Cancer Chemotherapy

MAKING CHEMOTHERAPY DRUGS WORK MORE EFFECTIVELY

The dose-delivery schedule of chemotherapy drugs can determinate their efficacy in killing cancer cells and the degree of toxicity to the patient. Conventional chemotherapy treatment often uses a maximum tolerated dose (MTD) of chemotherapeutic drugs, typically administered on a schedule that varies from once a week to every 21 days, allowing a period of rest so that healthy tissue has a chance to recover. Unfortunately, while the MTD schedule is convenient for oncologists, allowing them to squeeze more patients each month into their chemotherapy unit, the rest period enables cancer cells to recover and develop survival mechanisms such as new blood vessel growth into the tumor. This means that when the next high dose of chemotherapy is given 7-21 days later, the cancer cells have become more resistant. The administration of the MTD also exposes healthy tissues to more damage.

Some studies indicate that a better approach would be to lower the dose of conventional cytotoxic agents, reschedule their application, and combine chemotherapy drugs with antiangiogenesis agents to effectively interfere with cancer's various growth pathways and inhibit the production of blood vessels (Holland et al. 2000) (http://www.cancer.gov/clinicaltrials/developments/anti-angio-table).

This lower-dose approach, known as metronomic dosing, uses a dosing schedule as often as every day or alternates different chemotherapy drugs every other day instead of administering them all together the same day. An amount as low as 25% of the MTD, sometimes given on alternative days in combination with various signal transduction pathway inhibitors, targets the endothelial cells making up the vessels and microvessels feeding the tumor. Tumor endothelial cells then die with much less chemotherapy than cancer cells and the side effects to healthy tissue and the patient in general are dramatically reduced (Hanahan et al. 2000).

During standard chemotherapy, the typical 21-day rest period is enough to allow the tumor endothelial cells a chance to recover. However, with tighter chemotherapy dose scheduling, the slowly proliferating endothelial cells are unable to recover. In one study, mice were given the chemotherapeutic drug vinblastine at doses far below the MTD. This dose had little effect on tumor growth in the mice. A second group of mice was given the drug DC101 that inhibits the formation of new blood vessels into tumors (by blocking the induction of vascular endothelial growth factor). In the DC101 group of mice, tumor growth was slowed, as it was with the vinblastine, but then tumor growth resumed. However, in a third group of mice, a combination of the two drugs, at the low dose, resulted in full regression of the tumors with no recurrence for 6 months (Klement et al. 2000).

The administration of low doses of conventional chemotherapy drugs on a frequent basis with no breaks enables these drugs to invoke an antiangiogenesis effect, particularly when combined with a tumor endothelial cell-specific antiangiogenic drug (Gately et al. 2001; Man et al. 2002). There are clinical studies using antiangiogenic drugs (http://www.cancer.gov/clinicaltrials/developments/anti-angio-table). As will be described later in this protocol, certain dietary supplements have also been shown to interfere with angiogenesis.

At the time of this writing, a number of animal studies suggested that chemotherapy drugs could work better if the dosing schedule were changed. Human studies are ongoing, meaning it will be difficult to convince an oncologist to incorporate metronomic dosing instead of the standard MTD. While we cannot definitively recommend metronomic (lower dose/more frequent administration) chemotherapy at this time, the results of new human studies on this subject will be posted at www.lefcancer.org.

GOING BEYOND CHEMOTHERAPY

Conventional chemotherapy drugs too often show limited efficacy. Yet there is evidence indicating that the cancer cell-killing effects of these drugs can be enhanced if additional compounds are administered to the patient.

One approach is to inhibit the overexpression of receptor sites on cancer cells, which enables these cells to bind to growth factors that allow them to become resistant to the cell-killing effects of the chemotherapy drugs. Cancer cells use these signal transduction pathways as growth vehicles to escape natural regulatory control and also to protect themselves against the cytotoxic effects of cancer drugs. The utilization of these signal transduction inhibitors enhances the potential effect of low(er) dosing of chemotheraputic drugs.

Another therapeutic target is the endothelial cells that form new blood vessels. The process by which new blood vessels are formed is called angiogenesis, and cancer cells initiate blood vessel proliferation in order to fuel rapid growth (Hanahan et al. 2000). Agents that interfere with the formation of new blood vessels are an important part of a comprehensive treatment strategy.

Because cancer cells are stimulated to produce new blood vessels in response to a low-oxygen environment (hypoxia), the critical importance of boosting the oxygen-carrying capacity of blood was discussed earlier in this protocol.

Inhibiting Signal Transduction Pathways

All cells, both normal and cancerous, have molecular receptor sites on their surface. These sites are much like locks that may be opened or activated only by the correct molecular key. Once opened or activated, a chain of biochemical events occurs specific to that receptor. Cytokine growth factors are a class of substances that stimulate cell growth by a variety of mechanisms.

An example of such a pathway is the binding of transforming growth factor-alpha (TGF-alpha) to the epidermal growth factor receptor (EGFR) site. Such a binding is a growth pathway for many cancers, causing rapid cell proliferation. The overexpression of this pathway is also implicated in tumor cells that are resistant to cytotoxic drugs (including the interferons).

Interference with this pathway at the EGFR receptor site can effectively shut down overexpression and the subsequent cell proliferation, making the cancer much more vulnerable to therapy. Blocking the EGFR has been shown to inhibit tumor growth by interfering with cancer cell repair, tumor invasion, metastasis, and angiogenesis (Arteaga 2002; Wakeling et al. 2002).

Drugs that inhibit the EGFR showed promise in early studies but have failed in recent clinical trials when combined with

cytotoxic chemotherapy drugs. One of these EGFR inhibiting drugs is Iressa. One reason that Iressa and a similar-acting drug named Erbitux failed in human clinical studies is that an inadequate combination and dosing schedule of chemotherapy drugs may have been used to kill the cancer cells. Drugs such as Iressa will not cure cancer by themselves, but they could be of benefit if metronomic-dosing chemotherapy were used and/or during immune-augmentation therapy if they were used with drugs such as alpha interferon.

The objective of blocking the signal transduction pathway is to prevent cancer cells from mutating in a way that enables them to avoid destruction.

Natural Signal Transduction Inhibitors

As noted, molecular evidence and animal studies suggest that agents that inhibit certain growth signals used by cancer cells might work synergistically with metronomic cycled chemotherapy or be useful as post chemotherapy agents along with immune-augmentation therapy.

There are natural signal transduction inhibitors available, but because most of them are potent antioxidants, some cancer patients may choose to wait 2-3 weeks after chemotherapy ends to start using them.

Soy (genistein) extract is known to inhibit the epidermal growth factor (EGF) receptor via an interference with the TGF-alpha pathway (Bhatia et al. 2001).

Genistein is also known to block the induction of the basic fibroblast growth factor (bFGF), a potent growth and angiogenic factor in cancers such as renal cell carcinoma and malignant melanoma (Hurley et al. 1996). Additionally, genistein is known to block induction of the vascular endothelial growth factor (VEGF) considered essential for angiogenesis and tumor endothelial cell survival (Mukhopadhyay et al. 1995).

The blockade of the overexpression of the EGF receptor and the inhibition of the signaling pathways, bFGF and VEGF, is dose-dependent response. Soy genistein may be an effective adjuvant to conventional or metronomic chemotherapy, but human clinical studies are lacking, which is unfortunately the case with most nonpatented natural therapies. There is a controversy about the use of soy as a cancer treatment. A complete description of the pros and cons of high-dose genistein therapy can be found in the Cancer Adjuvant Therapy protocol.

Curcumin, an extract of the spice turmeric, is synergistic with genistein and inhibits angiogenic growth signals emitted by tumor cells. Curcumin acts via a different mechanism than genistein to inhibit the EGF receptor but is up to 90% effective in a dose-dependent manner. It is important to note that while curcumin has been shown to be up to 90% effective in inhibiting the expression of the EGF receptor on cancer cell membranes, this does not mean that it will be effective in 90% of cancer patients or reduce tumor volume by 90%. Because two-thirds of all cancers, however, over-express the EGR receptor and such overexpression frequently fuels the metastatic spread of cancer throughout the body, the suppression of this receptor is desirable.

Curcumin has a number of other antiangiogenic properties that appear to be synergistic with metronomic dosing chemotherapy. These potential synergistic and/or additive mechanisms include:

- Inhibition of the induction of basic fibroblast growth factor (bFGF). bFGF is both a potent mitogen (growth signal) for many cancers and an important signaling factor in angiogenesis (Arbiser et al. 1998).
- Inhibition of the induction of hepatocyte growth factor (HGF), overexpression is involved in hepatocellular (liver cell-related) carcinoma (Seol et al. 2000).
- Inhibition of the expression of COX-2, the enzyme involved in the production of PGE-2, a tumor-promoting prostaglandin (Zhang et al. 1999).
- Inhibition of a transcription factor in cancer cells known as nuclear factor-kappa B (NF-KB). Many cancers overexpress NF-KB and use this as a growth vehicle to escape regulatory control (Plummer et al. 1999).
- Increased expression of nuclear p53 protein in human basal cell carcinomas, hepatomas, and leukemia cell lines, which increases apoptosis (Jee et al. 1998).

Why Agents That Inhibit Angiogenesis and Block Signal Transduction Are Failing

Based on the multiple favorable mechanisms listed, higher-dose curcumin would appear to be useful for cancer patients. There are contradictions in scientific literature concerning curcumin intake at the same time as chemotherapy drugs. Some studies indicate enhanced benefit, whereas other studies hint at reduced benefit and even potential toxicity. The anticancer drug cisplatin is strongly enhanced with curcumin, (Navis et al. 1999), yet cisplatin kills cancer cells by generating free radicals, and curcumin is an antioxidant. Another study showed that low-dose curcumin inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of several different human breast cancer cells. This same study showed that curcumin inhibited cyclophosphamide-induced breast tumor regression in an in vivo animal model (Somasundaram et al. 2002). Another in vitro study involving curcumin's concomitant use with the chemotherapy drug Irinotecan indicated potential toxicity (Michaels et al. 2001), yet in and of themselves chemotherapy drugs are inherently toxic.

Whether high-dose curcumin is beneficial or detrimental depends on the type and dose of the chemotherapeutic drug used, the kind of cancer cell, and the dose of the curcumin. Until more definitive information is published, we prefer to err on the side of caution and recommend that chemotherapy patients wait 3 weeks after their last dose of chemotherapy before taking high-doses of curcumin.

Pharmaceutical companies are investing billions of dollars to develop drugs proven to interfere with cancer cell growth. Unfortunately, these drugs have failed to extend survival in late-stage cancer patients. In some of these clinical studies, tumor shrinkage is observed, but the patients still die. Experts remain convinced, however, that these drugs will eventually play a significant role in the treatment of cancer.

One reason these drugs are not working is that they usually suppress only one of the growth factors that cancer cells use to escape regulatory control. Scientists know of more than 20 growth factors used by tumors. Late-stage breast cancer cells, for example, may express as many as six different growth factors that induce angiogenesis. Cancer cells emit these growth factors to draw new blood vessels into tumors and/or overexpress the EGF receptor.

Human studies have tested angiogenesis inhibitors or EGF receptor blockers on late-stage patients whose cancer cells have mutated to become highly resistant. If these drugs were tested earlier in the disease process, some physicians believe they would work better. One problem is that the FDA restricts the testing of new cancer drugs to only patients who have failed all other proven therapies. Regrettably, we know that cancer cells mutate each time they are exposed to a new therapy. By testing new cancer drugs only on patients who have failed previous therapy, a tremendous burden of efficacy is being placed on these new compounds, that is, these drugs are expected to kill cancer cells in their most aggressive stages.

Some experts note that ultimately successful treatment using antiangiogenesis and signal transduction blockers may

depend on the use of a multidrug cocktail, one that
would block all known growth factors used by cancer cells. That would parallel the success in treating AIDS, in which several antiviral drugs that work by different mechanisms are combined into cocktails that have turned the condition into a manageable disease for some people.

Based on current knowledge, it would appear logical to simultaneously test a wide range of angiogenesis inhibitors and signal transduction pathway blockers on early-stage cancer patients. Such testing might be considered at the time that other cytotoxic therapies are administered or shortly thereafter.

The potential advantage of combining high potency genistein, curcumin, and green tea extracts is that they have been shown to suppress a wide variety of growth factors used by cancer cells. Considering the enormous cost of testing drugs that work in similar ways to genistein, curcumin, and green tea, it is doubtful that these nonpatented natural agents will be tested on cancer patients in the near future. The cancer patient is thus faced with deciding whether or not to incorporate these natural agents into their overall treatment program based on the data currently available.

Inhibiting Angiogenesis
Angiogenesis provides nourishment for the tumor's rapid propagation. Antiangiogenesis agents inhibit this new tumor blood vessel growth and are being studied as potential cancer therapies. As noted, genistein and curcumin have demonstrated molecular effects involved in the inhibition of new blood vessel growth into tumors. An extract from green tea may also be an effective antiangiogenesis agent.

The primary action of green tea is through its catechin, epigallocatechin gallate (EGCG), which blocks the induction of vascular endothelial growth factor (VEGF), considered essential in angiogenesis and tumor endothelial cell survival. In vivo studies have shown green tea extracts to have the following actions on human colon cancer cells:

Inhibition of tumor growth 58%
Inhibition of microvessel density 30%
Inhibition of tumor cell proliferation 27%
Increased tumor cell apoptosis 1.9-fold
Increased tumor endothelial cell apoptosis three-fold
(Jung et al. 2001b.)

The optimal dose of green tea, soy, and curcumin and when they should be taken will be discussed later in this protocol. Please note that EGCG is a powerful antioxidant, as are other polyphenols found in green tea. Some chemotherapy patients may choose to wait 3 weeks after chemotherapy has ended to initiate green tea (EGCG) supplementation.

As indicated near the beginning of this protocol, the most effective way of inhibiting tumor angiogenesis may be by guarding against hypoxia. It is crucial for cancer patients to maintain their blood oxygen-carrying capacity (as measured by hematocrit and hemoglobin) in the upper range of normal.