ANTHRACYCLINES

Varieties and Derivatives

The large and growing family of anthracyclines now includes over 2,000 known analogs. There are several anthracycline anti-cancer drugs, and many of the newer, synthetic versions were developed in the hopes of diminishing the cardiotoxicity while maintaining effectiveness. The following are mostly commonly used in cancer treatment today:

- Daunorubicin (Cerubidine, Daunomycin, Rubidomycin): The original anthracycline first developed in Europe.
- Doxorubicin (Adriamycin, Rubex): A cousin to daunorubicin, developed from mutated strain of *Streptomyces*; it is more commonly used than its progenitor.
- Epirubicin (Ellence, Farmorubicin(e), Farmorubicina, Pharmorubicin): Comparable to Doxorubicin in cancer targets and toxicity.
- Esorubicin: A synthetic derivative of doxorubicin, it may offer slightly less cardiotoxicity but significantly stronger bone marrow suppression, leading to a higher incidence of neutropenia.
- Aclarubicin (Aclacinomycin): Rated as less toxic than Doxorubicin and Daunorubicin.
- Idarubicin (Idamycin, Zavedos): Penetrates cell membranes more efficiently than other anthracycline antibiotic compounds.
- Amrubicin (Calced): A new, synthetic anthracycline, amrubicin has shown stronger anti-cancer activity than conventional anthracyclines without the cumulative cardiotoxicity. Developed in Japan, its testing and use in the US for small-cell lung cancer (and potentially breast cancer) has been expedited under the FDA's Orphan Drug Designation (Celgene Bio. 2008).
- Pirarubicin: A doxorubicin analog, it appears less cardiotoxic than doxorubicin and has shown in-vitro effectiveness against some doxorubicin-resistant cells.
- Valrubicin (Valstar): A semisynthetic derivative of doxorubicin used to treat bladder cancer. It is converted to N-trifluoroacetyladriamycin within the cell, and prevents the Topo II enzyme from initiating DNA transcription. In addition, accumulation within the cell inhibits protein kinase C. It is less toxic than doxorubicin, though this may be because the drug is delivered directly to the bladder, and very little is metabolized during treatment.
Mechanism of Action

updated by Katarina Lah (May 09, 2011)

Anthracyclines attack cancer cells by multiple mechanisms, inhibiting replication and damaging cells in ways that promote cell death. They work primarily by DNA intercalation[1]. In order for a cell to divide, the DNA in the cell's nucleus must be unraveled and then duplicated (a process known as transcription). Anthracyclines bind to portions of the unwound strand of nuclear DNA, halting the transcription process, which in turn prevents cell replication (Pratt, p. 155). DNA also occurs in other parts of the cell, particularly the cell's mitochondria, the cell's energy-generating structures, where it is used as a template for manufacturing proteins needed for cell function and survival. Anthracyclines also bind to mitochondrial DNA, inhibiting these most basic cellular functions (Ashley, p. 450).

Researchers are still working to understand the basic means by which anthracyclines interfere with DNA and basic cell processes. The better this is understood, the better the chances of developing forms of these drugs which lack cardiotoxicity and other serious side effects.

Among other details, scientists have found that anthracyclines inhibit the action of topoisomerase II ("Topo II")[2], an enzyme that unzips the DNA molecule for replication. It is anthracycline's interference with topoisomerase II that is credited with both its cardiotoxicity and mutagenic effects, since its Topo II inhibition leaves DNA breaks at even low concentrations, resulting in an accumulation of DNA damage following prolonged, repeated, or higher exposures (Pratt, p. 156).

Also, during metabolism by the cell, anthracyclines are believed to transform the body's more stable form of iron, ferritin, into a highly oxidative form; this reaction also generates damaging oxygen superoxides and hydrogen peroxide (Pratt, p. 156). The resulting oxidative damage to the mitochondria may be a culprit in the anthracycines' cardiotoxicity, particularly since cardiomyocytes (heart muscle cells) have less potent anti-oxidant defenses (Minotti et al, p. 200; Pratt, p. 162-163). Studies using iron chelators (drugs that pull iron from the blood stream) give weight to this theory in that patients treated with a chelator (dexrazoxane) experienced reduced cardiotoxicity during treatment. Unfortunately, at least for some cancers (notably breast), the chelator also decreased the anti-tumor effects of the anthracycline (Minotti, et al, p.
And, the ineffectiveness of common cardioprotective antioxidants, including vitamin E, has revealed the limits of the oxidation theory (Minotti, et al, p. 203; Pratt, p. 158).

Footnotes:

1. DNA intercalation is a process by which another molecule (called a "ligand") binds between base pairs of DNA. DNA intercalators are used to inhibit DNA replication in order to inhibit cell division, particularly in rapidly dividing cells such as cancer cells. Intercalation changes the shape and structure of DNA, promoting DNA mutations and therefore cancer. DNA-intercalating chemicals are therefore also potent carcinogens.

2. The genes of living organisms are contained in DNA - long molecules in the shape of a twisted ladder (or double helix), the "rungs" of which consist of paired amino acids. To perform the most basic functions or to divide and multiply, cells must unzip the DNA molecule, dividing the base pairs, in order to copy (transcribe) their sequence. Topoisomerase is an enzyme that unwinds and rewinds the DNA molecule for this purpose. There are two types of topoisomerase, known simply as type I and type II. Type II in particular (Topo II) is a common target of anti-cancer drugs, such as the anthracyclines. By interfering with the production of Topo II, these drugs prevent cells from dividing and, in the process, cause genetic damage that promotes cell death.

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