**A CASE OF INTENSIVE THERAPY OBTAINED A FAVORABLE QUALITY OF
LIFE FOR ADVANCED GASTRIC CANCER WITH DISTANT METASTASIS**

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Abstract

Chemotherapy administered to a case of non-resectable advanced gastric cancer with esophageal invasion and bone metastasis was found to be remarkably effective over two years and 4 months. For imaging investigation, the efficacy of the chemotherapy was judged to be a partial response (PR). Furthermore, DNA histograms prepared by flow cytometry as a diagnostic test for malignancy of cancer revealed changes in the primary lesion from an aneuploidy pattern to a diploidy pattern concomitant with the administration of chemotherapy. Since non-phasic metastasis to the cerebellum and the adrenals were detected subsequently, intensive therapy consisting of radical gastric resection, left adrenal resection and deep cerebellar nucleus resection combined with radiotherapy, was conducted with the objective of prolonging the survival of the patient. The total course extended for about 4 years and considering the stage of advanced cancer, we believe that a favorable quality of life (QOL) was achieved based on the Performance status(P.S) level, maintenance of a satisfactory level of meal consumption, continuation of employment at times other than hospital admission and a home-residence rate of 72.3 per cent.

Introduction

The effectiveness of chemotherapy for non-resectable gastric cancer accompanied by distant metastasis is poor (MacDonalds, Philip *et al.*, 1980; Wolly, Smith *et al.*, 1981; Preusser, Wilke *et al.*, 1987). In addition, various other associated problems, such as long-term hospital admission and Performance Status reduction, impose difficulties on

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the achievement of a favorable quality of life (QOL) (Takahashi and Nishioka, 1995). However, the only criteria for evaluating the efficacy of chemotherapy are the findings of imaging investigations, which do not reflect the degree of malignancy of cancer, and the judgment of chemotherapy efficacy and the survival time are not necessarily correlated. We experienced a case in whom chemotherapy was effective not only in terms of tumor imaging but also in favorable QOL with satisfactory long-term levels of P.S, meal intake and a home residence rate and flow cytometric analysis of DNA histogram (Sasaki and Ogino, 1986; Danova, Mazzini *et al.*, 1987) obtained from the tumor tissue showed improvement of the degree of malignancy as the improvement of the disease.

Figure 1a: Endoscopic picture showing Type 2 advanced gastric cancer in the cardia and invasion to the esophagus.

Case Report

The patient was a 38-year-old man who had dyspeptic symptoms after eating. Gastric cancer of the cardia was presumptively detected by barium meal study at a medical check

Figure 1b: Type 2 advanced gastric cancer was remarkably reduced and the esophageal lesion had disappeared after 2 courses of UFTMP therapy.

Figure 1c: Type 2 advanced gastric cancer was remarkably reduced and the esophageal lesion had disappeared after 4 courses of UFTMP therapy.

Figure 2a: Thoracic CT showing metastatic tumor of the right fourth rib. (b): Metastatic tumor had disappeared after 2 courses of UFTMP therapy.

Figure 3: Abdominal CT showing metastatic tumor in the left adrenal area.

Clinical course

Figure 4: Clinical course.

Figure 5: Macroscopic picture of resected stomach after chemotherapy.

Figure 6a: Histopathological picture of biopsy specimen before chemotherapy. Pathology of the Type 2 advanced gastric cancer was poorly differentiated adeno-carcinoma.

Figure 6b: Histopathological picture of resected stomach after chemotherapy. Cancer cells from the lesion of the gastric resection could not be detected by histopathological examination.

Figure 6c: Histopathological picture of resected left adrenal after chemotherapy. Poorly differentiated cancer cells similar to those of the primary lesion were observed in the left adrenal.

Figure 7a

Figure 7b

Figure 7c

Figure 7a: DNA histogram showing an aneuploidy pattern from biopsy specimens of gastric cancer before systemic chemotherapy. (b): DNA histogram showing a diploidy pattern from biopsy specimens and resected specimens of gastric cancer after systemic chemotherapy. (c): DNA histogram showing an aneuploidy pattern from resected specimens of tumor mass of adrenal gland after systemic chemotherapy.

up in March 1992, after which the patient was referred to our hospital. After admission, and upper gastrointestinal endoscopy (Figure 1a) demonstrated type 2 advanced gastric cancer of the cardia, which had extended to the esophagus. Biopsy specimens obtained from the tumor histologically revealed a poorly differentiated adenocarcinoma. In addition, thoracic CT (Figure 2a) demonstrated bone metastasis to the right fourth rib. After informed consent was obtained from the patient's family in April, he was administered UFTMP therapy [UFT (Uracil-Tegafur): cap 400 mg/m² p.o on days 1-28; MMC (Mitomycin C): 5 mg/m² IV on days 1 and 8; CDDP (Cisplatin): 50 mg/m² DIV on days 1 and 8] (Iwazaki, Yasutake *et al.*, 1993). After undergoing 2 courses of this systemic chemotherapy, the primary lesion that had been originally 6.5 x 3.5 cm was reduced to 4.5 x 2.5 cm (Figure 1b). In addition, not only the esophageal lesion but also the rib metastasis had disappeared (Figure 2b). Accordingly, the efficacy of the chemotherapy was judged to be a partial response (PR) for primary lesion had not disappeared. Carcino embryonic antigen (CEA) had decreased from 59.5 to 3.2 ng/ml. The analysis of degree of malignancy of the tumor using biopsy specimens yielded negative immunostaining results for the oncogene, p53. Moreover, the DNA histogram obtained by flow cytometry revealed an aneuploidy pattern had changed to a ploidy pattern in the course of the chemotherapy. Two more courses of the same chemotherapy

were administered to maintain the disease status. During this period, adverse effects such as nausea, vomiting and appetite loss were not observed, and data of blood chemistry analysis remained in the normal range.

TABLE I
Laboratory data on admission

<u>Peripheral blood</u>		<u>Serum</u>	
WBC	5400 / μ l	AFP	7 ng/ml
RBC	506×10^4 / μ l	CEA	166.8 $\uparrow$ ng/ml
Hb	16.2 g/dl	CA19-9	74 $\uparrow$ U/ml
Ht	46.6 %	CA72-4	32 $\uparrow$ U/ml
PLT	17.8×10^3 / μ l		
<u>Blood chemistry</u>			
ALP	195 IU/l		
GOT	26 IU/l		
GPT	30 IU/l		
γ -GTP	35 U/l		
LAP	164 GRU		
LDH	392 IU/l		
TBIL	1.2 mg/dl		
DBIL	0.2 mg/dl		
CHE	1140 IU/l		
T-CHO	261 mg/dl		
TG	1098 mg/dl		
BUN	12 mg/dl	TP	7.4 g/dl
CRE	0.9 mg/dl	ALB	67.6 %
Na	139 mM/l	α 1-G	2.9 %
K	4.3 mM/l	α 2-G	5.2 %
Cl	103 mM/l	β -G	9.0 %
24Ccr	97.6 ml/min	γ -G	15.3 %

In July 1994 (29 months after the first chemotherapy), CEA and carbohydrate antigen 72-4 (CA72-4) values were elevated again and abdominal CT disclosed a left adrenal tumor, which suggested hematogenous metastasis of the primary tumor. The patient was again admitted to the hospital in August 1994. On admission, he was found to be slightly obese, with a height of 175 cm and weight of 80 kg. Blood pressure was 124/76 mmHg

and the heart rate was 68/min. He had no symptoms such as anemia or icterus of the conjunctivae, swelling of the superficial lymph nodes or hepatomegaly. No abnormalities were found in the peripheral blood and by blood biochemistry analysis, although CEA, CA72-4, and carbohydrate antigen 19-9 (CA19-9) levels were elevated. Adrenal function test revealed slight elevation of urine 17-OHCS (Table I). Upper gastrointestinal endoscopy (Figure 1c) also showed a shallow depression that suggested a cType 0 IIc T1-like lesion of 4.5 x 2 cm at the cardia of the stomach. However, cancer cells were histologically not present on the biopsy specimens obtained from the gastric lesion. Bone scintigraphy to investigate the recurrence of bone metastasis showed negative results. Abdominal CT (Figure 3) demonstrated a 3.0 x 1.8 cm tumor image corresponding to the left adrenal, confirming the diagnosis of left adrenal metastasis. Rib metastasis, enlarged lymph nodes, liver metastasis and ascites were not observed. Time of recurrence is shown in the schematic chart of his clinical course (Figure 4). For the recurrence, 1 course of systemic chemotherapy by FLEP [(UFT: cap 400 mg/m² p.o on days 1-28; LV (Leucovorin): 100 mg/m² p.o on days 1-28; VP16 (Etoposide): 50 mg/m² DIV on days 1 and 8; CDDP: 50 mg/m² DIV on days 1 and 8)] was begun on July 25, 1994. Although the new chemotherapy was effective for decreasing the levels of CEA, CA72-4, and CA19-9, the size of the left adrenal gland tumor remained the same. Accordingly, the patient underwent total gastrectomy and extirpation of the left adrenal gland on September 20, 1994, at the First Department of Surgery of our hospital. Surgical laparotomy revealed that the stage of the cancer was sType 2 T3 (SS) H0P0N0M0D3, stage II, and the surgery was designated as radical cure B according to Japanese Classification of Gastric Carcinoma (The 13th Edition, 1999). Macroscopic findings of the resected gastric lesion (Figure 5) showed a shallow depression, suggesting a Type 0IIcT1 lesion with 4.5 x 2.0 cm in size located at the cardia of the stomach. The extirpated left adrenal gland was coalescent with the kidney. No cancer cells were detected on the gastric lesion or the resected lymph nodes by histopathological examination (Figures 6a, 6b) following the operation. The stage of the disease was diagnosed as Grade 3 based on the criteria of histopathological evaluation of chemotherapy for gastric cancer. However, histological examination of the tumor mass

of the adrenal gland revealed poorly differentiated adenocarcinoma cells similar to those of the primary lesion (Figure 6c). DNA histogram obtained by flow cytometry revealed again an aneuploidy pattern that had undergone transition to a diploidy pattern by the first chemotherapy, and tumor tissue from adrenal gland also showed aneuploidy pattern (Figures 7a, 7b, 7c). The patient had been scheduled to be discharged from hospital in November 1994.

However, the patient began to manifest a severe headache, and the values for the tumor marker, CEA, increased again, from 10.8 to 46.3 ng/ml. As the brain CT performed at that time revealed a small brain metastasis, his discharge was postponed and he underwent intensive therapy, including tumor extirpation and radiotherapy at the Neurosurgery and Radiology Departments of our hospital. Regardless of such therapies, he died of cachexia 18 months after the surgical laparotomy (survival time 1420 days).

Discussion

Non-resectable advanced gastric cancers accompanied by distant metastasis are treated by a variety of therapies, including systemic chemotherapy with combined multiple drugs (MacDonalds, Philip *et al.*, 1980; Wolly, Smith *et al.*, 1981; Preusser, Wilke *et al.*, 1987) and immunotherapy (Mizumoto, Ohoue *et al.*, 1989). However, outcome in such diseases has not been still satisfactory. There has been a recent trend in Japan toward an increase of cases in whom systemic chemotherapy for gastric cancer was effective to some extent. Nevertheless, there have been few reports (Nakata, Shigemitsu *et al.*, 1985; Ono, Ishikawa *et al.*, 1994; Tsuji, Suematsu *et al.*, 1994; Iwazaki, Okura *et al.*, 1994; Iwazaki, Maehiro *et al.*, 1996) documenting remarkable effectiveness of systemic chemotherapy in advanced gastric cancers. Moreover, complete response to the chemotherapy was not histologically confirmed in most of such cases. As to patients showing marked improvement of advanced gastric cancer by chemotherapy (Kurihara, Izumiet *et al.*, 1977; Tokimatsu, Yasutake *et al.*, 1989) have reported that such results had to be seen in [1] patients aged 70 years or older, [2] patients administered Tegafur as the main carcinostatic drug, [3] patients with type 2 gastric cancer without distant metastasis, and [4] patients with a tumor that was a histopathologically differentiated type of

adenocarcinoma. In other words, these findings suggest that the combined use of 5-FU and its derivatives may be effective for gastric cancer with histologically well-differentiated type without distant metastasis.

In our case, patients of 38 years old was in good general condition, type 2 gastric cancer with esophageal invasion and bone metastasis, and that the patient with a tumor that was a histopathologically poorly differentiated type of adenocarcinoma. However, the primary cancer and metastatic lesions were found to be remarkably decreased in size and denatured by chemotherapy (UFTMPtherapy) (Iwazaki, Yasutake *et al.*, 1993) of two courses.

At the present time, since the efficacy of chemotherapy are evaluated only by morphological of images investigations that do not reflect the biological malignant degree of tumors, efficacy of chemotherapy and the survival time (Takahashi and Nishioka, 1995) are not necessarily closely correlated. The rate and capacity of proliferation of a cancer are considered to be predicting factors for biological malignant degree. Recently, immunostaining technique (Sasaki and Ogino, 1986; Danova, Mazzini *et al.*, 1987; Hoshino, Prados *et al.*, 1989; ROBBINS, Vega *et al.*, 1987; Ploton, Menager *et al.*, 1986; Crocker, 1990;Gerdes, Lemke *et al.*, 1984; Lowe, Bodis *et al.*, 1994; James, Richard *et al.*, 1986; Korenaga, Okamura *et al.*, 1988; Olga and Galina, 1998; Saito, Korenaga *et al.*, 1991) that employs an antibody specific to an antigen (proliferating cell antigen), and is closely associated with the cell proliferation activity, have become available for predicting factors for proliferative capacity of a tumor. These markers includes BrdU (bromodeoxyuridine) (Hoshino, Prados *et al.*, 1989), PCNA (proliferating cell nuclear antigen) (Robbins, Vega *et al.*, 1987), AgNORs (Ploton, Menager *et al.*, 1986; Crocker, 1990), Ki67 (Gerdes, Lemke *et al.*, 1984), DNA histograms produced by flow cytometry (Sasaki and Ogino, 1986; Danova, Mazzini *et al.*, 1987) or oncogenes, such as p53 (Lowe, Bodis *et al.*, 1994).

The biological features of gastric cancer are considered to vary in accordance with tissue type. Differentiated cancers often demonstrate marked vascular infiltration leading easily to hematogenic metastasis and poorly differentiated cancers demonstrate high cell proliferative activity leading easily to lymph node metastasis and peritoneal implantation.

Analysis of the degree of malignancy of gastric cancer using a DNA histogram obtained by flow cytometry has shown that an aneuploidy DNA pattern is common in tumors that show a high level of cell proliferative activity, frequent lymph node metastasis and an especially marked tendency for deep-site infiltration (James, Richard *et al.*, 1986; Korenaga, Okamura *et al.*, 1988; Olga and Galina, 1998). In aspect of the tissue type of gastric cancers, it has been shown that there is a tendency that undifferentiated types have a rather higher level of susceptibility to anti-cancer agents than differentiated types (Saito, Korenaga *et al.*, 1991). It has also been reported that poorly differentiated types with an aneuploidy pattern show a higher level of susceptibility to anti-cancer agents than differentiated types by analyzes of DNA histograms obtained by flow cytometry (Maehara, Anai *et al.*, 1987).

In our case, biopsy specimens yielded negative immunostaining results for the oncogene, p53. Accordingly, we considered that p53 was normal, and we could not technically detect a mutants of p53. The DNA histogram obtained by flow cytometry in this case revealed an aneuploidy pattern, which had shown a diploidy DNA pattern concomitant with the course of remarkably effective chemotherapy. As a result, in spite of the fact that this was a case of non-resectable advanced gastric cancer, the treatment was remarkably effective with a favorable QOL (Takahashi and Nishioka, 1995) evaluated on the basis of long-term satisfactory P.S, meal intake levels, high rate of home residence for 2 years and a relatively long period until the appearance of adrenal metastasis.

Intensive therapy include chemotherapy should be performed with a case of this type. This active strategy may enable a better outcome to be achieved not only in terms of tumor imaging, but also in favorable QOL with satisfactory long-term levels of P.S, meal intake and a home residence rate.

In the future, we have to randomize comparisons of phase III study of chemotherapy with the use of best supportive care (BSC) alone in patients with non-resectable gastric cancer (Glimelius, 1994; Pyrhonen, 1995).

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