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Case Report

Clinical Effects of Hypomethylating Agents in Patients with Newly Diagnosed Myelodysplastic Syndrome Who Received DNA-Damaging Chemotherapy for Metastatic Breast Cancer

Dong Won Baek, Soo Jung Lee, Sang Kyun Sohn, Joon Ho Moon, Yee Soo Chae

Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, Kyungpook National University Cancer Research Institute, Kyungpook National University School of Medicine, Daegu, Korea

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Correspondence to
Yee Soo Chae
Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, Kyungpook National University Cancer Research Institute, Kyungpook National University School of Medicine, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea.
E-mail: yschae@knu.ac.kr

ORCID iDs
Dong Won Baek
https://orcid.org/0000-0003-4446-1549
Soo Jung Lee
https://orcid.org/0000-0003-0066-4109
Sang Kyun Sohn
https://orcid.org/0000-0002-1874-3959
Joon Ho Moon
https://orcid.org/0000-0003-3756-796X
Yee Soo Chae
https://orcid.org/0000-0002-8585-4982

Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

The cumulative risk of therapy-related myelodysplastic syndrome (t-MDS) in breast cancer patients exposed to chemotherapy and/or radiotherapy is significantly high compared to that in other cancer patients. This report reviews the use of hypomethylating agents (HMAs) to treat a 57-year-old woman newly diagnosed with MDS during palliative chemotherapy for metastatic breast cancer. Over a period of 6 years, the patient received several DNA-damaging chemotherapeutics including doxorubicin, cyclophosphamide, and paclitaxel. Repeated thrombocytopenia was the main reason for suspecting secondary hematologic malignancy. She was diagnosed with t-MDS based on bone marrow examination and her treatment history for breast cancer. While azacitidine was originally administered to stabilize MDS, it also stabilized the patient's lung and lymph node metastases without any major toxicity. Therefore, the current case highlights the promising effects of HMAs for treating t-MDS following heavily pretreated breast cancer.

Keywords: Azacitidine; Breast neoplasms; DNA methylation; Myelodysplastic syndrome

INTRODUCTION

Therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myeloid leukemia (AML) are both clonal hematopoietic stem cell disorders that result in abnormal hematopoiesis and account for 15%–20% of all MDS/AML cases [1]. The t-MDS is diagnosed based on a patient history of exposure to cytotoxic chemotherapy and/or radiation therapy for hematologic malignancies, as well as solid neoplasms. Importantly, MDS incidence is higher among patients who have been exposed to DNA-damaging therapy than among unexposed patients [1,2]. Moreover, patients with t-MDS have worse survival outcomes than patients with *de novo* MDS [3].

DNA-methylation plays an important role in tumorigenesis and cancer progression by interfering with cell cycle control, apoptosis, and DNA repair [4]. Furthermore, various genes

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affected by hypermethylation have already been reported to induce anticancer drug resistance and poor prognosis [5,6], making DNA-hypermethylation an attractive target for treatment and overcoming drug resistance by influencing tumor biology. Hypomethylating agents (HMAs) were first discovered in the early sixties, including 5-azacytidine (azacitidine, AZA) and its derivate 5-2′-deoxycytidine (decitabine, DAC). Although several studies have shown promising results for using HMAs to treat solid tumors [7], AZA and DAC are currently only approved by the US Food and Drug Administration for treating hematologic malignancies, such as MDS and AML.

The standard treatment for MDS depends on the disease status according to the International Prognostic Scoring System (IPSS), and is similar for patients with t-MDS [8]. In the case of young patients with a high-risk of transformation to AML, an allogeneic hematopoietic stem cell transplant can be beneficial, whereas HMA therapy can be an option for patients who are not transplant candidates or do not have a donor [9].

The cumulative risk of t-MDS for breast cancer patients exposed to chemotherapy and/or radiotherapy is known to be significantly higher when compared to other cancer patients [2]. However, t-MDS following breast cancer treatment is not fully understood yet. Therefore, this report reviews the use of HMAs to treat a 57-year-old woman newly diagnosed with MDS during palliative chemotherapy for metastatic breast cancer.

CASE REPORT

In March 2012, a 57-year-old Korean female was diagnosed with resectable invasive ductal carcinoma in her left breast. The pathologic results revealed hormone receptor positive and human epidermal growth receptor 2 (HER2) positive status. The patient was administered neo-adjuvant chemotherapy with 4 cycles of doxorubicin plus cyclophosphamide, followed by 4 cycles of docetaxel. At the time of the first chemotherapy, blood tests and complete blood counts showed no abnormalities. After modified radical mastectomy, the patient received adjuvant radiotherapy and trastuzumab with an aromatase inhibitor for a year and continued to take the aromatase inhibitor thereafter. In January 2014, the patient complained of a right supraclavicular lymph node enlargement, which turned out to be metastatic carcinoma. Therefore, the patient was administered palliative chemotherapy with capecitabine + lapatinib from March 2014. In July 2015, after the 24th chemotherapy cycle of capecitabine + lapatinib, multiple lung metastases were found in a chest computed tomography (CT). Due to these lung metastases, vinorelbine plus trastuzumab were administered until disease progression. **Figure 1** summarizes the overall treatments administered.

In April 2017, administration of ado-trastuzumab emtansine was delayed due to low platelet (PLT) count, in the range of 28,000–41,000/mm^3. Owing to repeated thrombocytopenia and a prolonged recovery after every chemotherapy, the patient underwent a bone marrow (BM) aspiration and biopsy in October 2018. BM examination revealed myelodysplastic syndrome with 3.7% blasts and a complex karyotype, and the following serum findings: white blood cell (WBC) count 1,170/mm^3 (absolute neutrophil count [ANC] 470/mm^3), hemoglobin (Hb) 10.8 g/dL, and PLT count 12,000/mm^3. According to the IPSS, the risk group was intermediate-2. Even though disease progression was found in both lungs and the brain, the patient requested systemic treatment for MDS and metastatic breast cancer. Therefore, the patient was given AZA subcutaneously at a dose of 75 mg/m^2 per day for 7 days every 4 weeks, along

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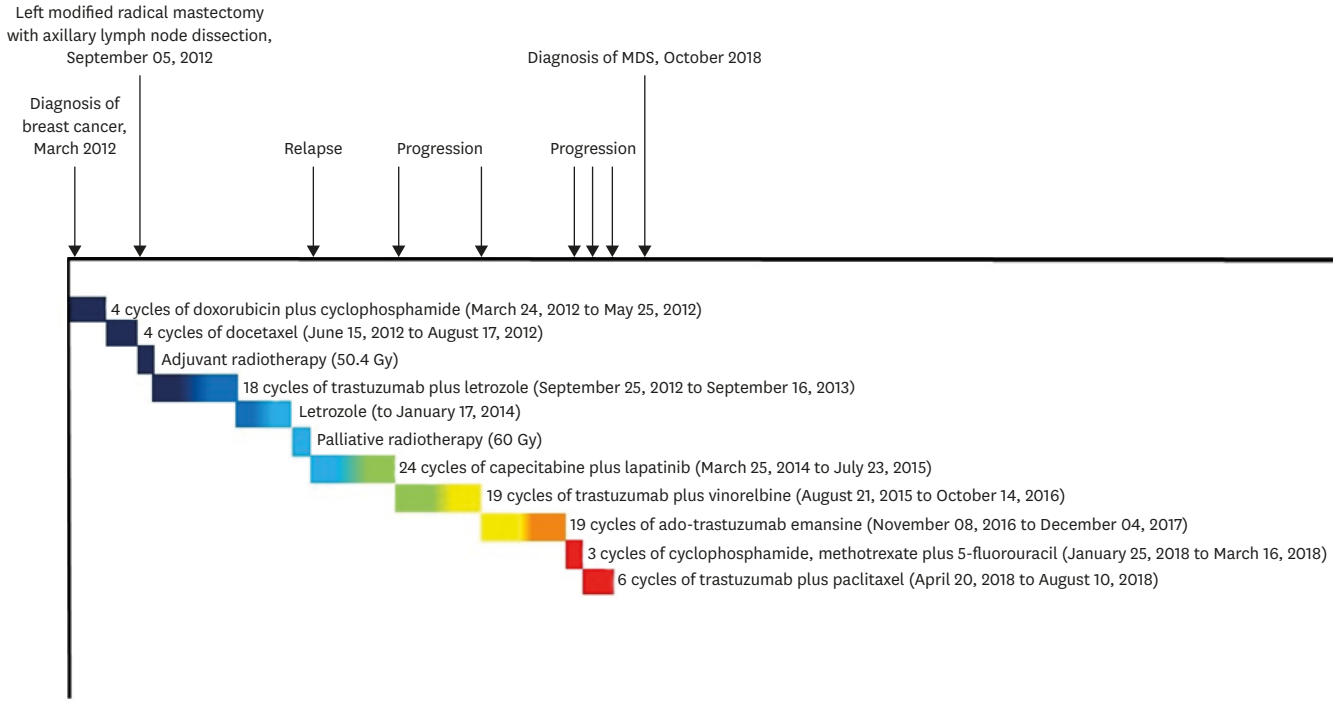

Figure 1. Treatment history for breast cancer.

with tamoxifen and anti-HER2 targeted therapy for metastatic breast cancer. This treatment was well tolerated, with only mild fatigue as a side effect.

After 4 cycles of AZA, the complete blood count improved as follows: WBC count 3,900/mm^3 (ANC 1,980/mm^3), Hb 10.1 g/dL, and PLT count 125,000/mm^3 without transfusion (**Figure 2**).

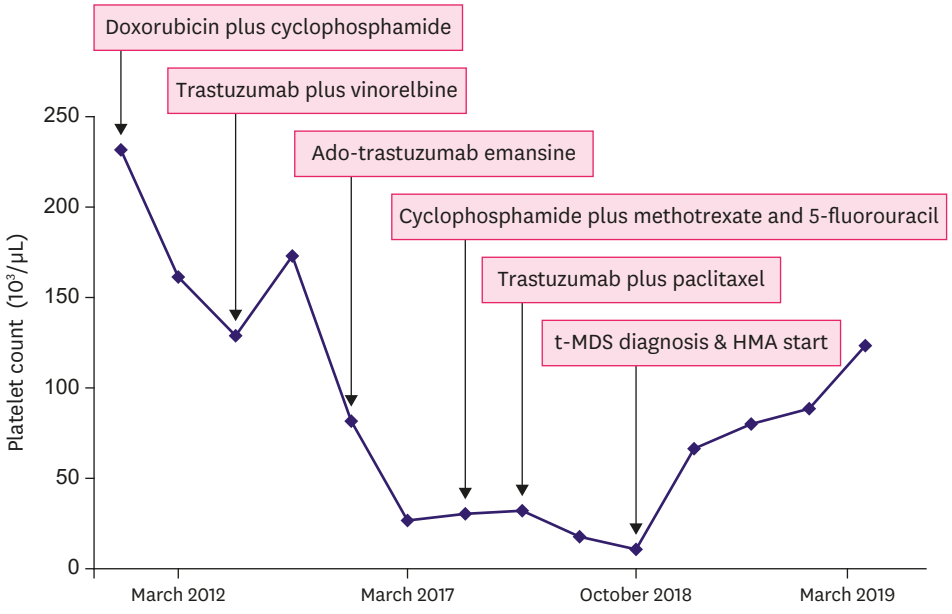

Figure 2. Improved platelets after hypomethylating agent therapy.
t-MDS = therapy-related myelodysplastic syndrome; HMA = hypomethylating agent.

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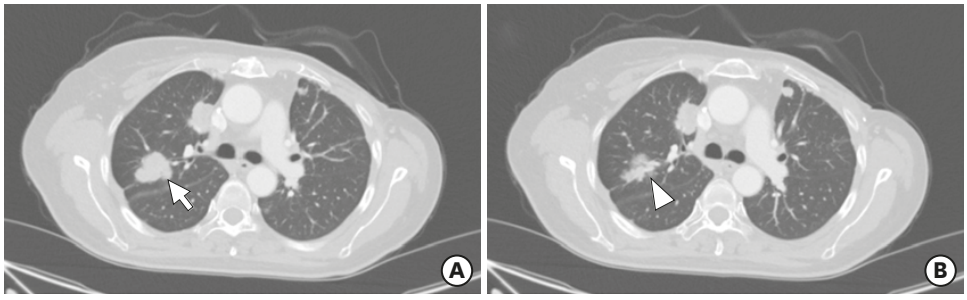

Figure 3. Chest computed tomography (CT) scan before (August 2018) and after (April 2019) the azacitidine (AZA) treatment. (A) Multiple lung metastases (arrow) were found in the chest CT scan. (B) After 4 cycles of AZA, size of right upper lung mass was decreased (arrowhead).

In the follow-up BM examination, the blasts were reduced to 2.4% and their karyotype was normal. Moreover, chest CT showed a slight decrease in the size of lung metastases and enlarged lymph nodes, suggesting a stable disease (**Figure 3**). Recently, the patient completed her 6th cycle of AZA with good performance and no further progression of metastatic breast cancer.

This study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUCH 2019-10-031), and informed consent was obtained.

DISCUSSION

This case report reviews the successful use of AZA to treat a heavily pretreated metastatic breast cancer patient newly diagnosed with MDS. The patient had already been treated for 6 years with several DNA-damaging chemotherapeutics including doxorubicin, cyclophosphamide, and paclitaxel. Repeated thrombocytopenia following chemotherapy led to concerns regarding secondary hematologic malignancy, which resulted in a diagnosis of t-MDS based on a BM examination combined with the treatment history for breast cancer. Although AZA was originally administered to stabilize MDS, it was also found to stabilize the patient's lung and lymph node metastases without any major toxicity.

The t-MDS is a heterogeneous and poorly defined disease. Although the exact mechanism is still unknown, its most likely cause is the accumulation of genetic mutations in myeloid clones induced by preceding cancer treatments [10]. Patients with t-MDS often show a similar level of cytopenia as *de novo* MDS, and high-risk cytogenetics are observed in a large number of patients. Breast cancer is the most common type of solid cancer in t-MDS patients, with a relatively longer latency period of up to 10 years [11]. As patients with t-MDS have a higher risk of transformation to AML and resistance to conventional therapies, their prognosis is generally poor with a median survival of 8 to 9 months [3]. The major risk factor for t-MDS in breast cancer survivors is a treatment history of chemotherapeutic agents and radiation [2], where doxorubicin is particularly well known to have a strong association with t-MDS in breast cancer patients [12]. As most cases of t-MDS develop in breast cancer patients heavily pretreated with cytotoxic chemotherapeutic agents, their treatment options are invariably limited due to treatment-related complications and comorbidities, or the cancer itself. However, significant developments in breast cancer treatments have recently improved survival while reducing adverse side effects and comorbidities. Therefore, based on their relatively mild or manageable side effects, HMAs can be reasonably selected for treating t-MDS patients with heavily pretreated breast cancer [7,13].

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The mechanism of HMAs in breast cancer is not completely understood yet. In the current case, the patient received AZA for MDS combined with tamoxifen and anti-HER2 targeted therapy without definitive clinical evidence on the concomitant use of these drugs. Izbicka et al. [14] reported that tamoxifen resistance frequently occurs due to the transcriptional inactivation of the estrogen receptor gene, and HMAs can restore the estrogen sensitivity in hormone-positive breast cancer cells. These findings were also supported by an *in vitro* experiment where epigenetic drugs such as AZA provided a potential therapeutic avenue for the management of anti-hormone-resistant breast cancer [15]. However, further studies are needed to evaluate whether anti-HER2 therapy has an additional synergistic effect on treatment with HMAs and tamoxifen in heavily pretreated hormone-positive HER2-positive breast cancer patients.

In the current case, the patient was administered AZA for t-MDS, regardless of her breast cancer, but her lung and lymph node metastases showed meaningful improvement after receiving AZA. However, it should be noted that the efficacy of HMAs in solid tumors is less evident compared to that in hematologic malignancies. In previous MDS studies, a sufficient follow-up time was proven necessary for evaluating the clinical response to HMAs. However, in most solid tumor studies, HMAs have been administered to patients at a highly pre-treated and advanced stage, meaning that the life expectancy has been invariably inadequate to identify the clinical benefits of HMAs for treating solid tumors. Therefore, this suggests that the benefits of HMAs for treating solid tumors should be explored in patients with earlier stage cancers.

In the current case review, when safely combined with tamoxifen, HMAs showed promising effects in t-MDS following heavily pretreated breast cancer. Although HMAs are still not approved for the treatment of solid tumors, recent preclinical evidence on the effect of HMAs in hormone-receptor-positive breast cancers highlights the need for well-designed prospective, randomized, controlled studies to identify the predictive role of HMAs in treating solid tumors.

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