CLINICAL VIGNETTE

Treatment-Related AML After Breast Cancer

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A 33-year-old female presented with a palpable breast mass. Imaging was suspicious for malignancy and core biopsy confirmed an estrogen receptor-positive, progesterone receptor-positive, and HER2-positive invasive ductal carcinoma. She underwent lumpectomy followed by adjuvant chemotherapy with docetaxel, carboplatin, and trastuzumab. She completed radiation treatment and started tamoxifen. She continued the trastuzumab in order to complete a year of treatment.

A complete blood count (CBC) was done on the day of her fifteenth trastuzumab dose. It demonstrated significant new cytopenias including hemoglobin of 9.9, white blood cell count of 2.2, absolute neutrophil count of 520, and platelets of 47. She reported that her husband just recovered from a viral infection, and she had noted in recent days some mild pharyngitis. She had no fevers, bleeding, body aches, diarrhea, cough, or other concerning symptoms. Given a mild lymphocytosis in her labs, she was sent home with follow-up at one week. Repeat CBC at that time demonstrated a further decrease in her counts. The patient was now having low grade fevers at home, increased pharyngitis, and significant low back pain comparable to when she had received pegfilgastrim during chemotherapy many months ago. She was started on antibiotics and more lab work up was sent. Basic labs were unremarkable as were heterophile antibody, B12, folate, and EBV and parvovirus titers. Abdominal ultrasound showed normal anatomy, including spleen size. The patient returned two days later for follow-up, and her symptoms had all resolved albeit her blood counts were worse. Peripheral blood FLOW cytometry and peripheral smear results had now returned from two days prior and were both consistent with acute myelogenous leukemia (AML). She was immediately directed to a transplant center and after confirmation of the diagnosis with bone marrow aspiration and biopsy, she was started on induction therapy. She was found to have inversion 16 on cytogenetics.

The above case is alarming given the two high-risk cancers diagnosed within less than a year in a young patient with no other personal or family history of malignancy. The question is whether her acute leukemia was treatment-related after her recent chemotherapy and radiation treatment for the breast cancer.

Chemotherapy and radiotherapy are the most common etiologies of secondary cancers.[1] Therapy-related AML (t-AML) and myelodysplastic syndrome (t-MDS) make up 10-20% of all AML diagnoses.[1] The number may be greater since billing codes do not distinguish between treatment-related and *de novo* disease.[2,3] Incidence of t-AML is rising likely due to increasing use of cytotoxic medications and improved survival after treatment of the primary malignancy.[1-4] The risk of chemotherapy-induced disease seems to be greater than with radiotherapy exposure but multiplies with dual use of these treatment modalities.[1,2] Furthermore, risk is dose-dependent.[1] The most common offending agents are alkylating agents and topoisomerase II inhibitors.[1-3] To a much lesser degree, antimetabolites may also increase the risk.[1,5] Taxanes, although used more frequently now in breast cancer management, have not been shown to increase the risk of t-AML.[2,3] Alkylating agents usually cause a preceding t-MDS while topoisomerase inhibitors usually do not have an MDS phase, and t-AML occurs much earlier with the topoisomerase inhibitors.[1-3,5] It is unclear what increases a person's susceptibility since the majority of patients treated with chemotherapy or radiation do not develop secondary malignancies.[5] Some authors conjecture it may be related to differences in drug metabolism, ineffective DNA repair, etc.[1,2,5] Evaluations of the effects of granulocyte colony-stimulating factors (G-CSF) and AML risk are conflicting.[2] Some reports suggest a potential increased risk while other larger reviews did not find an association.[2,3,5] One report hypothesized that patients who required G-CSF may have had underlying bone marrow issues that predisposed to AML, and thus, G-CSF was not the causative factor.[3]

It has been noted for many decades that AML risk is higher in breast cancer patients.[2] Even when treated with surgery alone, analyses show an increased risk of AML despite no exposure to further adjuvant therapy, suggesting certain underlying risk factors or inherent "susceptibility" for breast cancer, which may also predispose to AML.[1,2] While the risk of AML after breast cancer treatment increases in all age groups, one report found that the highest risk was in young patients (<50 years old).[2]

Prognoses appear to be worse in t-AML compared to *de novo* disease.[4,5] Complete remissions occur at lower rates and are less durable in the former.[5] Multiple factors may contribute to these findings. Bone marrow reserve and organ function may be compromised from prior treatment, preventing adequate treatment for the hematologic malignancy.[5] High-risk cytogenetics are often seen in this subset of disease, leading to more treatment resistance.[4,5] Cytopenias may be a larger issue and supportive care less effective due to bone marrow

deficits.[5] Many patients still are coping with the primary malignancy when t-AML is diagnosed.[5] However, patients with favorable cytogenetics such as inversion(16), t(15;17) and t(8;21) have comparable outcomes to those with *de novo* disease.[5] Despite the differences noted in the t-AML patient population, treatment follows the same guidelines as *de novo* disease.[4,5]

The patient above received adjuvant treatment for her early stage ER+, HER2+ breast cancer. Within about six months of completing cytotoxic chemotherapy, she was diagnosed with AML. Her case is not clearly treatment-related. While t-AML can come on within months of prior treatment, those cases were generally associated with anthracycline use, which the patient did not receive. Furthermore, the patient did not receive the usual chemotherapy agents associated with t-AML. The risks with taxanes have not been noted and while carboplatin is an alkylating agent associated with t-AML, it usually occurs years later with a preceding MDS as discussed above. Furthermore, the patient had favorable cytogenetics, while the majority of t-AML come with more complex genetic abnormalities. The rapid onset also is not consistent with the cytogenetics.

Given her recent exposure to trastuzumab, the patient received induction chemotherapy with mitoxantrone, cytarabine, and etoposide to lower the risk of cardiotoxicity. Given remission noted on several subsequent bone marrow biopsies, she proceeded with consolidation with the traditional 7+3 regimen and subsequently high-dose cytarabine given her low-risk cytogenetics. She had one sister who was a HLA-match, but given her favorable disease, stem cell transplant was deferred until first relapse.

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