Therapy-related leukemia after breast cancer

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 presence/absence of prior chemotherapy: conditioning 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 role of determining a therapy-related leukemia is 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.

Risk factors for the development of therapy-related leukemia

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<tr>
<th>Adjuvant chemotherapy</th>
<th>Radiotherapy</th>
<th>G-CSFs</th>
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<td>Patients who receive adjuvant chemotherapy have more probability to develop t-AML than those who do not.</td>
<td>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.</td>
<td>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.</td>
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Alkylation 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 leukemicogenic
- Shorter onset (1-3 years)
- No previous MDS phase
- Translocations involving MLL gene (11q23)
- Better outcome
- Anthracyclines

Polymorphisms involved in therapy-related leukemia

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

Polymorphisms in DNA repair genes

- RAD51
- XRCC3

Polymorphisms in drug-metabolizing enzymes

- CYP2A4, GST, NQO1

Metabolism of many cytostatic drugs (taxol, irinotecan, doxorubicin, cyclophosphamide, etc.)


- C667T, A1298C
  - Reduced activity

- RAD51-G135C
  - It is a central protein in HR repair pathway. It is regulated by BRCA1/2
  - RAD51 overexpression
  - RAD51 paralog that interacts directly and stabilizes RAD51.
  - Genomic instability

Genome-wide approaches

- Deeper understanding of gene polymorphisms
- Novel pathways
- Novel susceptibility genes

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 leukemicogenic 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 chemotherapy 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

- Individual risk
- Counseling of patients
- Novel pathways
- Novel susceptibility genes

REFERENCES


Additional references to be included