Early occurrence of acute myeloid leukemia following adjuvant radiotherapy and higher cumulative dose of cyclophosphamide in carcinoma breast

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Abstract
We report a case of cancer breast developing acute myeloid leukemia (AML) within a relatively short interval of two and a half years of her primary treatment. This could be attributed to post operative radiotherapy and a higher cumulative dose of cyclophosphamide (14.4 gm) which had to be given as a part of her combination chemotherapy regimen, initially as adjuvant and then later as salvage chemotherapy. The successful salvage therapy for secondary AML instituted in this case is also discussed.

Key Words: Cancer breast, Leukemia, Chemotherapy, Radiotherapy, Second malignancy.

Introduction
Second malignancies in long term survivors of cancer following exposure to radiation or chemotherapy are well documented. Secondary leukemia as a second malignancy after radiation is of special significance since it emerges, typically 1 to 5 years compared with solid cancers which have a latent period of around 10 years.1

Even though the relative risk of secondary leukemia may be quite high, the absolute incidence is relatively low, thereby making this a very small risk in terms of the risk-benefit analysis for the established role of chemotherapy in cancer breast.

The present report highlights a case of acute myeloid leukemia (AML) diagnosed within 2 years following completion of her primary treatment for breast cancer.

Case Report
A 62 year old, cancer of right breast, previously treated in March 2000 presented in August 2003 with generalized weakness, weight loss, loss of appetite and multiple bruises all over the body. Complete blood count revealed a hemoglobin level of 5.2gm/dl, total leukocyte count of 44,380 cells/mm$^3$, with multiple blast cells in peripheral smear. Bone marrow biopsy and immunophenotyping established the diagnosis as AML.

In March 2000, the patient underwent modified radical mastectomy, reported as infiltrating duct carcinoma with none of the ten resected axillary nodes involved. Estrogen and progesterone receptors showed 98% and 2% nuclear positivity respectively. Postoperative radiotherapy was delivered to the chest wall and regional lymphatics to a total dose of 50Gy in 25 fractions over 5 weeks. Adjuvant CMF chemotherapy consisting of cyclophosphamide (C), methotrexate (M) and 5-fluorouracil (F) was started four weeks after completion of radiotherapy. The doses based on her body surface area were – cyclophosphamide 800mg, methotrexate 60mg and 5-fluorouracil 750mg each given on days 1 and 8 and repeated at four weekly
intervals. Following four cycles of CMF, she developed right-sided malignant pleural effusion, which was treated by pleurodysis with 60mg of bleomycin. In view of the disease progression, chemotherapy regimen was changed to 6 cycles of cyclophosphamide 800mg (days 1 and 8), doxorubicin (A) 80mg (day 1) and 5-fluorouracil 750mg (days 1 and 8) – (FAC) delivered at 4 weekly intervals. The cumulative doses of chemotherapeutic agents thus delivered were cyclophosphamide 14.4gm, 5-fluorouracil 14.45gm, doxorubicin 450mg and methotrexate 480mg over a total duration of 10 months. Following completion of chemotherapy in March 2001, she was started on tamoxifen, 20mg daily.

Patient is currently being managed on the lines of AML, M₃ and has received induction chemotherapy regimen in form of daunorubicin (45 mg/m² days 1 and 2 as infusion over 2 hours) and cytosine arabinoside (100 mg/m² days 1 to 5 as continuous infusion over 24 hours). Following induction, consolidation therapy with high dose cytosine arabinoside (3 gm/m² twice a day on day 1, 3 and 5) for 3 such cycles at 4 weekly intervals was delivered. She has tolerated the treatment fairly well with symptomatic relief and hematological remission.

**Discussion**

Secondary leukemias, are well recognized in long term survivors of cancer. The risk of leukemia has been attributed to the specific alkylating agent, the cumulative dose, total duration of treatment and combination of radiotherapy and chemotherapy.² Although the exact incidence is difficult to estimate because of the variety of agents, doses and combinations, it is around 5%.³ The carcinogenic potential of alkylating agents and radiation is related to their mechanism of action on DNA. Alkylating agents are electrophilic and cause DNA damage by formation of DNA adducts. Of the commonly used alkylating agents, melphalan is highly leukemogenic, while cyclophosphamide is graded at a lower scale, possibly on account of its relatively stem cell sparing effect.³ Curtis et al² observed that the mean interval between the initial diagnosis of breast cancer and development of leukemia was 5 years, although it may range from 1.7 to 12.5 years. Relative risk (RR), the excess risk of developing leukemia when compared with the control group, was reported to be 10.0 with alkylating agents alone (95% CI: 3.9-25.2) while for radiotherapy alone it was 2.4 (95% CI: 1.0-5.8). However, the combined effect of the modalities increased the risk significantly to 17.4 (95% CI: 6.4-47.0). Risk increased significantly with the cumulative dose of cyclophosphamide (RR: 1.5-9.4 for doses ranging from less than 10gm to over 30 gm), but there was little increase in the risk with doses less than 20,000mg. However, in Indian patients the cumulative dose of cyclophosphamide for the secondary leukemia could be lesser in view of the lower body mass than those of the Western population. With increasing treatment duration, the risk reportedly rises, being 1.7 for a duration of less than 12 months. Risk was highest within 2 to 2.9 years of initiation of therapy (RR: 21.2), tending to normalize after 7 years (RR: 1.8).²

Shapiro et al⁴ reported that following 6 months of adjuvant CMF in cancer breast, the risk of AML or myelodysplasia could increase to approximately two fold, being equivalent to about 5 excess cases per 10,000 treated patients at 10 years. Risk with doxorubicin containing regimens was found to be only slightly higher than in the general population. Risk was significantly higher in the group receiving both radiation and chemotherapy.

On the contrary, the ECOG concluded that with standard doses of cyclophosphamide, the risk of secondary AML is not much higher than in the general population.⁵ Management of these cases is usually undertaken on lines of the standard protocols of AML. These patients have a consistently poor outcome with an overall death rate of 86%.⁶

To the best of our knowledge, this is the first case to be reported in the Indian subjects as per the Medline search. In the present case, the risk was not markedly increased as the treatment period was only 10 months with cumulative dose of cyclophosphamide being less than 20 gm, so the possible reason though not clearly ascertainable could be the synergistic effect of radiation and chemotherapy.

This case highlights that in situations requiring salvage chemotherapy following initial adjuvant treatment, a conscious decision has to be made after weighing the benefits and the small, though tangible risk of secondary leukemia. In all such cases, it might be reasonable to minimize the risk further by avoiding alkylating agents as second line chemotherapy.

**References**

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