Dynamic Chiropractic

CHRONIC / ACUTE CONDITIONS

Have You Ever Wondered How Chemotherapy Drugs Work? Part 1

A PRACTICAL GUIDE FOR COMPLEMENTARY HEALTH CARE PRACTITIONERS

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In the course of running a practice, certain patients and/or their family members may develop cancer. In these cases, it is not uncommon for them to consult with you regarding nutrition, supplementation and other adjunctive measures that can be considered part of complementary management of their condition. As such, it is valuable to have a working knowledge of how medical interventions act to help reduce the tumor burden.

Our academic curriculum generally does not provide information on how physicians decide which chemotherapy drugs to use on a particular cancer patient. This article provides a basic overview of the various classes of chemotherapy agents that are commonly used, along with the mechanism of action through which they kill cancer cells or interrupt their growth.

The Cell Cycle

As many chemotherapy drugs exert their effects at specific points in the life cycle of the cell, a quick review of the cell cycle is in order. The normal cell cycle consists of the following sequential stages:

- G0 Phase - resting diploid cells that are not dividing;
- G1 Phase - cells that have recently divided and are committed to continued proliferation;
- S Phase - stage at which divided cells undergo DNA synthesis;
- G2 Phase - premitotic rest interval (checkpoint to see if DNA has properly reproduced itself);
- M Phase - mitotic phase; chromosome condensation with cell division.

Of particular interest is the fact that solid malignant tumors contain the following three cell types: cells that are not dividing and are terminally differentiated; cells that continue to proliferate; and non-dividing cells that are currently quiescent but may be recruited into the cell cycle. Large tumors harbor more non-proliferating cells, which potentially makes them more resistant to agents that selectively target dividing cells.

Combination Chemotherapy

Many oncologists use a combination of chemotherapy drugs concurrently in the treatment of most cancers. The thinking behind this method is as follows: 1. A combination of chemotherapy drugs allows the therapy to target all phases of the cell cycle, resulting in superior additive effects. 2. Different classes of chemotherapy agents target specific phases of the cell cycle. 3. The combination approach also reduces overall toxicity of chemotherapy by not compounding toxicities of drugs that work via a similar mechanism of action. 4. This approach has also been shown to reduce drug-resistance problems.

Classes of Chemotherapy Agents

A standard way to classify chemotherapy agents is put them into one of two categories: cell cycle

(phase-specific drugs) and non-cell cycle (non-phase-specific drugs). The cell cycle (phase-specific) drugs have their greatest killing effect when a cell is dividing; certain drugs target specific cell phases (e.g., M phase). Non-cell cycle (non-phase-specific drugs) often remain in the cell and wait for cell division to occur, upon which they exert their anti-cancer effects or bind to key enzymes, inhibiting their function. [These drugs will be discussed in detail in part 2 of this article.]

The following are some of the commonly used cell cycle-dependent chemotherapy drugs and the specific stages of the cell cycle during which they exert their effects. It is most interesting to note how many chemotherapy agents are actually derived from natural botanical sources.

G1 Phase: Asparaginase and corticosteroids.

S Phase: Anti-metabolites. These drugs are structural analogues to naturally occurring metabolites involved in DNA and RNA synthesis. They alter critical pathways to prevent cancer cells from synthesizing DNA or RNA. They exert their cytotoxic effects either by competing with normal metabolites for the catalytic or regulatory sites of a key enzyme, or by substituting for a metabolite that is normally incorporated into DNA or RNA. Examples include capecitabine, doxorubicin, floxuridine, gemcitabine, mercaptopurine, prednisone, thioguanine, cytarabine, fludarabine, hydroxyurea, methotrexate, and procarbazine.

G2 Phase: Some of the phase-specific agents that target cancerous cells include the following:

- Bleomycin. An antibiotic that generates free radicals to destroy DNA. Thus, concurrent antioxidant supplementation may reduce its efficacy.
- Irenotecan and topotecan. These drugs are derived from the Chinese ornamental *Camptotheca acuminata*; they inhibit DNA topoisomerase I, which interrupts the elongation phase of DNA replication. Topoisomerase enzymes normally separate the strands of DNA so they can be copied. These drugs are used in the treatment of certain leukemias, as well as lung, ovarian, GI, and other cancers.
- Mitoxantrone. Also a topoisomeras II inhibitor. *Note:* The use of topoisomerase II inhibitors increases the risk of developing a second cancer - acute myelogenous leukemia, which has been seen as early as 2-3 years after the drug was given.

M Phase:

- Mitotic inhibitors. These are often plant alkaloids and other compounds derived from natural products. They inhibit mitosis or inhibit enzymes from making proteins needed for cell replication. They work primarily in the M phase, but can damage cells in all phases. They are used to treat many different cancers including breast cancer, lung cancer, myelomas, lymphomas, and leukemias. They often cause peripheral nerve damage (supplementation with alpha-lipoic acid may reduce this side effect or help repair the nerve damage, as it has been shown to do in diabetic neuropathy).
- Vinca alkaloids. They are derived from the periwinkle plant (*Vinca rosea*) and block polymerization of microtubules, resulting in impaired mitotic spindles. Examples: vinblasine, vincristine, vinorelbine.
- Podophyllotoxins or Epoipodophyllotoxins (compounds derived from *Podophyllum peltatum*) inhibit DNA topoisomerase II activity, blocking DNA synthesis. Example: etopiside.
- Taxanes are semi-synthetic compounds from the yew plant. They promote microtubular assembly and stability, blocking cell cycle mitosis. Examples: paclitaxel or Taxol, docetaxel.
- Epithilones (e.g., Ixempra).

Editor's note: Look for part 2 of this article in the Aug. 12 issue. Dr. Meschino will continue his discussion of chemotherapy agents, focusing on non-phase-specific drugs.