Therapy-related leukemia after breast cancer

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Introduction to therapy-related leukemia

Therapy-related myeloid neoplasms are a direct consequence of mutational events induced by cytotoxic therapy of prior neoplasm. They represent up to 10% of all myeloid neoplasms and its incidence is strongly related to age. They include therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndromes (t-MDS). They are divided into two major groups depending on the preceding treatment: that due to alkylating agents and/or radiation and that due to DNA topoisomerase II inhibitors.

The latency period between primary malignancy and secondary leukemia depends on the cytotoxic drug, its cumulative dose and dose intensity of previous therapy. Besides, the risk of developing a therapy-related leukemia can be increased by individual predisposing factors.

Almost all t-AML patients show cytogenetic alterations, with a high frequency of complex karyotypes. Patients generally have poor prognosis and outcomes compared with AML *de novo* cases and have an intrinsic resistance to conventional therapies used for leukemia.

Therapy-related leukemia after breast cancer

Breast cancer is the most frequent cancer and the second leading cause of cancer death among women in developed countries. It represents the most common neoplasm preceding t-AML and the average latency time between breast cancer and secondary leukemia is 4 years.

The treatment for breast cancer can have genotoxic effects in progenitor hematopoietic cells that lead to its leukemic transformation. Host factors such as polymorphisms in drug-metabolizing enzymes and in DNA repair genes may increase individual risk.

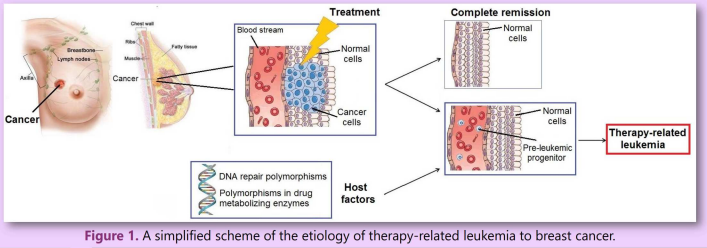


Figure 1. A simplified scheme of the etiology of therapy-related leukemia to breast cancer.

Risk factors for the development of therapy-related leukemia

Adjuvant chemotherapy

Patients who receive adjuvant chemotherapy have more probability to develop t-AML than those who do not.

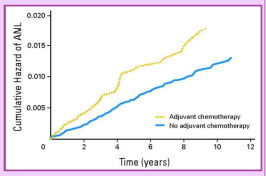


Figure 2. Cumulative probability of t-AML after adjuvant chemotherapy among breast cancer patients.

Alkylating agents

- Dose-dependent effect
- Longer onset (5-7 years)
- Previous MDS phase
- Cytogenetic alterations in chromosomes 5 and 7
- Worse outcome
  Melphalan> Cyclophosphamide

Topoisomerase II inhibitors

- No dose-dependent effect, but more leukemogenic
- Shorter onset (1-3 years)
- No previous MDS phase
- Translocations involving MLL gene (11q23)
- Better outcome
  Anthracenediones> Anthracyclines

Radiotherapy

Radiation therapy following breast-conserving surgery has improved patients survival.

However, patients treated with radiotherapy have a dose-dependent increased risk of developing leukemia.

The risk is higher when radiotherapy is combined with chemotherapy.

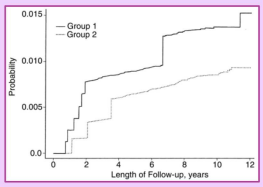


Figure 3. Probability of developing a secondary leukemia after radiation (group 1) or without radiation (group 2)

Study	Relative risk
Curtis *et al.*, 1992	2.4
Smith *et al.*, 2003	2.38
Crump *et al.*, 2003	1.6
Renella *et al.*, 2006	4 7.2
Le Deley *et al.*, 2007	3.9
Zhang *et al.*, 2011	6.67

G-CSFs

Cytokines granulocyte colony-stimulating factors (G-CSFs) are used to reduce the duration of neutropenia in cancer patients receiving chemotherapy, which leads to better outcomes and survival.

They regulate proliferation, differentiation and maturation of myeloid progenitors. They induce alterations in cellular ploidy and increase the risk of developing t-AML.

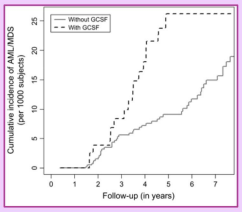
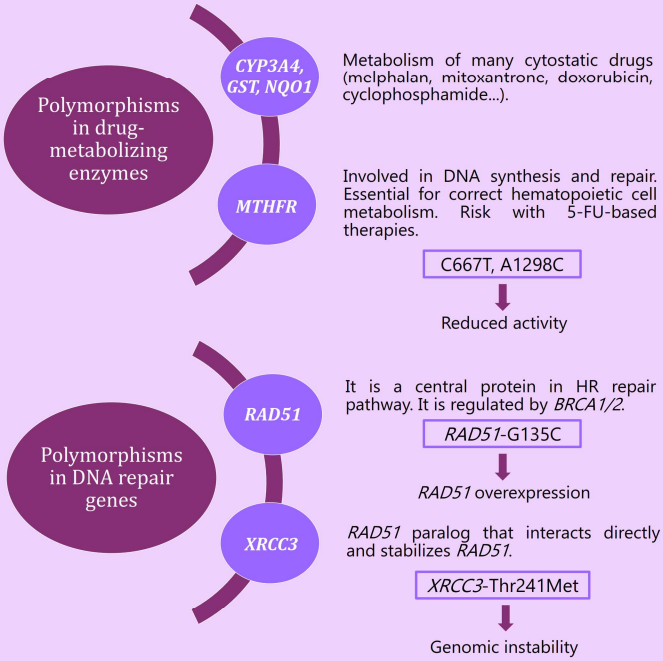


Figure 4. Cumulative incidence of t-AML among women treated with and without G-CSFs.

Study	Relative risk
Smith *et al.*, 2003	6.16
Le Deley *et al.*, 2007	6.3
Hershman *et al.*, 2011	2.14

Polymorphisms involved in therapy-related leukemia

Polymorphisms in drug-metabolizing enzymes or in DNA repair may predispose certain individuals to develop a t-AML. This increased susceptibility may be due to inability to detoxify chemotherapeutic drugs and/or to repair genetic damage induced by prior treatment.



Conclusions

- It is important to estimate the risk of secondary leukemia to determine the risk-benefit ratio of each treatment.
- Chemotherapeutic agents, radiotherapy and G-CSFs increase the risk of developing a secondary leukemia after breast cancer.
- Topoisomerase II inhibitors are more leukemogenic than alkylating agents.
- Radiotherapy increases the risk of developing a secondary leukemia, nevertheless the type of adjuvant chemotherapy used.
- The addition of G-CSFs to intense chemoterapy regimens contributes to leukemogenesis, although its potential toxicity needs further study.
- Breast cancer patients who develop a secondary leukemia present more frequently polymorphisms in drug-metabolizing enzymes (such as *MTHFR)* and in DNA repair genes (such as *RAD51* and *XRCC3*).

New future approaches

- **Deeper understanding of gene polymorphisms**
  - Individual risk
  - Counseling of patients
- **Genome-wide approaches**
  - Novel pathways
  - Novel susceptibility genes

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