Leukemias Induced By Chemotherapy

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INTRODUCTION

The therapy-related leukemias are the direct consequence of mutational events induced by a genotoxic therapy (chemotherapy and/or radiotherapy) used to treat a primary malignancy. Due to the improved survival rates of many cancers and the increasing use of chemotherapeutic regimes, the incidence of secondary leukemias has risen. The most frequent and widely studied type of secondary leukemia is the therapy-related acute myeloid leukemia, t-AML (many authors include the therapy-related myelodysplasia, t-MDS, in this clinical entity). The reason why the leukemias are the most frequent secondary neoplasias is because the hematologic cells have favourable properties for the clonal expansion of one cell with accumulated harmful mutations: they obtain their nutrients directly from the blood and have the ability to migrate through the bloodstream. The incidence of t-AML varies between 10-20%, and the prognosis is worse than *de novo* AML. Despite the prompt diagnosis and treatment, the t-AML patients have a 5-year survival rate of less than 10%. It has been described the complex karyotype at diagnosis such as the strongest prognostic indicator of poor outcome.

OBJECTIVES & METHODS

OBJECTIVES

- ✓ To describe the causes and features of therapy-related leukemias.
- ✓ To analyze the leukemogenic effect of chemotherapeutic drugs.

SEARCH STRATEGY

PubMed and ScienceDirect database were the main sources of information.

SELECTION CRITERIA

- ✓ Keywords used were "secondary leukemias", "t-AML", "therapy-related leukemias", "alkilating agents", "DNA topoisomerase II inhibitors"
- ✓ Articles were selected from 1990-2014

CHEMOTHERAPEUTIC DRUGS

Table 1. There are two kinds of drugs administered which can induce the leukemogenic process: the alkilating agents and the DNA-topoisomerase II inhibitors. The secondary leukemias can be divided in two groups according to the treatment regimen applied for the previous neoplasia.

CHEMOTHERAPY TREATMENT	ALKILATING AGENTS	DNA-TOPOISOMERASE II INHIBITORS
INCIDENCE OF SECONDARY LEUKEMIAS	1 - <20%	2 - 12%
MECHANISMS/ CYTOTOXIC EFFECT	Formation of interstrand and/or intrastrand cross-links in DNA. Cell cycle NON-specific activity Cytotoxic effect: **dosage-dependent.**	Intercalate on double strand DNA and stabilize the topoisomerase II-DNA complex. Induce the rupture of double strand DNA. Cell cycle arrest at G_2.
GENETIC ABNORMALITIES	Cytogenetic abnormalities. More frequent: complete or parcial deletion of chromosome 5 or 7 (putative tumor supresor genes).	Chromosome aberrations. More frequent: Translocations of MLL gene, involving region 11q23. Less frequent: t(8;21), t(3;21); Inv(16), t(8;16).
CLINICAL MANIFESTATIONS	Long latency period: between 2-10 years. Pancytopenia and myelodisplastic syndrome (MDS) previous to t-AML	Short latency period: between 6 months-2 years. No preceded by myelodisplastic syndrome. ↑ Acute Linfoblastic Leukemia (t ALL) ↓ Acute Promyelocytic Leukemia (t APL)
EXAMPLES OF SUBSTANCES	✓Triazines: ✓Dacarbazine ✓Temozolomide ✓Chloroethylnitrosureas	✓Mitoxantrone ✓Doxorubicin ✓Daunorubicin ✓Epipodophyllotoxins

SUSCEPTIBILITY: CLINICAL FACTORS

Age: Exposure to treatment with alkilating agents or DNA-topoisomerase II inhibitors in childhood does **NOT** confer increased susceptibility. Early childhood (<3 years) can be a protector factor against the secondary leukemia development.

Clinical risk factors in therapy based on:

TOPOISOMERASE II INHIBITORS

- Intermittent schedules
- Preceding L-asparginase administration
- Primary ALL

ALKILATING AGENTS

- Higher cumulative dose
- Older age
- Splenectomy
- Radiotherapy

t-AML *versus de novo* AML

- The Microsatellite Instability (MSI+) phenotype is more frequent in therapy-related leukemias, consequence of Mismatch Repair Mechanisms alterations.
- Complete or partial deletion of chromosomes 5 and 7 are more frequent in t-AML patients.
- T-AML is more refractory to treatment than *de novo* AML because:
  1. The systemic injury caused by prior therapy compromise the ability of these patients to receive intensive chemotherapy regimen.
  2. Prior chemotherapy causes a rapid emergence of multidrug resistant phenotype in t- AML stem cells.
- The chromosome aberrations and gene mutations observed are identical. However, the frequencies of these alterations may differ between t-AML and their *de novo* counterparts.

DRUG-DNA INTERACTION

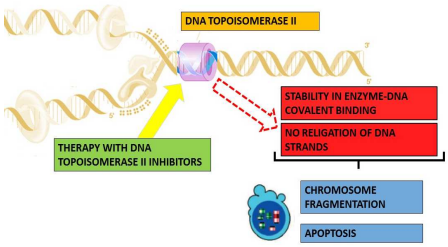


Figure 1. The DNA-topoisomerase II inhibitors arrest the religation process catalyzed by DNA topoisomerase II and stabilize the enzyme-DNA covalent binding. Treatment with these agents induces chromosomal fragmentation, DNA deletions and rearrangements, cell cycle arrest at G2 and activates the apoptotic pathway. These drugs are considered the most widely used anticancer agents.

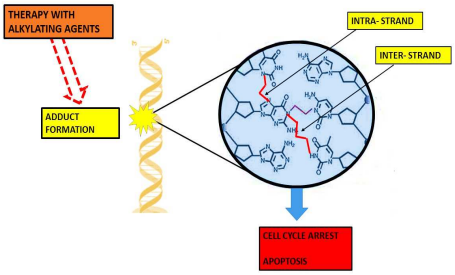


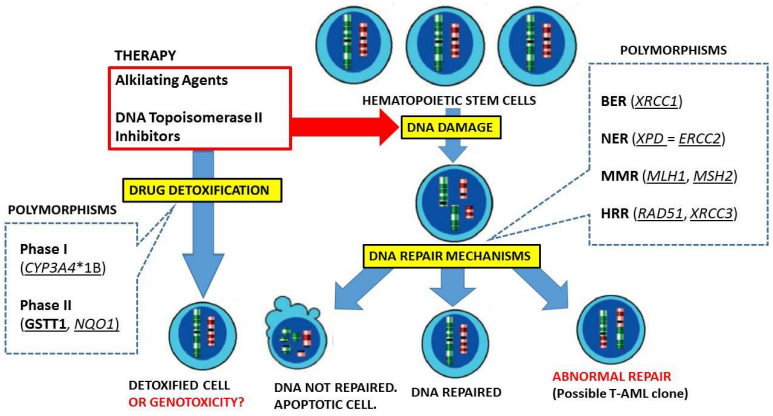
Figure 2. Alkilating agents have reactive groups that interact covalently to nucelophilic sites of DNA and produce direct DNA damage by the creation of inter- or intrastrand crosslinks (intrastrand crosslinks appears to be more harmful for the cell). As a result, induce the adduct and diadduct formation and it has been demonstrated that the cytotoxicity is proporional to diadduct formation. The t-AML cases after the alkilating agents exposure are more common.

SUSCEPTIBILITY: GENETIC FACTORS

Genetic factors. Genetic predisposition (specifically polymorphic variants) may be involved in the secondary leukemias development. The main candidates to be responsible of susceptibility are genes implicated in therapy response:

- Drug detoxification mechanisms: Phase I, Phase II
- DNA repair pathways: Homologous and Non Homologous Recombinational Repair Mechanisms

Figure 3. The diagram collects representative polymorphisms and the pathways in which are involved.



There are also strong evidences of the correlation between inherited cancer syndromes and a genetic predisposition to therapy-related leukemias: Neurofibromatosis (NF), Li-Fraumeni Syndrome or Fanconi Anemia (FA).

CONCLUSIONS

Increased understanding of therapy-related leukemias susceptibility will contribute:

- To prevent its development in patients with certain polymorphisms and risk factors
- To increase the treatment effectiveness (alternative drugs for these patients are being investigated)

PHARMACOGENETIC: TOWARDS PERSONALIZED MEDICINE