Introduction

- Therapy – related leukemia (t-MN) is far from being a well known syndrome, but progress is being made. It is a distinctive clinical syndrome in patients with preceding solid tumor or hematologic malignancies that were treated with cytotoxic procedures. Because there is an increasing number of cured patients at risk of developing Therapy – Acute Myeloid Leukemia due to prior radio or chemotherapies, bigger efforts are made in order to gain further knowledge.

- There is close association between distinct subtypes of t-MN and the nature of previous treatment:
  - Alkylating agents: MDS with chr. 7 and/or 5 loss/rearrangement/deletion
  - Latency from 3-7 years after cytotoxic exposure
  - Topoisomerase II inhibitors: Balanced translocations involving MLL, AML1, ...
  - Younger age, directly AML and shorter latency after exposure

- It gives us a unique chance to assess the effects of carcinogenesis and mutagens in humans, and to analyse individual predisposing factors.

Methodology

As a literature review, information was extracted from several articles on scientific databases, searching for the following key-words: secondary malignancies, therapy-related leukemia, topoisomerase II inhibitors. Other material was consulted in order to solve concept misunderstandings. For the written report, the most relevant information was selected.

Objectives

The aim of this work is to understand what are therapy-related leukemias, specially the role that topoisomerase II inhibitors have on them. In this line, find information about what these agents cause and if there are any alternative treatments in order to avoid their use.

Topoisomerase II inhibitors

- Topoisomerase II is a critical enzyme that relaxes supercoiled DNA by transiently cleaving and religating both strands of the double helix through the formation of a covalent cleavage intermediate.

- Biological function: crucial for insuring genomic integrity
- Mechanism of action: Block the enzymatic reaction through religation and enzyme release, leaving DNA with a permanent strand break (=apoptosis).
  - Leukemogenic and antineoplastic effect: chromosomal breakages resolved by chromosomal translocation (leukemic transformation)

- Side effects: Onset of a wide spectrum of secondary malignancies due to topoisomerase II inhibitors administration (high potential to generate translocations)
- Clinical profile:
  - Rarely preceded by t-MDS
  - Shorter latency (2-3y from 1st exposure)
  - Rapidly progressive leukemia

- Individual susceptibility factors:
  - Genetic polymorphisms in GST genes with variant alleles related with a decrease in enzymatic activity
  - Higher DNA damage
  - Greater toxicity
  - Reduced survival

Drug metabolizing enzymes:

- DNA repair processes:
  - Higher rates of repair
  - Inhibition of apoptosis, committed cell survives
  - Higher rates of repair
  - Persistence of mutations

Effective strategy for cancer chemotherapy:

- Topoisomerase II inhibitors
- Topoisomerase II catalytic inhibitors
- Most of the clinically active agents
- Drug’s nature related to molecular phenotype of t-MN

Some examples

- Etoposide
- Mitoxantrone
- Epirubicin

New treatments

- Poor hematopoietic reserves make the administration of standard AML therapy difficult because of:
  - Low tolerance for the high toxicity of treatments used
  - Multidrug resistance phenotype (t-MN emerges during the treatment of previous chemotherapy)

- Previous screening:
  - Strongest predictors for severity/overall survival = cytogenetic abnormalities
  - Treatment algorithm for patients performance status (Fig. 3.)

- New therapies with AAV vectors:
  - Gene therapy is becoming a new reality in different treatments
  - Some interesting results with AAV8-IL24 in MLL-AF4 - Acute Limfoblastic Leukemia cells
  - IL24 induces apoptosis, immunomodulatory and antiangiogenic effects in cancer cells

- Alternative drugs:
  - Daunoril: Catalytic inhibitor of hTopoisomerase IIa, similar to etoposide but without severe DNA damage
- Treatment algorithm for the management of t-MN patients

Discussion

Effective anticaner treatments lead to a progressive disappearance of leukemogenic agents in protocols, gene therapy is a promising tool.

Important to aware clinicians about the pros and cons of using topoisomerase II inhibitors

It is of high priority to gain further knowledge of topoisomerase II inhibitors and their role on therapy – related leukemia

Bibliography