Clinical Outcome of Gastric Cancer Patients with Bone Marrow Metastases

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Abstract
Background: Gastric cancer with bone marrow metastases is known to pursue a rapidly deteriorating clinical course. We conducted a retrospective analysis to evaluate clinical manifestations and prognosis of gastric cancer patients with bone marrow metastases.

Methods: Between September 1994 and February 2006, 39 gastric cancer patients with pathologically confirmed bone marrow dissemination were selected.

Results: The majority of the patients showed younger age, poorly differentiated adenocarcinoma or signet ring cell carcinoma, thrombocytopenia, anemia, elevated lactate dehydrogenase and alkaline phosphatase. Poor prognostic factors for survival were serum sodium ≤133 mmol/l [relative risk (RR) 4.57; 95% CI 1.99–10.52; p < 0.001], the presence of lung metastasis (RR 3.47; 95% CI 1.48–8.15; p = 0.007) and the presence of peritoneal seeding (RR 2.17; 95% CI 1.06–4.43; p = 0.036). Median survival durations after bone marrow metastases for patients without any adverse factors (n = 19, 48.7%) and those with 1–3 adverse factors (n = 20, 51.3%) were 67 and 23 days, respectively (p = 0.013). Patients without any adverse factors did benefit from palliative chemotherapy (p = 0.048).

Conclusion: We suggest that gastric cancer patients with bone marrow metastases should receive more tailored therapies according to different risk factors in order to enhance survival.

Introduction

Despite a recent decline in incidence during the second half of the 20th century, gastric cancer is still the second most common cause of cancer-related death worldwide [1]. In addition, gastric cancer is the most commonly diagnosed malignancy in Korea, Japan, China, South America and Eastern European nations, with the lowest frequency observed in the United States and Canada [2].

Metastatic gastric cancer is a therapeutic challenge for medical oncologists, especially those with bone marrow metastases. Bone marrow metastases occur in many solid tumors such as breast, lung, prostate and gastric cancer [3–5]. Recent studies indicate that the presence of malignant cells in the bone marrow implies a rapidly deteriorating clinical course that is often refractory to conventional treatment in several solid tumors [6–8]. However,
the clinical features and optimal treatment had not been systematically investigated in gastric cancer with bone marrow metastases owing to a relative rarity of this subset. Moreover, the incidence of bone marrow metastases may be underestimated in gastric cancer patients because bone marrow biopsy is not a routine clinical practice. Rather, there have been anecdotal case reports on successful treatment with systemic chemotherapy in gastric cancer patients with bone marrow metastases [9, 10].

In this study, we retrospectively analyzed the clinicopathologic features, treatment outcome and prognostic factors for survival in gastric cancer patients with bone marrow metastases. In addition, we attempted to identify a subgroup of patients who would potentially benefit from palliative chemotherapy.

**Patients and Methods**

**Patients**

Between September 1994 and February 2006, a total of 1,598 patients received palliative chemotherapy for metastatic, unresectable or recurrent gastric cancer at Samsung Medical Center [11]. Of these patients, 39 patients were identified to have pathologically confirmed bone marrow dissemination. Hence, the prevalence of bone marrow metastasis confirmed by bone marrow biopsy was 0.024% in this series.

**Methods**

We retrospectively reviewed the records and analyzed the following clinical data: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, histology of tumor, signs and symptoms at presentation, reasons for bone marrow biopsy, site of metastasis at the time of bone marrow involvement, time from gastric cancer diagnosis to bone marrow involvement, laboratory findings such as hemoglobin, leukocyte count, platelet count, serum lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), albumin, sodium, calcium, total bilirubin, uric acid and coagulation profile.

**Treatment**

Of 39 patients, 20 patients (51.3%) received palliative chemotherapy after the diagnosis of bone marrow dissemination: 13 patients (65.0%) had taxane-based and 7 patients (35.0%) received 5-fluorouracil (FU)-based chemotherapy. The taxane-based chemotherapy included docetaxel (Taxotere, Aventis) or paclitaxel (Taxol, Bristol-Myers Squibb) and cisplatin. The 5-FU-based regimens included modified FOLFOX (oxaliplatin, leucovorin, 5-FU) and modified FOLFIRI (irinotecan, leucovorin, 5-FU).

**Statistics**

The primary endpoint of the study was overall survival, calculated using the Kaplan-Meier product-limit method. Overall survival was measured from the date of bone marrow involvement to the date of death. Survival rates were compared for statistical differences using the log-rank test and generalized Wilcoxon test. Multivariate analysis was performed using stepwise Cox proportional hazards regression modeling. p values <0.05 were considered statistically significant and all p values corresponded to 2-sided significance tests.

Factors included in the univariate analyses were as follows: age, sex, performance status, histologic grade, hemoglobin, leukocyte count, platelet count, serum albumin, sodium, calcium, AST, ALT, ALP, LDH, uric acid, metastasis to liver, lung, bone, ovary, leptomeninges, peritoneum and administration of palliative chemotherapy at the time of diagnosis of bone marrow metastasis. Laboratory variables were initially recorded as continuous variables and later dichotomized according to the median value of each variable.

**Results**

**Patient Characteristics**

The baseline characteristics of 39 patients are provided in table 1. The median age was 47 years (range 26–68). The majority of patients had either poorly differentiated adenocarcinoma (28/39, 71.8%) or signet ring cell adenocarcinoma (9/39, 23.1%). The median interval from the diagnosis of gastric cancer to the detection of bone marrow involvement was 161 days (range 0–2,860). The most common site of metastasis at the time of diagnosis of bone marrow involvement was bone (79.5%) followed by lymph node (43.6%), peritoneum (38.5%) and lung (23.0%). Bone scintigrams were performed in 29 (93.5%) cases among 31 patients with bone metastases. Bone scintigrams revealed multiple abnormal bone lesions in 27 patients, while only 2 patients had less than 2 sites of involvement (1 patient with rib and ilium and another patient with thoracic spine). There were only 3 patients (7.7%) who developed hypercalcemia despite of widespread bone metastases. Most patients underwent bone marrow biopsies for evaluation of thrombocytopenia (69.2%) and disseminated intravascular coagulopathy (DIC, 20.6%).

The common presenting symptoms at the time of bone marrow involvement were bone pain (43.6%), active bleeding (20.6%), dyspnea (12.8%), abdominal pain (5.1%) and general weakness (5.1%). One patient had altered mental status caused by hypercalcemia, and 4 patients were asymptomatic. The median serum ALP and LDH levels at the time of diagnosis were elevated to 573 IU/l (range 108–6,242) and 1,531 IU/l (range 353–30,800), respectively. The median serum albumin, sodium and platelet counts were lower than the normal range: 3.4 g/dl (range 2.1–4.4), 133 mmol/l (range 119–145) and 44,000/ mm³ (range 5,000–273,000), respectively.
Treatment Outcome

The median number of chemotherapy cycles that patients received after the diagnosis of bone marrow involvement was 2 (range 1–8). Most of the patients (35/39, 89.7%) died of tumor progression, 3 of brain hemorrhage and 1 of embolic brain infarction following DIC. There were no chemotherapy-related deaths. The median sur-

| Table 1. Patient demographics and pathologic features | Patients |
|-----------------------------------------------|----------|
| Median age, years               | 47 [26–68] |
| ≤50                           | 24 (61.5)  |
| >50                          | 15 (38.5)  |
| Male sex                      | 21 (53.8)  |
| ECOG performance status       |           |
| 0–1                          | 18 (46.2)  |
| ≥2                           | 21 (53.8)  |
| Tumor grade                   |           |
| Well/moderately differentiated | 2 (5.1)    |
| Poorly differentiated/signet ring cell | 37 (94.9) |
| Site of involvement           |           |
| Bone                          | 31 (79.5) |
| Lymph node                    | 17 (43.6) |
| Peritoneum                    | 15 (38.5) |
| Lung                          | 9 (23.0)  |
| Ovary                         | 5 (12.8)  |
| Pleura                        | 5 (12.8)  |
| Liver                         | 4 (10.3)  |
| Adrenal gland                 | 3 (7.7)   |
| Reason for bone marrow biopsy |           |
| Thrombocytopenia              | 27 (69.2) |
| DIC                           | 8 (20.6)  |
| Leukoerythroblastic reaction  | 2 (5.1)   |
| Anemia                        | 2 (5.1)   |
| Blood counts and chemistry    |           |
| Hemoglobin, g/dl              | 8.9 [3.7–13.0] |
| White blood cells, n/mm³      | 7,750 [1,050–21,300] |
| Platelets, n/mm³              | 44,000 [5,000–273,000] |
| AST, IU/l                     | 50 [17–403] |
| ALT, IU/l                     | 35 [6–352] |
| ALP, IU/l                     | 573 [108–6,242] |
| LDH, IU/l (n = 33)            | 1,531 [353–30,800] |
| Calcium (corrected), mg/dl    | 9.2 [8.4–17.6] |
| Albumin, g/dl                 | 3.4 [2.1–4.4] |
| Sodium, mmol/l                | 133 [119–145] |
| PT, s                         | 16.1 [13.5–27.6] |
| aPTT, s                       | 41.5 [33.6–73.4] |
| Fibrinogen, mg/dl (n = 35)    | 168 [51–424] |
| D-dimer, μg/ml (n = 32)       | 39.3 [0.21–91.3] |

Figures are number of patients with percentages in parentheses and medians with ranges in brackets. PT = Prothrombin time; aPTT = activated partial thromboplastin time.

| Table 2. Univariate analyses of prognostic factors for survival | Patients | MST days | 95% CI | p value |
|---------------------------------------------------------------|---------|----------|--------|---------|
| Age               | ≤50 years | 24 | 29 | 0–64.5 | 0.736 |
|                   | >50 years | 15 | 48 | 7.6–88.4 | 0.908 |
| Sex               | Male      | 21 | 44 | 9.6–78.4 | 0.816 |
|                   | Female    | 18 | 32 | 0–86.1 | 0.703 |
| ECOG performance status | 0–1 | 18 | 62 | 14.2–109.8 | 0.179 |
|                   | ≥2        | 21 | 26 | 20.0–32.0 | 0.031 |
| Histology         | Well/moderately differentiated | 2 | 17 | – | 0.309 |
|                   | Poorly differentiated/signet ring cell | 37 | 48 | 6.3–89.7 | 0.006 |
| Hemoglobin        | ≤8.9 g/dl | 20 | 62 | 11.6–112.4 | 0.038 |
|                   | >8.9 g/dl | 19 | 29 | 16.2–41.8 | 0.070 |
| Platelets         | ≤44,000/mm³ | 20 | 44 | 0–100.9 | 0.070 |
|                   | >44,000/mm³ | 19 | 32 | 0.7–63.3 | 0.020 |
| Albumin           | ≤3.4 g/dl | 23 | 25 | 10.9–39.1 | 0.020 |
|                   | >3.4 g/dl | 16 | 52 | 14.8–89.2 | 0.038 |
| AST               | ≤50 IU/l | 20 | 61 | 4.18–117.8 | 0.006 |
|                   | >50 IU/l | 19 | 23 | 6.3–43.7 | 0.277 |
| ALT               | ≤35 IU/l | 21 | 61 | 28.1–93.9 | 0.038 |
|                   | >35 IU/l | 18 | 25 | 11.6–34.4 | 0.002 |
| ALP               | ≤713 IU/l | 20 | 26 | 23.8–28.2 | 0.150 |
|                   | >713 IU/l | 19 | 67 | 28.1–89.2 | 0.077 |
| Sodium            | ≤133 mmol/l | 21 | 25 | 11.5–38.5 | 0.031 |
|                   | >133 mmol/l | 18 | 87 | 62.1–111.9 | 0.050 |
| LDH (n = 33)      | ≤1,531 IU/l | 17 | 67 | 40.1–93.9 | 0.050 |
|                   | >1,531 IU/l | 16 | 17 | 5.24–28.7 | 0.150 |
| Bone metastasis   | Yes       | 31 | 52 | 19.3–84.7 | 0.089 |
|                   | No        | 8  | 9  | 0–23.8  | 0.031 |
| Lung metastasis   | Yes       | 9  | 17 | 0–40.3  | 0.031 |
|                   | No        | 30 | 52 | 27.8–76.2 | 0.077 |
| Leptomeningeal seeding | Yes | 5  | 17 | 14.9–19.1 | 0.032 |
|                   | No        | 34 | 48 | 2.3–93.7 | 0.083 |
| Peritoneal seeding | Yes       | 15 | 26 | 18.6–33.4 | 0.031 |
|                   | No        | 24 | 52 | 24.4–79.6 | 0.077 |
| Liver metastasis  | Yes       | 4  | 17 | 8.2–25.8 | 0.077 |
|                   | No        | 35 | 52 | 13.8–90.3 | 0.029 |
| Bone involvement only | Yes | 9  | 80.0 | 24.5–135.5 | 0.031 |
|                   | No        | 30 | 26.0 | 18.0–34.0 | 0.031 |

MST = Median survival time.
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vival time from the diagnosis of bone marrow involvement was 44 days (range 2–252). The median survival times from bone marrow involvement were 20 days in the best supportive care group (range 2–137 days) and 67 days (range 5–252) in the palliative chemotherapy group (p = 0.026).

Prognostic Factor Analyses
At univariate analyses, AST >50 IU/l (p = 0.006), ALT >35 IU/l (p = 0.038), albumin ≤3.4 g/dl (p = 0.020), serum sodium ≤133 mmol/l (p = 0.031), serum lactate dehydrogenase (p = 0.002) and the presence of lung metastasis (p = 0.031) all adversely influenced survival with statistical significance (table 2). Clinical parameters that were included in the multivariate analysis were Eastern Cooperative Oncology Group (ECOG) performance status, albumin, AST, ALT, serum sodium, lung metastasis, liver metastasis, bone metastasis, peritoneal seeding, and administration of palliative chemotherapy after bone marrow involvement. Using the forward Cox regression model, significant poor prognostic factors for survival were delineated as follows (table 3): serum Na ≤133 mmol/l [p < 0.001; relative risk (RR) 4.57; 95% CI 1.99–10.52], the presence of lung metastasis (p = 0.007; RR 3.47; 95% CI 1.48–8.15) and the presence of peritoneal seeding (p = 0.036; RR 2.17; 95% CI 1.06–4.43).

To identify a subgroup of patients who would potentially benefit from palliative chemotherapy, 39 patients were divided into 2 subgroups according to the multivariate results: patients without any adverse factors, and patients with 1–3 adverse factors. Nineteen patients (48.7%) had no adverse factors and 20 patients (51.3%) had more than 1 adverse factor. The median survival was 67 days (range 2–252) and 23 days (range 3–122) as shown in figure 1 (p = 0.013), respectively.

Among 19 patients without any adverse factors, palliative chemotherapy was given in 9 (47.4%) patients. As shown in figure 2, there was a longer survival duration in patients with palliative chemotherapy than in patients with best supportive care only (96 and 44 days, respectively; p = 0.048). Compared with this group, there was no significant survival difference between palliative chemotherapy (n = 11; 29 days, range 5–101) and best supportive care only group (n = 9; 17 days, range 3–122) among patients who had any adverse factors (p = 0.128).

Table 3. Multivariate Cox regression analyses

| Parameter                  | p value | RR (exp. B) | 95% CI    |
|----------------------------|---------|-------------|-----------|
| Serum Na ≤133 mmol/l       | <0.001  | 4.57        | 1.99–10.52|
| Lung metastasis            | 0.007   | 3.47        | 1.48–8.15 |
| Peritoneal seeding         | 0.036   | 2.17        | 1.06–4.43 |

Fig. 1. Forward Cox regression analysis of survival according to the adverse factors.

Fig. 2. Subgroup analysis according to systemic chemotherapy in patients without any adverse factors.
Discussion

Although it is not common to encounter gastric cancer patients with bone marrow dissemination in the clinic, clinical features and optimal treatment options are yet to be elucidated. The aim of the study was to analyze clinical features and treatment outcome and to delineate prognostic factors in this particular subset of patients. To the best of our knowledge, this is the first report to focus on clinical features and survival in gastric cancer patients with disseminated carcinomatosis of the bone marrow. The great majority of the patients showed younger age, histologic type with poorly differentiated adenocarcinoma or signet ring cell carcinoma, elevated LDH and ALP, thrombocytopenia, anemia and extensive bone metastases, which coincide with a previous report [9]. Approximately half of the patients had bone pain at the time of diagnosis. Of note, about 50% of the patients had a good performance status (ECOG 0–1), although the median survival time of all patients was very short (44 days, range 2–252). Our recently published paper on prognostic analyses of all metastatic/recurrent gastric cancer patients (n = 1,455) who received first-line chemotherapy from September 1994 to February 2005 at our institution demonstrated that bone marrow metastasis was one of the significant adverse factors along with performance status (ECOG 2–4), no previous gastrectomy, white blood cell count >6,370/μl, albumin ≤3.6 g/dl, bilirubin >0.5 mg/dl, ALP >85 U/l, calcium ≤8.9 mg/dl, presence in bone, ascites, and the presence of measurable lesion at the time of first-line chemotherapy [11]. The median survival time for patients with bone marrow metastases was 4.0 months as compared with 8.7 months for patients without bone marrow metastases (p < 0.001). We undertook this study to analyze clinical features and outcome in this subset of patients in order to better understand the disease and to optimize therapeutic strategies.

Based on the observation that some of the patients achieved long-term survival, we attempted to identify the patients who may experience palliative benefit from chemotherapy. In this study, low serum sodium (<133 mmol/l), the presence of lung metastasis and the presence of peritoneal seeding were identified as adverse prognostic factors. Subsequently, patients with 1–3 adverse factors did extremely poorly, with a median survival time of 23 days. On the other hand, patients without any adverse factors showed a favorable median survival time of 96 days and did benefit from palliative chemotherapy. Although limited by a relatively small number of patients and its retrospective nature, our data suggest that palliative chemotherapy should be considered in a specific subset of patients. Nevertheless, these results should be externally and/or prospectively validated in future studies.

As shown in our previous data along with others, bone metastasis and peritoneal seeding have been known as poor prognostic factors in metastatic gastric cancer patients [11–14]. Unlike other studies of gastric cancer, lung metastasis was also defined as a poor prognostic factor in the current study. This unique finding in patients with disseminated bone marrow may be related to a pathway of hematogenous metastasis, from the stomach to the liver through the portal vein, proceeding to the lung, and then to the bone marrow [15, 16].

In some solid tumor types such as lung, prostate or breast carcinoma, leukoerythroblastic reactions were the most frequently observed findings in peripheral blood test [17–20]. Unlike these reports, there were only 2 cases which had leukoerythroblastic reactions at the time of diagnosis of bone marrow infiltration in our series. Most common peripheral blood findings were thrombocytopenia with or without DIC. Therefore, thrombocytopenia in gastric cancer patients may be considered as one of the indicative sign for clinicians to proceed with bone marrow biopsies.

Although it is a difficult decision both for physicians and patients whether to proceed with aggressive treatment, we recommend to administer more tailored therapies stratified based on risk factors to enhance treatment outcome. As shown in recent studies for metastatic gastric cancer patients undergoing chemotherapy [11, 12], further analysis on larger series of patients for validation of the current results is warranted.

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