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Case Report

Single-Agent Weekly Carboplatin for Disseminated Carcinomatosis of Bone Marrow Arising from Breast Cancer. A Case-Report

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Abstract

Disseminated bone marrow carcinomatosis (DBMC) is an infrequent manifestation of advanced breast cancer which can be accompanied by life-threatening clinical complications. The optimal management of the condition is unknown due to the paucity of published studies. We report a case of young female patient with DBMC as a part of the systemic relapse of hormone receptor positive, HER2 negative breast cancer. At the onset of DBMC, due to severe thrombocytopenia (18,000/mm^3) and clinical deterioration, she required hospitalization and platelets transfusions. Her Eastern Cooperative Oncology Group Performance Status was 3. After doxorubicin failure, considering her familial history of multiple relatives with breast cancer, single-agent weekly carboplatin has been started at the dose AUC 2 with gradual normalization of the marrow function, important clinical amelioration and without significant toxicity. The survival time from DBMC diagnosis was 11 months. BRCA testing was not performed. In some very carefully selected patients with DBMC, single-agent weekly carboplatin may be considered as a treatment option.

Keywords: *Bone Marrow Carcinomatosis; Disseminated Carcinomatosis of Bone Marrow; Breast Cancer; Carboplatin; Thrombocytopenia*

Abbreviations

DBMC: Disseminated Bone Marrow Carcinomatosis; BC: Breast Cancer; ER: Estrogen Receptor; PR: Progesterone receptor; ECOG: Eastern Cooperative Oncology Group; HRD: Homologue Recombination Deficiency; AUC: Area Under Curve; PARP1: *Poly ADP-Ribose polymerase 1;* OS: Overall Survival

Introduction

The term Bone Marrow Carcinomatosis or Disseminated Carcinomatosis of Bone Marrow (DBMC) refers to its diffuse infiltration by neoplastic cells accompanied by "clinically important" hematological dysfunction, as opposed to the mere presence of foreign non-hematopoietic cells in the bone marrow biopsy without any significant blood cells count alteration in laboratory studies [1].

Among solid tumors, breast cancer (BC) is one of the most common causes of DBMC [2]. The prevalence of DMBC in patients with BC is about 0.2% [3].

The prevalence of the majority of common clinical and pathological features like age, histology, estrogen receptor (ER), proges-

terone receptor (PR), HER2 receptor and Ki-67 proliferation index are not different between BC patients with and without DBMC, while the proportion of initial stage IV among patients with DBMC is greater than expected [4].

In patients with initial stage I to III, the time from initial diagnosis to DMBC development may vary in a very wide range [1,5,6].

Bone metastasis are present in almost all BC patients with DBMC [3]. Activation of osteoclasts may play a central role in the molecular pathogenesis of the DBMC, although the exact molecular mechanism by which the malignant clone adopt the diffuse instead of circumscribed pattern of growth is unknown [7].

The combination of thrombocytopenia and anemia is the most common hematological alteration in DBMC [4].

In BC patients, the coexistence of DMBC and disseminated intravascular coagulation and/or hemolytic angiopathic anemia may take place [6,8,9].

As clinical trials almost invariably have near-normal hemoglobin level, as well as leucocyte and platelet counts, as their key inclusion criteria, patients with DMBC are automatically excluded from the participation in these studies [10].

This notoriously reduces our knowledge about safety, efficacy and comparative effectiveness of major cytotoxic, endocrine and targeted therapies for DBMC treatment, and makes it excessively dependent on data from small series and single-case reports, severely prone to selection and reporting biases.

Thus, in everyday practice, decisions on management of BC patients with DCBM heavily rely on experts´ opinion and treating oncologist´s personal experience and intuition.

Recently, the tumor-site "agnostic" approach, in which the treatment of a particular patient is driven by relevant molecular alterations regardless of tumor localization and histology, has shown to be successful and gained the regulatory approval [11]. This new paradigm, in addition, may grant an opportunity to choose a better treatment in situations in which high-quality evidence is lacking.

Unfortunately, in developing countries the access to molecular diagnostic tests and new targeted therapies may be markedly reduced due to monetary constraints. However, we suppose that in low-income environments, in some cases, the presence of a molecular target may be inferenced from the clinical data with a high enough probability to justify the correspondent treatment without the exact knowledge of the molecular etiology of the disorder.

We report a case of a young, pretreated BC patient with DBMC and unfavorable performance status with clinically meaningful response to carboplatin monotherapy.

Case Report

A 35 years old female Venezuelan-born patient has been admitted at in-inpatient department of our Hospital on February 2019 with thrombocytopenia (platelet count 18,000/mm^3), anemia (Hb 10.1 g/dl) and shortage of breath.

Her mother died from breast cancer at the age of 33, her father died from pancreatic cancer, her two maternal female cousins died from breast cancer when they were 26 years old, and her other male cousin died from leukemia. Her ethnic-racial background was judged as of African and Native American stems without any known Jewish ancestry.

She was diagnosed with stage IIIC (T4 N1 M0) left breast carcinoma on August 2016. Immunophenotype of the tumor was as follows: ER 85%, PR 80%, HER2 negative, Ki-67 40%. After five cycles of doxorubicin plus docetaxel neoadjuvant chemotherapy she underwent left total mastectomy and axillar lymphadenectomy on January 2017, followed by adjuvant radiotherapy, tamoxifen and leuprolide.

On January 2018, left axillar relapse has been detected. It has been removed surgically, and bilateral oophorectomy has been performed.

On February 2019, systemic relapse with lung (pulmonary carcinomatous lymphangitis and metastatic nodules), lymph node (mediastinal lymph node enlargement), liver, bone and bone marrow involvement was diagnosed. (Figure 1).

Bone marrow core biopsy showed infiltration with ER positive, PR positive, HER2 negative breast cancer cells. (Figure 2) Her Eastern Cooperative Oncology Group (ECOG) performance status was 3.

With platelet counts below 20,000/mm^3, first-line chemother-

Figure 1: Magnetic resonance image of cervical and thoracic spine shows diffuse marrow involvement. A. Sagittal STIR image shows abnormal hyperintense signal in the posterior elements and vertebral bodies. B. Sagittal T1 weighted image shows abnormal diffuse hypo-intensity.

Figure 2: Bone marrow core biopsy. A: Bone marrow core biopsy shows infiltration by neoplastic cells arranged in solid nests with wide cytoplasm, moderate nuclear pleomorphism and evident nucleoli, compatible with a metastasis of ductal carcinoma of the breast. They are surrounded by desmoplastic stroma. Hematopoietic cells and normal components other than bone trabeculae have been replaced by infiltrating tumor cells (H&E stain, x100). B: Detail of neoplastic cells (H&E stain, 400x). C: Neoplastic cells express GATA 3 and Estrogen Receptors, which confirms their breast origin (Immunohistochemical stain for GATA3, 100x).

apy with weekly doxorubicin has been started. However, after two weeks of treatment, platelet counts have been further decreased and platelet transfusions were needed.

With patients´ familial history in mind, the homologue recombination deficiency (HRD) was presumed. However, as testing for BRCA and other HRD-related genes was not available, as well as the access to Poly(ADP-ribose) polymerase-1 (PARP1) inhibitors, we decided to switch the treatment to carboplatin at the dose Area Under Curve (AUC) 2 on weekly schedule plus pamidronate at conventional doses.

Since then, patients´ platelets count has been increasing until it reaches normal values (Figure 3). It was accompanied by a reciprocal decrease of Ca 15-3 level. Her clinical status was quickly improving, and she was successfully discharged.

Figure 3: Temporal evolution of platelets counts and CA 15-3 levels in relation to carboplatin treatment. Disseminated bone marrow carcinomatosis.

She turned asymptomatic and continued weekly carboplatin on out-patient basis for four months more. The response was classified as partial, and no significant toxicity has been observed. Thus, we decided to modify the treatment to carboplatin plus docetaxel administered on 21-days schedule.

On September 2019, after five months of carboplatin and one month of docetaxel therapy, bone scan and magnetic resonance image have shown the disease progression, We decided to switch the treatment to ribociclib plus fulvestrant combination. However, before this treatment could be started, on October 2019, she developed cognitive and behavioral disturbances requiring hospitalization. Encephalitis and brain metastasis were ruled out and it was interpreted as unspecified psychotic disorder. Treatments with risperidone and palliative care have been initiated. She died on January 2020. The overall survival time since the DBMC diagnosis was 11 months.

Discussion and Conclusion

We presented a case of patient with BC associated DMBC with rapid and clinically meaningful response to carboplatin associated with the U-turning of platelet count and symptoms, and the induction of partial remission which allowed the patient lives with a good quality for several months.

We explain the improvement experienced by the patients on carboplatin therapy by the probable existence of an undiagnosed genetic alteration in one of the HRD-related genes, in line with her pedigree data.

The inability to perform the genetic test to discard or corroborate this hypothesis is the main limitation of our work.

A relationship between BRCA mutations and sensitivity to platinum-based chemotherapy in BC has been reported, although a controversy with this respect persists [12,13].

The best management strategy for BC patients with DBMC is not well-defined.

To our knowledge, two large and one small single-center retrospective case-series reporting on therapeutic regimens used for DMBC treatments and their results have been published on the last decade.

The study by Kopp., *et al*. collected data from a large university cancer center in Germany between 1995 and 2008. Twenty out of 22 (90.9%) patients underwent oncologic treatment. In all treated patients, only cytotoxic chemotherapy has been used as the initial therapy of DBMC. Taxanes and anthracyclines, predominantly combined among them, but also with other drugs, as well as in the form of single-agent therapy, were the most frequently employed cytotoxic drugs. Conventional doses and schedules have been used [3].

Estimated median overall survival (OS) in this series was 19 months (95% confidence interval [95% IC]: 10.5 to 27.5 months). However, grade 3/4 hematological toxicity have been observed in 10 out of 20 (50%) of patients). Febrile neutropenia occurred in five out of 20 (25%) patients. Authors concluded that aggressive cytotoxic therapy "aiming at high response rate" can allow durable control of disease, without "undue complications" [3].

A study by Demir., *et al*. conducted at a university oncology center in Turkey was based on the population of BC patients treated in the period from 2003 to 2012 and was focused mainly on patients' characteristics. Twenty-seven patients with DBMC have been compared with the same number of matched controls [4].

Fourteen out of 27 patients received systemic therapy, one was treated with endocrine therapy and the remaining 13 with cytotoxic agents, mainly anthracyclines and taxanes. The median survival time of DBMC patients was 6.4 months (95% CI: 0 to 19.7 months) possibly reflecting a high proportion of patients with brain metastases. Authors stated that combined chemotherapy "is not mandatory" and "weekly dosed single-agent chemotherapy may be also an acceptable option for these patients" [4].

A more recent Japanese study by Shinden., *et al*. referred to the period 2014 to 2016 included four patients. Two out of four were treated with the combination of cytotoxic agent (paclitaxel) and a targeted drug (trastuzumab). One patient was treated with endocrine therapy and was alive at 24 months of the follow-up. Median OS in this series was 17 months [1].

Several recent single-case reports, almost all from Japan, suggest favorable results associated to the treatment with a combination of cytotoxic and targeted agents, or alternatively, to the endocrine therapy, pointing out the contemporary trend in the patterns of care of DBMC: to treat the target, if it is present [5,8,9,14]. Two studies used antiresorptive agents either denosumab or zoledronic acid [8,9].

In our case, we followed the recommendation of the Turkish group favoring single-agent weekly chemotherapy. To our knowledge, this is the first report on single-agent platinum compound for the treatment of BC related DBMC.

The survival time in our case was inside the range of expected values observed in two most important studies. The low level of toxicity associated to weekly carboplatin may be an additional advantage in low/middle income countries where recombinant thrombomodulin is not always available.

We hypothesize that in DBMC, as in BC in general, there may be no unique preferred therapeutic regimen, and the treatment of each patient needs to be individualized according to the tumor subtype and presence of actionable targets.

Further investigations in the field of DBMC addressing the potential role of platinum compounds in the management of the disease are needed.

In summary, we believe that in some very carefully selected patients with DBMC, despite their suboptimal PS, single-agent weekly carboplatin may be a therapeutic option.

Conflict of Interest

No author declared any financial interest or any conflict of interest.

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