Symptomatic Bone Marrow Involvement in Breast Cancer – Clinical Presentation, Treatment, and Prognosis: A Single Institution Review of 22 Cases

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Abstract. *Aim: In contrast to marrow micrometastasis, development of symptomatic bone marrow involvement (bone marrow carcinomatosis, BMC) is a rare event in the course of metastatic breast cancer; published evidence on the outcome with systemic treatment is even more scarce. The objective of this study was to provide our institution's experience with the clinical presentation, prognosis, treatment, and associated complications of marrow involvement in breast cancer. Patients and Methods: Twenty-two breast cancer patients with BMC diagnosed between 1995 and 2009 were analyzed. Results: All patients presented with osseous metastases at the time of diagnosis of BMC. Anemia was the most prominent hematologic sign present in 17/22, followed by thrombocytopenia. Cytotoxic treatment was offered to 21/22 of patients. The majority showed an improvement of cytopenia following treatment (10 out of 14 anemic patients, 6 out of 9 thrombocytopenic patients, all 4 leukopenic patients). The complication rate was acceptable, with only 5 grade 3 or 4 events related to cytopenia (febrile neutropenia, bleeding). The estimated median overall survival from the date of BMC diagnosis was 19 months. After 4 years, 4 of the patients were still alive. Interestingly, prognosis from the time of first diagnosis of BMC was independent of the duration of metastatic disease before BMC had been diagnosed. Conclusion: Bone marrow involvement has to be considered in breast cancer patients, in particular in those with bone metastases and otherwise unexplained cytopenia. The peripheral blood smear can serve as a simple diagnostic tool, but the extent of erythroblastosis is not correlated with survival. Even with severe BMC-associated cytopenia, aggressive combination treatment regimens are indicated, since most patients show improved marrow function after chemotherapy and long-lasting survival is possible.*

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Key Words: Breast cancer, bone marrow carcinomatosis, metastasis.

Diffuse infiltration of the bone marrow by malignant cells can result in cytopenia and thus poses a difficult problem in the treatment of affected patients. However, despite its clinical relevance, this complication has received little attention. Prostate cancer and gastric adenocarcinoma are the malignancies which are primarily associated with the occurrence of bone marrow carcinomatosis (BMC) (4).

Although systemic spread to the bone marrow and lungs is now known to occur early in the course of breast cancer (5), the development of clinically relevant marrow involvement is a rare event. There is a paucity of published data on the epidemiology, diagnosis, treatment, and outcome of breast cancer patients diagnosed with classical marrow carcinomatosis. From a clinical point of view, BMC is most frequently considered in patients suffering from advanced disease presenting with cytopenia, which is considered out of proportion to the cytotoxic treatment the patient has received (4). The typical leukoerythroblastosis seen is thought to result from extramedullary and intrasinusoidal hematopoiesis, as well as fibrosis (8), such that BMC can be confused with myelofibrosis (15).

Many questions remain unresolved regarding clinical presentation, treatment, and prognosis of breast cancer complicated by symptomatic marrow involvement. No special subtypes of breast cancer – based on histology, grading, or receptor status – have been identified so far which are at increased risk of developing this complication. It is unclear whether the diagnosis can rely on evaluation of the peripheral blood or whether bone marrow biopsy is mandatory. Even though various regimens have been recommended regarding systemic treatment, the optimal dosage and combination of cytotoxic drugs in such patients has not been established. We retrospectively analyzed our

Table I. *Patient characteristics at primary diagnosis of breast cancer.*

Pt.	Age (years)	Gender	Histology/grading	ER/PR expression	Her2neu expression	Stage
1	54	M	Invasive ductal/2	Pos/neg	Pos	IIIB
2	55	F	Invasive ductal/3	Pos/pos	Neg	IIIB
3	43	F	Invasive ductal/ 2-3	Pos/pos	NA	IV
4	52	F	Invasive ductal/3	Pos/neg	Pos	IIIB
5	43	F	Invasive ductal/NA	Pos/pos	Neg	I
6	44	F	Invasive lobular/3	Pos/pos	Neg	IIIB
7	37	F	Invasive ductal/2	Pos/pos	Neg	I
8	44	F	Invasive ductal/2-3	Neg/neg	Neg	IIA
9	49	F	Invasive ductal/NA	Neg/neg	NA	IV
10	41	F	Invasive lobular/2	Pos/pos	Neg	IV
11	39	F	Invasive lobular/3	Neg/pos	NA	IIA
12	64	F	Invasive ductal/2	Neg/neg	Pos	IIB
13	49	F	Invasive ductal/3	Neg/pos	Neg	IIA
14	67	F	Invasive lobular/NA	Pos/pos	NA	IV
15	60	F	Invasive ductal/2	Neg/neg	Neg	IIA
16	59	F	NA/NA	Pos/neg	Neg	IV
17	36	F	Invasive ductal/3	Pos/pos	NA	IV
18	60	F	Invasive lobular/3	Pos/neg	Neg	IIIB
19	45	F	Invasive lobular/2	Pos/neg	Neg	I
20	41	F	Invasive ductal/2	Pos/pos	Neg	IIB
21	58	F	Invasive lobular/2	Pos/pos	Neg	IV
22	34	F	Invasive ductal/2-3	Pos/pos	Neg	IIIA

M: Male; F: female; ER, estrogen receptor; PR, progesteron receptor; NA, not available; pos: positive; neg: negative.

database for breast cancer patients with BMC in order to shed light on the clinical presentation at the time of diagnosis of BMC and the clinical course of the patients when treated with systemic chemotherapy.

Patients and Methods

Patients were treated at the Southwest German Cancer Center of the University of Tuebingen Medical Center. Patients with metastatic breast cancer were included in the analysis if bone marrow involvement was confirmed by trephine biopsy, by bone marrow cytology, or by demonstration of a leukoerythroblastic blood smear containing erythroblasts in combination with cytopenia of at least common toxicity criteria grade 1 in one or more lineages. Twenty-two patients were identified fulfilling these criteria. A review of all patient files was performed. The study proposal was presented to the Institutional Review board, which approved the analysis.

A descriptive statistical analysis was performed using SPSS Software (version 15.01; SPSS GmbH Software, Munich, Germany).

Results

Patient characteristics at initial diagnosis of breast cancer. Between 1995 and 2008, a total of 12970 first contacts of breast cancer patients were registered at the Comprehensive Cancer Center. During this time, 1 male and 21 female patients were identified fullfilling the criteria for BMC as defined above. Baseline patient characteristics are summarized in Table I. The median patient age at diagnosis was 47 years (range, 32-67 years). Seven patients presented with metastatic disease at initial diagnosis, the remaining 15 patients had localized disease. The most common histology was invasive ductal carcinoma (n=14), 7 patients had invasive lobular carcinoma histology, no information was available in one case. Only six cases were estrogen receptor negative, four cases were negative for both estrogen and progesterone receptor. Her2neu was found to be overexpressed in 3 patients, Her2-neu status was not determined in five patients treated before the approval of trastuzumab. Two patients were found to be triple negative for receptors. In four cases, the pathology report did not contain information on the grading; the remaining tumor samples were graded as grade 2 or 3.

Patient characteristics at first diagnosis of marrow involvement. Patient characteristics at the time of first diagnosis of BMC are given in Table II. BMC was confirmed by bone marrow histology (n=17) or by documentation of a leukoerythroblastic blood smear (n=5). All patients had detectable metastases, most notably bone metastases, which were present in all cases.

The majority of our breast cancer patients suffering from BMC developed marrow involvement within less than 5 years after primary diagnosis of breast cancer (n=16). Within the course of metastatic disease, BMC was diagnosed after a median of 31 months from the date of

Table II. *Patient characteristics at first diagnosis of bone marrow carcinomatosis from breast cancer.*

Pt.	Interval since first diagnosis (months)	Number of prior treatment regimens	Diagnosis of BMC histology/ cytology	Normoblasts blood smear*	Leukopenia (CTC grade)	Anemia (CTC grade)	Thrombopenia (CTC grade)	Metastatic site
1	26	1	Histology	94	0	2	4	Bone
2	34	-	Peripheral blood smear	5	0	0	0	Bone, liver
3	85	4	Histology	0	0	0	0	Bone
4	46	0	Histology	70	0	2	2	Bone, liver
5	139	3	Histology	8	2	0	1	Bone, liver
6	109	0	Histology	3	0	2	4	Bone, skin
7	82	0	Histology	0	1	2	0	Bone
8	35	4	Histology	1	0	0	1	Bone, liver
9	77	3	Histology	1	2	2	0	Bone
10	34	1	Peripheral blood smear	16	0	2	3	Bone, liver
11	121	2	Histology	1	3	2	4	Bone, liver, brain
12	23	0	Histology	0	0	2	0	Bone
13	3	0	Peripheral blood smear	2	0	1	4	Bone, liver, brain
14	6	0	Histology	1	0	4	0	Bone
15	45	5	Histology	1	0	2	0	Bone, liver
16	16	0	Peripheral blood smear	8	0	3	0	Bone, liver
17	2	2	Histology	3	0	0	0	Bone, liver
18	57	2	Histology	3	0	1	0	Bone
19	196	0	Histology	10	0	3	1	Bone
20	61	1	Peripheral blood smear	1	0	2	0	Bone
21	92	2	Histology	0	0	1	0	Bone
22	59	0	Histology	0	0	3	0	Bone, liver

*Normoblasts were quantified as number per 100 nucleated white blood cells.

verification of metastatic disease, 46 months after initial diagnosis (range, 2-196 months) and after a mean of one prior treatment (range, 0-5, Table II). All patients had known metastasis to bone, while 10 had hepatic and 10 had lymph node metastases. The typical hematologic pathology was anemia, which was present in 17 patients, followed by thrombocytopenia in 9 patients, and leukopenia in 5 patients.

Correlation of diagnostic findings of BMC. The diagnosis of marrow involvement was made from the peripheral blood and/or from a positive bone marrow aspirate/trephine biopsy. Out of the 17 patients with documented tumor cells in the bone marrow, 12 also had leukoerythroblastic blood smears. The number of erythroblasts detected on peripheral blood smears showed large-scale variation (Table II), but did not correlate with patient outcome (correlation coefficient r=0.065).

Considering trephine biopsy or bone marrow aspiration as the gold standard for the diagnosis of BMC, the results suggest a sensitivity of a leukoerythroblastic smear of 75%. The data do not allow the calculation of specificity or predictive values. None of the remaining patients, all of whom had leukoerythroblastic blood smears by definifition, had a negative trephine biopsy.

Response to treatment and overall survival. Out of 22 patients, 20 received chemotherapy for the treatment of BMC. The regimens initially applied were docetaxel/adriamycin (n=6), gemcitabine/vinorelbine (n=5), liposomal doxorubicine (n=1), capecitabine (n=1), epirubicin/cyclophosphamide (n=3), docetaxel (n=1), gemcitabine (n=1), paclitaxel/5-fluorouracil (n=1) and docetaxel/gemcitabine (n=1). In four cases, the first cycle of chemotherapy was reduced in dose. In four patients, the second treatment cycle had to be postponed. Reasons were prolonged cytopenia (n=2), non-hematological toxicity (n=1), and discontinuation of treatment for other reasons (n=1). The dose of cytostatic agents used was reduced in the second cycle in two patients.

Best reponse to chemotherapy regarding measurable lesions as determined by the treating physicians at the time was a partial remission in six patients, six further patients achieved a stable disease. Ten patients had grade 3/4 hematological toxicity. The best response rate was documented after treatment with docetaxel/adriamycin (n=5). All four patients with leukopenia showed a normalization following systemic treatment. However, one patient with normal total white blood count at the initiation of treatment showed prolonged grade 3 leukopenia after treatment. Ten patients with anemia showed improvement or normalization of hemoglobin levels. On the other hand, hemoglobin levels

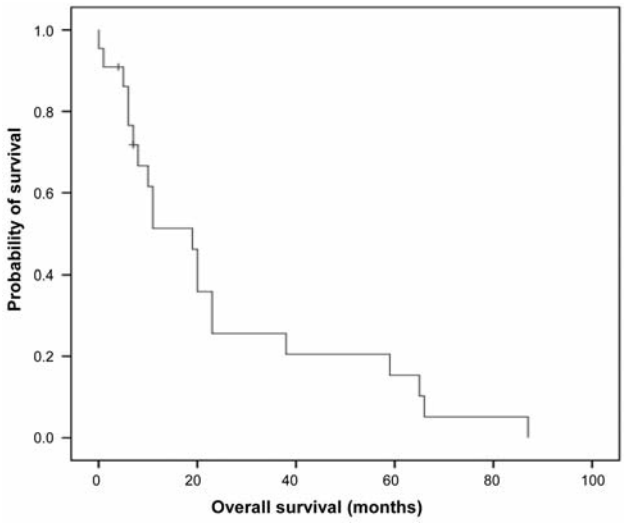

Figure 1. *Overall survival after diagnosis of bone marrow carcinomatosis (BMC). A Kaplan-Meier analysis of all patients after diagnosis of BMC shows a median survival of 11 months (95% confidence interval, 10.5-27.5 months).*

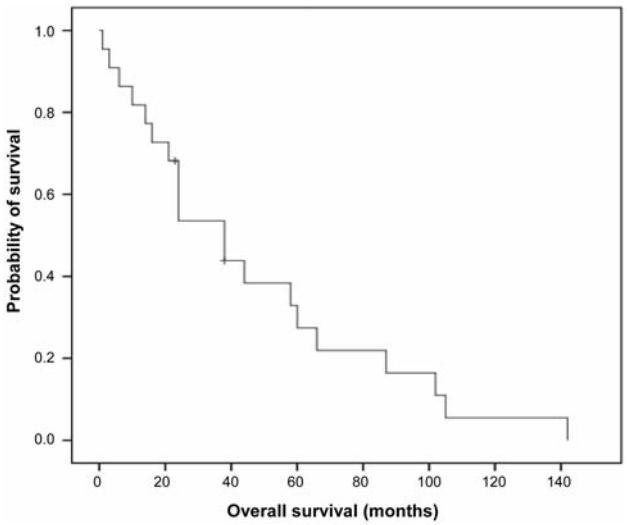

Figure 2. *Overall survival after first diagnosis of metastasis. Median survival after the first diagnosis of metastasis was 31 months (95% confidence interval, 23-53 months).*

dropped in two patients and cytopenia remained at the same CTC-grade in two further patients. Six out of nine patients presenting with thrombocytopenia showed improvement (n=1) or normalization of the platelet counts (n=5). Five patients displayed higher grade thrombocytopenia following the first treatment after BMC compared with platelet levels before treatment. Ten patients received at least one further line of cytotoxic treatment.

Estimated overall survival from the date of diagnosis of BMC is shown in Figure 1 (median survival 19 months). Figure 2 illustrates the overall survival from the diagnosis of metastatic disease.

Complications of cytotoxic treatment in BMC. Five patients developed febrile neutropenia, two cases were treated in hospital. Five patients experienced bleeding complications, including three grade 3 events and one grade 4 event.

Discussion

Occult micrometastatic spread of breast cancer cells to the bone marrow has been described in up to one third of patients with stage I–III disease at the time of diagnosis and is known to be prognostic in regard to risk of relapse (3). In contrast, clinically apparent BMC is a rare manifestation of metastatic breast cancer. Among the 12970 patients treated at our institution between 1984-2008, only 0.17% were identified with this condition. However, the data may underestimate the actual incidence, because our institutional database does not specifically include the parameter 'bone marrow carcinomatosis' and because treating physicians may have missed the diagnosis. Nevertheless, the number may serve as a rough indicator for the range of the true incidence. Despite the limited number of cases, the present report characterizes one of the largest series of breast cancer-associated BMC and contains several important findings. The presence of BMC is proven by the demonstration of carcinomatous cells infiltrating the bone marrow in a diffuse pattern (4). In clinical routine, the presence of a leukoerythroblastic peripheral blood smear is considered a sign of marrow infiltration (10, 11), as long as other causes such as hemolysis, myelodysplastic syndromes, and myeloproliferative syndromes are ruled out.

In our patient cohort, BMC developed in patients with high or intermediate grade tumors. The distribution of hormone receptor expression mirrored the expected pattern in grade 2 or 3 tumors (14). In 1987, Kamby *et al*. suggested that the bone marrow may be the primary soil of metastatic bone disease in breast cancer, such that typical osseous metastases would arise by invasion from the marrow (6). A close association between bone marrow involvement and bone metastasis is confirmed in our series, where all patients suffering from BMC had evident bone metastases. However, whereas bone metastases can be expected in a large proportion of patients suffering from metastatic disease (7), most of them will obviously present with focal proliferation resulting in mostly osteolytic bone metastases rather than in a diffuse infiltration pattern of the bone marrow. In our series, extraosseous organ metastases were detected in only half of the patients.

BMC developed both early and late in the course of metastatic disease. However, when the survival of patients with early-onset BMC (interval less than 36 months from first diagnosis of breast cancer, n=9 patients) was compared with late-onset BMC (>36 months interval, n=13 patients), there was no significant statistical difference in survival measured from the time of diagnosis of BMC. Median survival was 20 months in the early-onset marrow group vs. 19 months in the late-onset group (log-rank test: chi-square=0.754, p=0.38; data not shown).

Based on gene expression patterns, separate subtypes of breast cancer can be distinguished (9), which may not only correlate with different histologic and immunohistochemical features, but also with their preferred site of metastatic spread (12). Among patients suffering from bone metastases, a phenotype characterized by estrogen receptor expression in the absence of progesteron receptor has been identified in 38% of cases, whereas the respective phenotype was demonstrated in only 6% of patients without bone metastases (13). In our series, however, even though the limited number of cases precludes meaningful statistical analysis, beyond the absence of G_1 tumors, no particular subtype seems to dominate among the patients suffering from BMC.

At the time of diagnosis of BMC, cytopenia, in particular anemia, was a frequent finding. Thus, a high level of suspicion is advisable in particular in patients suffering from intermediate or poorly differentiated tumors with bone metastases and otherwise unexplained anemia. The appearance of erythroblasts in the peripheral blood smear was an indicator with a fair sensitivity. However, trephine biopsy may be necessary to verify the diagnosis.

Anemia and thrombocytopenia as the most prominent signs of BMC did not pose a major problem in the further course of treatment. Dose delays and dose reductions were necessary in rare cases only, and treatment-induced cytopenia remained within an acceptable range. Many patients showed an improvement of their cytopenia following treatment. Thus it is justified to apply chemotherapeutic regimens with a high response rate in order to improve bone marrow function. The fear of cytopenic complications, such as febrile neutropenia or bleeding events, should not prevent physicians from administering efficient combination chemotherapies.

Pursuing a rather aggressive approach is also supported by the prognosis, which was suprisingly good in this cohort: The estimated median overall survival from the time of diagnosis of BMC was 19 months. Individual patients may experience prolonged disease control despite this difficult condition. From the perspective of the initial diagnosis of metastatic disease, the median overall survival was 31 months, emphasizing the fact that diagnosis of BMC should not be regarded as a poor prognostic indicator. Our data are in line with previously published case reports, where low-dose capecitabine and also maximum tolerable dose combination chemotherapy regimens resulted in remission of BMC for extended periods of time (1, 2).

In summary, BMC should be suspected in patients suffering from high- or intermediate-grade breast cancer with bone metastases and otherwise unexplained cytopenia. The presence of erythroblasts in the peripheral blood smear is diagnostic, with an approximate sensitivity of 75%. Although BMC is typically accompanied by cytopenia, systemic treatment aiming at high response rates can be administered without an undue increased risk of cytopenic compliations. Long-lasting disease control can be achieved, even in this clinically challenging situation.

Acknowledgements

Hans-Georg Kopp is supported by the Max Eder Stiftung, Deutsche Krebshilfe, Bonn, Germany and by grants from the German Research Foundation (SFB685, project A7; SFB 773, project C6).

Declaration of Competing Interests

The Authors declare that they have no competing interests.

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Received July 29, 2011
Revised September 27, 2011
Accepted September 29, 2011