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Review of Cases of Bone Metastasis from Gastric Cancer

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We investigated the diagnosis and treatment of 18 cases of bone metastasis from gastric cancer since 1991. The key to the diagnosis was pain in 13 cases, and an elevated serum alkaline phosphatase (ALP) value in 5 cases. The diagnosis was established by bone scintigraphy in every case. The bone scan findings consisted of hot spots at 1 to 3 sites in 6 cases but were numerous in the 12 other cases. The elevations in ALP values were marked in the cases with numerous metastases. They fluctuated with treatment, and were useful as markers. Surgery was performed in 3 of the cases with synchronous bone metastasis, but the patients died within 3 months. Chemotherapy was performed in 11 cases, and radiotherapy in 9 cases (some cases overlapped). The pain was alleviated by radiotherapy in every case. Best supportive care alone was administered in 3 cases. The median overall survival time was 9 months, but in 6 of the 8 cases treated with new anticancer drugs, principally S-1, it was 16 months. And the new anticancer drugs also appeared to be useful for bone metastasis. When ALP values rise and pain develops, it is important to suspect bone metastasis, establish the diagnosis using bone scintigraphy or other methods and begin therapy quickly.

Key words: bone metastasis, gastric cancer, S-1, radiation, chemotherapy

Introduction

Most bone metastases from gastric cancer were largely observed as just one of the metastases to more than one organ in the same patient, and their prognosis was very poor in the past[1)2)]. Bone metastasis from gastric cancer is less common than peritoneal metastasis or liver metastasis[3)]. Many reports have stated that the clinical frequency of bone metastasis from gastric cancer is low, being present in only 1.4-1.5% of surgical cases[4)5)]. However, the frequency is clinically affected by the level of interest in bone metastasis. Moreover, since bone metastasis has been reported in as much as 12.7-19.5% of autopsies[6)], it seems that its frequency cannot really be taken lightly. Bone metastasis is often very painful, and since QOL is greatly diminished when fractures develop, early diagnosis and treatment is essential.

It has been considered an indication for palliative therapy alone, and intensive therapy has not been performed. On the other hand, novel anticancer drugs effective against gastric cancer have recently become available, and there have been many reports of improved therapeutic efficacy against recurrent gastric cancer and advanced gastric cancer[7)～10)]. We also have administered them to recent patients with bone metastasis from gastric cancer, and have had good response. We therefore assessed the diagnosis and treatment in cases of bone metastasis from gastric cancer.

Subjects

Between 1991 and 2003, a total of 1,091 cases of gastric cancer were treated in our department, and among the metastases, both synchronous and metachronous, there were 100 cases of peritonitis carcinomatosis, 83 cases of lymph-node metastasis to at least group 3 lymph nodes, and 57 cases of liver metastasis. However, the subjects of this study were the 18 patients with bone metastasis encountered during that same period. The bone metastasis was

Table 1 Eight cases of synchronous bone metastasis from gastric cancer

Case	Sex	Age	Bone scan	Ope.	Radiation	Chemotherapy	Prognosis
1	M	65	Numerous	−	+	S-1	8M
2	M	70	1-3	−	−	5Fu + LV → S-1 + TXL	20M
3	M	57	Numerous	−	−	5Fu + MTX → S-1	16M
4	F	86	1-3	Gastrectomy	+	None	3M
5	M	60	Numerous	Gastrectomy	−	None	1M
6	F	69	1-3	−	−	5Fu + EP + CDDP	3M
7	F	53	Numerous	−	−	S-1 → TXL	16M
8	F	33	Numerous	Oophorectomy	−	None	2M

5Fu: 5-Fluorouracil, LV: Leucovorin, TXL: Paclitaxel, MTX: Methotrexate, EP: Epirubicin hydrochloride, CDDP: Cispllatin.

Table 2 Ten cases of metachronous bone metastasis from gastric cancer

Case	Sex	Age	Bone scan	Post ope. term	Radiation	Chemotherapy	Prognosis
9	F	54	Numerous	5Y10M	+	None	2M
10	F	56	Numerous	3M	−	None	3M
11	M	66	Numerous	8Y 1M	−	S-1	12M
12	M	33	Numerous	4Y 6M	+	MTX + 5Fu	4M
13	F	68	Numerous	3Y 1M	−	5Fu + LV	15M
14	M	78	1-3	5M	+	None	4M
15	M	49	Numerous	2Y	+	None	3M
16	F	69	1-3	8M	+	S-1	9M alive
17	F	62	Numerous	2Y	+	S-1 → CDDP + CPT-11	12M alive
18	M	57	1-3	4Y	+	S-1 + CPT-11 → S-1	36M alive

CPT-11: Irinotecan hydrochloride.

synchronous in 8 cases (Table 1), and metachronous in the other 10 cases (Table 2). There were 9 men and 9 women, and their ages at the time of diagnosis ranged from 33 to 86 y.o. (median age: 62 y.o.). The bone metastasis was associated with metastases to other organs in 9 (50%) of the cases. The histological type of the primary tumor was differentiated in 3 of the synchronous cases but undifferentiated in 5 other cases. It was also differentiated in 1 of the metachronous cases but undifferentiated in 9 other cases.

Welch's t test was used to perform the statistical analysis. A probability of <0.05 was considered significant.

Results

Diagnosis

The initial manifestation was pain in 13 cases (72%), and in 2 of those it was in the form of a fracture. In 6 cases of the 13 cases the serum alkaline phosphatase (ALP) value had risen to above 500 IU/L. The clue to the diagnosis was the ALP elevation alone without pain in 5 cases (27%). The diagnosis was established by bone scintigraphy in every case. In the cases of metachronous bone metastases, the intervals between the initial operation and the diagnosis ranged from 4 months to 8 years with the median interval of 2 years.

The bone scintigraphy findings consisted of hot spots at 1-3 sites in 6 cases, and numerous hot spots in the 12 other cases. Comparisons between the ALP values and the bone scintigraphy findings revealed mild increases, with a mean value of 356 ± 201 IU/L, in the cases with no more than 3 metastases, whereas there were marked increases, to 2,620 ± 2,200 IU/L, in the cases with numerous metastases, and the difference was significant ($p = 0.017$). The ALP values varied with the treatment, falling when it was effective and increasing when the patients' conditions deteriorated (Figure).

Treatment

Surgery was performed in 3 of the cases of synchronous bone metastasis, 2 of which were gastrectomies performed because of bleeding and stenosis. In the other case, surgery was performed for an

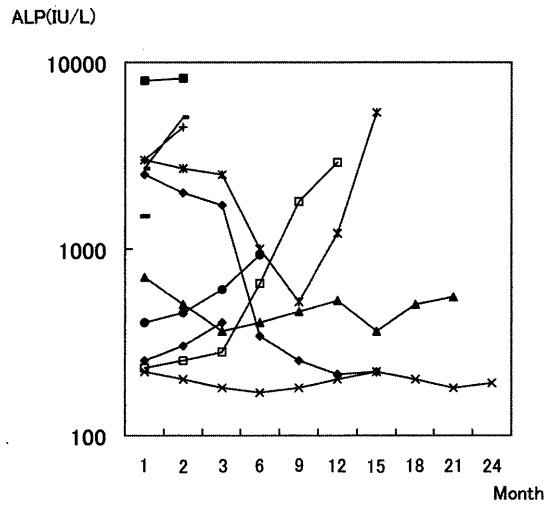

Figure The fluctuation of serum alkaline phosphatase (ALP)

ovarian tumor, and the subsequent postoperative diagnosis of ovarian metastasis and bone metastasis from stomach cancer was made. The patients' physical conditions were poor in all 3 cases, making it unwise to start chemotherapy postoperatively.

Chemotherapy was performed in all 5 of the synchronous cases not treated surgically, and in 6 of the metachronous cases. Chemotherapy could not be started in 7 (39%) of the 18 cases because of the patients' general conditions. Their performance status were grade 3 or 4. In the 6 most recent cases S-1, or S-1 in combination with other anticancer drugs, has been used as the treatment of first choice, and in 2 of the other cases S-1 was used as second-line therapy.

Radiation therapy was used in combination in 5 of them, and used alone in 4 cases. The pain was alleviated by radiotherapy in every case and in 2 of them it was resolved completely. Palliative therapy was used alone in 3 cases.

Disseminated intravascular coagulation (DIC) sometimes develops in patients with bone metastasis and was observed in 3 of the cases in the present study. In these 3 cases DIC developed after intervention, such as surgery or radiotherapy. Their condition rapidly deteriorated and they died without receiving chemotherapy.

A review of the patients' outcomes revealed no differences according to the time of the metastases, the median survival time being 9 months. All of the patients for whom chemotherapy was not performed died within 6 months. Eight patients were treated with S-1, their median survival time was 16 months.

Discussion

Bone scintigraphy is useful in making the diagnosis[3)6)], so we perform bone scintigraphy all of our cases. It not only makes it possible to establish the diagnosis but to judge the degree of metastasis, and it is useful in choosing methods of treatment as well. However, there is also the problem of radiation exposure, and there have been no reports on the use of bone scintigraphy for screening. In the literature, bone scintigraphy was performed only after bone metastasis was suspected based on abnormal laboratory values or clinical manifestations.

Serum ALP values become abnormal when bone metastasis occurs, and abnormally high values are said to often occur before any symptoms develop[4)5)]. In the present study, the ALP values had risen to more than 50% above normal in 60% of the patients, however no clinical manifestations were observed in half of them. A correlation has also been found with the degree of bone metastasis detected by bone scintigraphy, and since the values fluctuate with the course of treatment, they seem to be useful as a marker of bone metastasis. As a bone metabolic marker to use for a diagnosis of bone metastasis, there are a bone formation marker and a bone resorption marker. Until recently ALP was the only available bone formation marker, and it is utility for osteoblastic bone metastasis such as prostatic cancer[11)]. Because there is much osteoclastic bone metastasis, as for the breast cancer and the lung cancer, bone resorption markers such as carboxyterminal crosslinked telopeptide collagen (ICTP), type I collagen cross-linked N-telopeptide (NTX) are considered to be utility than ALP recently [12)13)]. More examination is necessary in gastric cancer in future. Assessment of treatment for bone metastases has been performed on the X-rays or bone pain relief generally[14)], but there was few report in the cases from gastric cancer because of its poor prognosis.

Radiotherapy is effective as a means of alleviating

pain, but it does not seem to improve the outcome[5].

Chemotherapy is usually considered ineffective in these types of cases, but there is also a report of a slightly better outcome in patients who received chemotherapy[2]. Many cases are also complicated by metastasis to other organs, and their general condition has deteriorated. In our study, chemotherapy could be given to 55% of the patients. In the past MTX/5-FU sequential therapy has been reported to be useful in some studies. Efficacy of chemotherapy can also be expected in cases complicated by DIC, but the patients' survival time is no more than 5-19 months[15][16]. Novel anticancer agents, such as S-1, CPT-11[9], and Paclitaxel[10] have recently become available on the market, and the efficacy of chemotherapy for gastric cancer has improved. S-1, in particular, has had a 44-49% efficacy rate in late-phase clinical trials, and the 50% survival time of 207-250 days, is better than what had previously been attained[7][8]. Cases of marked efficacy of S-1 have been reported even in cases complicated by DIC as a result of bone metastasis[17][18]. Six of the 8 patients treated with these drugs in the present study survived for a year or more, and the new anticancer drugs appeared to be useful against bone metastases as well. Chemotherapy should be considered for a case of good performance status such as grade 0, 1 and 2.

Conclusions

The outcome of patients with bone metastasis is still poor, but it is the same as with other recurrences, some degree of improvement in QOL and improvement in outcome can be expected in response to treatment with radiotherapy and new anticancer drugs. When ALP values rise and pain develops, it is important to suspect bone metastasis, establish the diagnosis using bone scintigraphy or other methods and begin therapy quickly.

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胃癌骨転移症例の診断と治療

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1991年よりの胃癌の骨転移症例18例について，その診断と治療について検討した．同時性が8例で，異時性が10例である．骨以外の他臓器への転移が9例(50%)に合併していた．4例が高分化型で，14例が低分化型であった．診断の契機は疼痛が13例（72%）で，他の5例はALP値の上昇であった．確定診断は，全例で骨シンチグラフィによりなされた．骨シンチグラフィの所見では6例がhot spotが3個以内で，12例では多発していた．ALP値の上昇は多発例で顕著であり，また治療により変動し，マーカーとして有用であった．同時性骨転移の3例に手術が行われたが，3ヵ月以内に死亡した．化学療法を11例に行い，放射線照射を9例（重複あり）に行った．3例は緩和療法だけを施行した．放射線照射により疼痛は全例で軽快し，2例では消失した．全体の生存期間の中央値は9ヵ月であった．S-1を中心とした新規抗癌剤を投与した8例中6例が1年以上生存し，中央値は16ヵ月となり，骨転移に対しても有用と考えられた．骨転移を治療の対象と考え，ALP値の上昇，疼痛の発現に際しては，骨転移を疑い，骨シンチグラフィ等により診断し，治療を開始することが重要である．