Biphenotypic Acute Leukemia Following Intensive Adjuvant Chemotherapy for Breast Cancer: Case Report and Review of the Literature

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Abstract: The risk of secondary leukemia in breast cancer patients who receive adjuvant chemotherapy is an open question. We describe the case a 38-year-old woman who developed acute leukemia 18 months after completion of intense adjuvant chemotherapy with prophylactic granulocyte colony-stimulating factor (G-CSF) support and chest wall irradiation. The diagnosis of biphenotypic T-cell acute myeloid leukemia (AML) was based on morphologic and immunophenotypic criteria. Chromosomal analysis of blasts revealed multiple trisomies and tetrasomies. The patient failed to respond to induction and salvage chemotherapy and died 4 months later. This case of acute leukemia occurred in a cohort of 65 high-risk breast cancer patients who were given intense adjuvant chemotherapy during the last 5 years in our hospital. This is the first case reported in the literature of acute leukemia following intensive adjuvant chemotherapy plus continuous prophylactic G-CSF, which is an actively investigated therapeutic strategy. Vigilance and investigation are needed to determine the leukemogenic potential of intense adjuvant chemotherapy plus radiotherapy in breast cancer patients. A brief review of the literature that deals with acute leukemia that develops after adjuvant chemotherapy for breast cancer and with secondary biphenotypic acute leukemia is presented.

Key Words: biphenotypic acute leukemia, breast cancer, intensive chemotherapy, leukemogenesis risk

Breast cancer is a common malignancy with a lifetime risk of dying of this disease of 1 in 26 women (1). Postsurgical adjuvant systemic therapy and local radiotherapy improves the prognosis by reducing tumor recurrence and disease-related death in a number of patients with early stage breast cancer (2,3). In parallel, the long-term risk of malignant complications increases as a potential problem in this group of patients, not however imposing any significant alteration in the established risk:benefit ratio of adjuvant treatment (4). Leukemia and myelodysplastic syndromes, particularly the RAEB-t subtype, are major complications in this setting (2,5). Here we report the case of a young woman who developed biphenotypic acute leukemia (BAL) 1.5 years after completing intense adjuvant chemotherapy plus radiotherapy for operable breast cancer and review the relevant literature. To our knowledge this
• briasoulis et al. is the first case reported in the literature of acute leukemia following intense adjuvant chemotherapy with continuous prophylactic granulocyte colony-stimulating factor (G-CSF), which is a therapeutic strategy presently in evolution.

CASE REPORT

A 38-year-old woman was admitted to the hospital with a 1-week history of high fever and chills. She had undergone modified radical left mastectomy 2 years earlier for a T2N1M0, grade III mixed ductal/lobular breast adenocarcinoma. Following primary surgical treatment the young woman was offered intense sequential chemotherapy that consisted of four cycles of epirubicin 110 mg/m² followed by four cycles of CMF (cyclophosphamide 840 mg/m², methotrexate 80 mg/m², and 5-fluorouracil 840 mg/m²). Treatment was administered every 2 weeks with prophylactic subcutaneous G-CSF injected on days 3–12 throughout the treatment period. Following completion of chemotherapy the patient also received 50 Gy irradiation to the chest wall and regional lymph nodes, and an additional 10 Gy boost to the tumor bed with a linear accelerator, and continued with medical ovarian ablation using monthly injections of luteinizing hormone-releasing hormone (LHRH) agonist triptorelin for 1 year.

One and one-half years later, this patient presented to the hospital with low-grade fever and chills. On examination she had cervical lymphadenopathy, and full blood counts were suggestive for acute leukemia: hematocrit 27.8%, hemoglobin 9.4 g/dl, white blood cell count 16.8 × 10⁹/L with 78% blasts, and platelets 24 × 10⁹/L. Biochemistry tests were normal except for a high serum lactic dehydrogenase level (LDH 1310 IU/L).

A diagnosis of biphenotypic T-cell acute myeloid leukemia (AML) was assigned based on morphologic and immunophenotypic criteria. Myelogram revealed an 80% infiltration of bone marrow with two distinct blast populations: one of small size that resembled lymphoblasts and another larger with basophilic cytoplasm and cytoplasmic granules. Flow cytometry of a bone marrow aspiration confirmed the diagnosis of a mixed lineage leukemia that expressed both T-lymphoid (CD3 cytoplasmic positive, CD2 positive, and CD7 positive) and myeloid differentiation (CD33 positive and CD15 positive) immunophenotype markers. A double immunofluorescence staining was applied for the detection of cell surface and intracellular antigens by FACScan, and data acquisition and analysis was performed with the CELLQest (Becton Dickinson, San Jase, CA). Immunophenotype fulfilled the criteria of the definition for biphenotypic acute leukemia (BAL) according to the European Group for the Immunological Classification of Leukemia scoring system (6,7).

Cytogenetic analysis revealed hyperploidy with an invariable number of 58 chromosomes in 45% of analyzed metaphases. Trisomies of chromosomes 4–8, 10, and 19, tetrasonies of chromosomes 13 and 18, and an extra X chromosome were observed. There were no deletions of the long arms or monosomy for chromosomes 5 or 7, which is considered a characteristic of treatment-related AML (8). The only structural abnormality observed was augmentation of the 7q arm with genomic material of unknown origin.

Upon establishing a diagnosis, the patient started combined induction chemotherapy with aracytine 100/m² on days 1–7, idarubicin 10/m² on days 1–3, vincristine 2 mg on days 1 and 7, and prednisone 40 mg/m² on days 1–7. Unfortunately she had a poor response to chemotherapy and following a second course of treatment her bone marrow was still infiltrated with 57% blasts. Due to a lack of a compatible bone marrow donor, it was decided to shift her to salvage chemotherapy with idarubicin, fludarabine, high-dose aracytine and G-CSF support (Ida-FLAG) (9). This also proved ineffective and the patient died 2 weeks later of a stroke due to thrombocytopenia.

DISCUSSION

Postsurgical adjuvant chemotherapy is an established therapeutic option for high-risk breast cancer patients (10). Adjuvant polychemotherapy with CMF or an anthracycline-containing regimen typically produces an absolute 10-year survival improvement of about 7–11% in women less than 50 years old at presentation and about 2–3% for those...
more than 50 years old (3). The addition of postoperative chest wall and regional lymph node irradiation reduces local-regional recurrence and may also prolong survival in selected patients (11).

In addition to this benefit, a 10-fold increased risk of acute nonlymphocytic leukemia and myelodysplastic syndrome observed in breast cancer patients treated with neoadjuvant chemotherapy raises some concerns for those patients. However, an overall 0.7% cumulative incidence of secondary acute leukemia recorded in this population of patients is largely surpassed by the 7% survival benefit they gain with chemotherapy (12).

The patient reported here was the first to develop acute leukemia among a population of slightly more than 700 breast cancer patients who received adjuvant postsurgical chemotherapy and/or radiotherapy in our care over the last 10 years, yet another patient was diagnosed with myelodysplastic syndrome (RAEB-t). Notably this patient was one in a cohort of 65 patients who were treated with intense adjuvant chemotherapy and prophylactic G-CSF throughout the treatment period. Whether G-CSF receptors, which have been shown to be potentially expressed on biphenotypic leukemic cells, played some role in this event stands only as a remote hypothesis (13).

We believe that this case shows some peculiarities in regard to the type of leukemia and the timing of its occurrence that are possibly related to the preceding intense chemotherapy course. Secondary to adjuvant chemotherapy, acute leukemia usually develops 2–4 years after chemotherapy and is of the nonlymphoid type (14–18). Our case was a biphenotypic acute leukemia that developed at the early end of the risk period for developing acute leukemia. Karyotypic abnormalities and poor outcome to treatment and prognosis are characteristics of biphenotypic acute leukemia as compared to AML and acute lymphoblastic leukemia (ALL), and this was the case with our patient (19,20). Poor prognosis is obviously related to the underlying chromosome abnormalities.

**LITERATURE OVERVIEW**

A number of studies have shown an increased risk for leukemia in breast cancer patients who receive adjuvant chemotherapy (14,15,21–23). Other studies suggest that the combination of radiotherapy with adjuvant chemotherapy may further enhance this risk (5,12).

Treatment-related second malignancies, primarily leukemia, and non-Hodgkin’s lymphomas have consistently been reported in patients treated with alkylating agents for Hodgkin’s disease (24). In breast cancer patients, alkylating agents, mitoxantrone, and etoposide have most commonly been associated with an increased risk of leukemia (5,15,25), while secondary acute leukemia (t-AML) with mutated p53 and an extremely poor prognosis has been attributed specifically to alkylating agents (5).

Dose dependency for the development of secondary malignancies has been suggested for radiotherapy, melphalan, and cyclophosphamide when this exceeds a total dose of 20 g (5). However, there is limited, if any, evidence of an increased incidence of acute leukemia and myelodysplasia in patients who were given intense or prolonged adjuvant chemotherapy for breast cancer (26–28). Post-surgical high-dose chemotherapy was not found to be related to increased risk for secondary malignancies among breast cancer patients who received autologous bone marrow transplant, although a higher incidence of AML was observed in patients transplanted with peripheral CD34-positive cells after chemotherapy priming (29,30).

In intensive adjuvant chemotherapy with continuous prophylactic G-CSF support, which is a novel therapeutic strategy being developed, the presented case of secondary leukemia appears to be the first to appear in the medical literature thus far. Intense adjuvant chemotherapy entered clinical trials for selected high-risk breast cancer patients in the last few years (31–34) following preliminary evidence that higher-dose chemotherapy within the conventional dose range might result in better disease-free and overall survival rates (2,35). Intense adjuvant chemotherapy regimens are currently being investigated as National Cancer Institute (NCI)-sponsored high-priority clinical trials (SWOG-S9623) (36).

**CONCLUSION**

It is well known that breast cancer patients given adjuvant chemotherapy plus radiotherapy are at increased risk of developing secondary acute leukemia. Our case raises an issue of awareness for a potential leukemogenic risk in breast cancer patients who receive intense adjuvant chemotherapy with prophylactic G-CSF support and radiotherapy. We suggest that low-risk breast cancer patients should be treated with caution and that intense adjuvant treatment strategies should be avoided until the potential risks for treatment-related late sequelae are determined.

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