EJMO

DOI: 10.14744/ejmo.2017.65365
EJMO 2017;1(3):160-163

Research Article

Gastric Cancer Patients with Bone Marrow Metastasis: A Single-Center Experience and Review of the Literature

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Abstract

Objectives: The purpose of this study is to investigate bone marrow metastasis in patients with Gastric cancer.

Methods: We retrospectively evaluated patients with gastric cancer who applied to our clinic between 2010-2016.

Results: 896 patients with gastric cancer were included in the study. Patients had metastatic bone marrow in 8 patients. When the laboratory results were evaluated; in 5 patients trombocytopenia with anemia were present, 2 patients had only tromboscytopenia, one patient had only anemia. In all patients white blood cell count was within normal range. The median survival of the 8 patients in our study was 72 days. In our chemoteraphy group (6 patients) median survival was 77 days (range, 49 to 145 days), in the non-treatment group was 7,5 days (range, 3 to 12 days).

Conclusion: Gastric cancer with bone marrow metastasis is usually seen in younger patients, and is related to poorly differantiated subtypes and is a disease with worse prognosis. Median survival with paliative chemotraphy is under 3 months.

Keywords: Bone marrow metastasis, gastric cancer, signet ring cell

Gastric cancer is an important cause of cancer-related mortality. Median survival in metastatic gastric cancer is under 1 year. According to 2015 World Health Organization data, with 814.000 deaths per year, gastric cancer is the 4th leading cause of cancer-related mortality rate.[1] When planning treatment for gastric cancer, it is important to determine whether or not there is metastasis. Metastasis in gastric cancer is usually observed in the liver, peritoneum, and lymph nodes and less frequently in ovaries, lungs, central nervous system, and bone.[2] Bone marrow is a rare region for metastasis and usually reported as case reports and case series in the literature. Bone marrow involvement in gastric cancer as in all solid tumors associated with worse prognosis.[3-7]

In this study, we aimed to retrospectively evaluate the data of 896 patients diagnosed with gastric cancer between 2010 and 2016 and present the clinicopathologic and demographic features of 8 patients in whom bone marrow metastasis was detected among the 54 patients who underwent bone marrow biopsy.

Materials and Methods

The data of 896 patients who presented at our clinic with gastric cancer were retrospectively screened. Upon detecting cytopenia in 10 patients at the time of diagnosis and in 44 patients during follow-up, bone marrow biopsy was performed for these 54 patients, and in 8 of these patients (0.9%), bone marrow metastasis was detected. All patients were diagnosed by performing bone marrow biopsy. Patient's sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, reasons for undergoing bone marrow biopsy, gap between diagnosis

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Submitted Date: September 24, 2017 **Accepted Date:** September 25, 2017 **Available Online Date:** September 29, 2017

and bone marrow metastasis detection, gap between bone marrow metastasis detection and time of death, chemotherapy regime, duration of chemotherapy, hemoglobin level, white blood cell count, platelet count, alkaline phosphatase (ALP) level, lactate dehydrogenase (LDH) level, and calcium level were analyzed.

Results

Five (62.5%) of the patients were male, and 3 (37.5%) of them were female. Median age was 45.5 years (range, 26–52 years). According to the World Health Organization classification, 6 patients had signet ring cell carcinoma and 2 patients had poorly differentiated adenocarcinoma. Two of the patients developed bone marrow metastasis during follow-up (1.5 and 62 months later). The remaining 6 patients had bone marrow metastasis at the time of diagnosis. In 3 of these 6 patients, bone marrow biopsy was performed owing to cytopenia, followed by detection of cancer metastasis and then the diagnosis of gastric cancer based on systemic scanning (first presentation cytopenia). When the bone marrow metastasis was detected, in 6 of the patients the ECOG performance status was ≤2, and in the remaining 2 patients, it was >2. The synchronous metastasis regions accompanied by bone marrow metastasis were bone in 6 patients (75%), ovaries and peritonea in 2 patients (25%), and liver in 1 patient (12.5 %). Median survival of the patients after bone marrow metastasis was 72 days (range, 3–145 days). Two patients with bad ECOG performance status (ECOG 3–4) were followed up with best supportive care. Four patients received DCF regime (docetaxel/cisplatin/5-fluorouracil), and 2 patients received CF regime (cisplatin/5-fluorouracil). Median number of cures the patients received was 3. Four of the 6 patients had synchronous bone metastasis and received bisphosphonates. Median survival time in patients who had bone marrow metastasis at the time of diagnosis was 77 days (range, 49–145 days), and the median survival time in patients in whom bone marrow metastasis developed during follow-up was 7.5 days (range, 3–12 days).

When the laboratory results were evaluated, 5 patients had thrombocytopenia with anemia, 2 patients had only thrombocytopenia, and 1 patient had only anemia. In all patients, the white blood cell count was within the normal range. When the bone marrow metastasis was detected, alkaline phosphatase and LDH were elevated in all patients, median ALP was 901 IU/L (range, 555–3512 IU/L), and median LDH was 554 IU/L (range, 230–1538 IU/L). Although bone metastasis was present ın 6 patients, calcium levels were not elevated in any of the patients. Patient features are presented in Table 1.

Discussion

Bone marrow involvement in non-hematologic malignancies is a not a frequent yet expected finding. In the literature, bone marrow metastasis is more commonly reported in prostate, breast, and lung cancers than in other solid organ tumors.[3-7] Bone marrow metastasis in gastric cancer is rare, and it is presented as a case series in the literature.[8-11] A 39-patient series by Kim et al.[9] reported the bone marrow metastasis incidence to be 0.024%. In our study, the incidence of bone marrow metastasis in gastric cancer was 0.9%. The median diagnosis age for gastric cancer is 69 years (12). However, bone marrow metastasis is seen in younger patients, as noted in the previously reported

Table 1. Demographic, clinicopathological and laboratory characteristics of patients with bone marrow metastasis

Case	Age/ Sex	Histolojik grage	Other site of in volvement	Cause of bone marrow biopsy	Time of BMM	Treatment after the diagnosis of BMM	Survival after the diagnosis of BMM (days)	ALP (IU/L)	LDH (IU/L)	Calcium (mg/dl)
1	39/F	Poorly differentiated	Bone, Over, Peritoneum, Liner	Thrombocytopenia, Anemia	After 40 days	BSC	12	907	1740	7.4
2	52/M	Signet ring cell	Bone	Thrombocytopenia	Synchronous	5 cycles DCF	145	2873	234	8.5
3	48/M	Signet ring cell	Not	Thrombocytopenia, Anemia	Synchronous	3 cycles DCF	90	930	477	9.4
4	45/M	Poorly differentiated	Bone	Thrombocytopenia, Anemia	After 62 months	BSC	3	3512	399	8.5
5	49/M	Signet ring cell	Bone	Anemia	Synchronous	2 cycles DCF	74	895	230	7.9
6	26/F	Signet ring cell	Over, Peritoneum	Thrombocytopenia, Anemia	Synchronous	3 cycles DCF	80	730	632	8.7
7	36/F	Signet ring cell	Bone	Thrombocytopenia, Anemia	Synchronous	3 cycles DCF	70	582	938	9
8	46/M	Signet ring cell	Bone	Thrombocytopenia	Synchronous	2 cycles DCF	49	555	1528	10

BMM: bone marrow metastasis; LDH: lactate dehydrogenase; ALP: alkali phosphatase; BSC: best supportive care; DCF: docatexel/cisplatin/5-fluorouracil; CF: cisplatin/5-fluorouracil normal range

case series. The median age reported by Kim et al.[9] was 47 years, whereas that by Kwon et al.[10] was 46 years. In our study, the median age was 45.5 years, which is consistent with the literature.

Although the most common sites of metastasis in metastatic gastric cancer are the liver and peritoneum[2], the most frequent synchronous site of bone marrow metastases in stomach cancer is bone, and liver and peritoneal metastases are much less common. In a study by Kim et al.[9], the most common synchronous metastasis regions were the bone (31/39), lymph node (17/39), peritoneum (15/39), and lungs (9/39).

Similarly, in other studies, bone has been reported to be the most common synchronous metastasis region. In our study, 6 (75%) of 8 patients had bone metastasis, 2 patients had peritoneum metastasis, and 1 patient had liver metastasis; this is consistent with the literature. The most likely causes of this spreading pattern are that cancers with bone marrow metastasis are poorly differentiated, and signet ring cell carcinomas and probably cytokines and adhesion molecules released from these poorly differentiated cancer cells interact with bone microenvironment more compatibly than with other organ microenvironments; therefore, cancer preferentially spreads to these regions. In a study by Kusumoto et al.[8], in cases of gastric cancers with bone marrow metastasis, elevated receptor activator of nuclear factor kappa-B ligand expression in the gastric tissue was reported to play an important role in pathogenesis.

The most common hematologic abnormality in patients with bone marrow metastasis in gastric cancer is thrombocytopenia. In the case series reported by Kim et al.[9], the incidence of thrombocytopenia was 69.2%; in the series reported by Ekinci et al.[11], the incidence was 100%, and they reported thrombocytopenia to be the most common hematologic abnormality. In our study, thrombocytopenia incidence was 87.5%, which was consistent with the literature. For this reason, in patients with gastric cancer, refractory thrombocytopenia should be a cautionary sign, and bone marrow biopsy must be considered. In addition, ALP and LDH values were high in all our patients; ALP and LDH values should also be cautionary signs for bone and bone marrow metastasis in gastric cancer.

In metastatic gastric cancer patients, median survival without treatment is between 2 and 4 months. Median survival increases with treatment but cannot exceed 1 year.[13,14] Gastric cancer patients with bone marrow metastasis have worse prognosis, and their median survival is less than 3 months.[15] In the series reported by Kim et al.[8], the median survival time of all patients was 44 days: in the group without treatment, 20 days, and in the chemotherapy group, 67 days ($p<0.02$). In the 26 cases reported by Kwon et al.[10], the median survival time of all patients was 37 days: in the group without treatment, 11 days, and in the chemotherapy group, 121 days ($p<0.01$). The median survival of the 8 patients in our study was 72 days. In our chemotherapy group (6 patients), the median survival was 77 days (range, 49–145 days), and in the group without treatment, it was 7.5 days (range, 3–12 days). In our study of few patients, the median survival of the patients who received palliative chemotherapy was significantly increased compared with that of the group without treatment, which was consistent with the literature. Studies in the literature have shown that if patient's performance status is appropriate to receive chemotherapy even modified doses of chemotherapy increase survival. Unfortunately, because of the fact that studies on bone marrow metastasis in gastric cancer were all retrospective and case quantities were insufficient, the ideal chemotherapy regime is unknown. Larger case series are thus required.

Solid tumors rarely metastasize to the bone marrow, but this is not usually seen as the first presentation. When malignant epithelial cells are found in a bone marrow biopsy performed for any reason, although immunohistochemical dyes are helpful for diagnosis, a systemic scanning must be performed. A series of 101 cases reported by Xaio et al.[16], wherein a bone marrow biopsy was performed and non-hematological malignant involvement was detected, in 50 cases, they were able to detect the primary tumor. In these 50 cases, the most common tumors detected were with 11 cases (22%) lung and gastric cancer. Three patients in our study presented with cytopenia, and stomach cancer was diagnosed in a systemic scan performed after the detection of malignant epithelial cells in bone marrow biopsy.

As a result, bone marrow metastasis in gastric cancer is usually seen in younger patients, is related to poorly differentiated subtypes, and is a disease with worse prognosis. Median survival with palliative chemotherapy is under 3 months. When refractory cytopenia or thrombocytopenia is detected, bone marrow biopsy must be considered. In the primary tumor research of a patient with malignant epithelial tumor cells detected in the bone marrow, we suggest that esophagogastroscopy be performed even if there are no symptoms or radiological evidence.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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