Dynamic Chiropractic

HEALTH & WELLNESS / LIFESTYLE

# Have You Ever Wondered How Chemotherapy Drugs Work? Part 2

James P. Meschino, DC, MS

As outlined in part one of this series [July 15 *DC*], a standard way to classify chemotherapy agents is to put them into one of two categories: cell cycle (phase-specific) and non-cell cycle (non-phase-specific). The cell-cycle (phase-specific) drugs, discussed in detail in part one, have their greatest killing effect when a cell is dividing whereby certain drugs target specific cell phases. 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. The following are some of the commonly used non-cell-cycle-dependent chemotherapy drugs:

*Alkylating Agents* impair cell function by forming covalent bonds with amino, carboxyl, sulfhydryl and phosphate groups in biologically important molecules. The most important sites are DNA, RNA and cellular proteins. These are also known as intercalating agents. Examples: nitrogen mustards, which bind to DNA (e.g., cyclophosphamide); nitrosureas - lipid soluble, can enter brain (forms free radicals)(e.g., streptozocin); platinum agents (heavy metal complex producing inter-strand breaks of DNA with cross-linking adducts, thus inhibiting DNA synthesis (cispatinum, carboplatinum, oxaplatinum); alkyl sulfonates (e.g., busulfan); triazines (e.g., Dacarbazine; and ethylenimines (e.g., hexamethylmelaninine).

*Anthracyclines* (tumor-killing antibiotics) interfere with enzymes involved in DNA replication. They work in all phases of the cell cycle and thus are used widely in various cancers. They can permanently damage the heart if given in high doses. Lifetime dose limits are often placed on these drugs for this reason. Concurrent supplementation with coenzyme $Q_{10}$ has been shown to protect the heart muscle in cases of Adriamycin use. Examples of anthracyclins include:

- Doxorubicin
- Adriamycin
- Danorubicin
- Epirubicin
- Idarubicin
- Actinomycin-D
- Bleomycin - kills via free-radical attack
- Mitomycin-C
- Mitoxantrone - an anti-tumor antibiotic that is similar to doxorubicin, including potential for heart damage. It is also a topoisomerase II inhibitor, and can lead to the development of leukemia. It is used in the treatment of prostate and breast cancer, and in lymphoma and leukemia.

*Targeted Agents:* Some of the newer chemotherapy drugs are classified as targeted agents. Examples include monoclonal antibodies, small molecules and endocrine therapy agents. Here is a brief discussion of each, including a few examples:

Monoclonal antibodies target specific protein antigens (receptors, signal transduction enzymes or proteins) that are dysregulated in a cancer cell. These drugs destroy the dysregulated protein (in

some cases a protein receptor on the cell surface that is over-expressed or overactive and is sending messages into the cell to encourage continued cell division). Examples include Rituxan, which targets CD20 antigen found on B-cell lymphocytes in non-Hodgkin lymphoma; herceptin - targets HER-2 receptor on breast cells that is over-expressed in up to 40 percent of breast cancer patients; Campath - targets CD52 antigen in B-cell and T-cell lymphocytes in chronic lymphocytic leukemia; and Avastin and related MAB's - destroys receptors on blood vessels to prevent stimulation of new blood vessels growing to feed the tumor.

Small molecules inhibit some of the key pathways that drive cancer cell division (particularly tyrosine kinase inhibitors): Examples include:

- Imatinib (Gleevec) - binds to ATP binding site, inhibiting tyrosine kinase from phosphorylating its substrates.
- Gemfitinib - inhibits epidermal growth factor receptor-tyrosine kinase signal transduction.
- Erlotinib - blocks HER-1receptor- tyrosine kinase signal transduction in non-small-cell lung cancer.
- Sunitinib - tyrosine inhibitor associated with inhibiting signals from over active epidermal growth factor receptors and vascular endothelial derived growth factor (the chemical that stimulates growth of new blood vessels to feed the tumor).
- Sorafenib - another tyrosine inhibitor with similar function to Sunitinib.
- Velcade - a proteoasome inhibitor used in multiple myeloma that ultimately blocks NF-Kappa beta and its effects on cell division.
- Torisel - blocks mTOR protein involved in proliferation and angiogenesis (the formation of new blood vessels).

Endocrine therapy: Tamoxifen and Raloxifen are selective estrogen receptor modulators (SERMs) that compete with estrogen for binding to estrogen receptors - slowing cellular proliferation. Aromatase inhibitors block aromatase enzyme (estrogen synthase) in fat cells, stromal cells, breast cancer cells, which converts androstenedione into estrone.

Relevance to Your Practice

Understanding the influence these drugs have on killing cancer cells or interrupting their mitotic potential is critical when deciding what dietary or supplementation practices are synergistic to or in conflict with the action of the drug. In addition to these chemotherapy agents, there are also other oral drugs used (often off-label use) in the management of these cases, which should also be factored in to the nutrition and supplementation advice provided to a patient. (A future article will address the off-label use of these drugs in cancer management. )

One of the highlights of my professional career has been to teach a course on the adjunctive nutritional management of cancer to medical doctors and oncologists who are candidates in the Fellowship In Integrative Cancer Therapy Program taught through a division of the American Academy of Anti-Aging Medicine. These doctors have been most receptive and appreciative of the evidence-based protocols, and many use this information for the purpose of incorporating targeted nutritional and supplementation practices into the management of their cancer patients. In return, I have learned a great deal about medical cancer therapy from these practitioners and other speakers at these conferences, including much of the information presented in this article.

AUGUST 2010