液質もほぼ改善し PS も 4 から 1 へと QOL の向上もみられた．

癌悪液質に対しては栄養治療以外，特別な治療は施行していないので，CHT の効果と考え，その機序について以下の如く考察した．即ち，CHT による抗腫瘍効果により癌細胞の活性が減弱し，その結果，癌細胞からの Th2 サイトカインの生産低下と，癌組織内の炎症反応低下に伴い酸化型マクロファージから還元型マクロファージが優位となって Th2 サイトカインが抑制されて Th1/Th2 バランスが Th1 優位となり癌悪液質が改善された．

一時とは言え，抗腫瘍効果と癌悪液質の改善がみられた事は特筆に値する．今後はこの方面の究明が待たれる．