Dose-Dense Chemotherapy

Dose-dense chemotherapy (DDC) is a concept of chemotherapy administration that is being used more and more. Understanding DDC requires an understanding of tumor cell replication and growth, sometimes referred to as the Gompertzian growth curve. This theory represents the fact that tumor growth follows a mathematically predictable growth curve, with rapid growth initially, then leveling off to slower growth. For example, while a tumor is small and often undetectable by available tests, its cells grow very rapidly. Eventually, the tumor reaches a size where it outgrows the available nutrients and blood supply, and tumor growth slows down.

Cells are most sensitive to chemotherapy when they are rapidly dividing, therefore the early stage, smaller tumors are often more sensitive to chemotherapy. This is also why surgery may be used to remove as much of the tumor as possible, leaving a small number of cells to then be treated by chemotherapy. Standard chemotherapy regimens call for a standard dose of chemotherapy given every 3 or 4 weeks, depending on the regimen, allowing for healthy cells to recover between doses (such as blood counts, oral mucosa, and GI lining). However, we now understand that this 3-week break may also allow the now smaller, more rapidly dividing tumor cells to start growing rapidly again.

Dose-Dense Chemotherapy (DDC) aims to achieve maximum tumor kill by increasing the rate of chemotherapy delivery, not by increasing dosage (which is the theory behind many stem cell transplant protocols). By administering the same doses of chemotherapy previously given every 3 weeks on an every 2 week schedule instead, the chemotherapy interrupts the rapid growth phase of the tumor cells. Thus, the medications interfere with the Gompertzian curve, hitting the tumor cells at the time when they are just beginning to grow rapidly again. In other words, "hit them while they are down." This model was called the Norton-Simon model, after the researchers who first described it.

You may ask, why we haven't tried this before? The concern has always been that giving chemotherapy more frequently would lead to low white blood counts and infection, a potentially deadly combination in a patient receiving chemotherapy. Through the use of growth factors (Neupogen, Neulasta, Leukine), we are able to have faster recovery of white blood cells, decreasing the chance of infection. Several DDC studies have shown a higher incidence of anemia (low red blood cell count) and bone pain (likely related to the use of a growth factor) with these regimens, but the DDC regimens also mean a decrease in the length of therapy by 4-6 weeks, which may be appealing to some.

What types of cancer is DDC used in?

Studies have found that premenopausal women with high-risk disease (hormone receptor negative, Her2 positive, and lymph node positive) derive the greatest benefit from DDC in breast cancer treatment. These studies have shown improvement in ten-year survival in pre-menopausal patients with hormone receptor positive tumors by 22%, and by 35% in those with hormone receptor negative tumors. This study also found that the use of DDC does not seem to be associated with an increased risk of developing treatment induced menopause or amenorrhea. This is an important finding because early menopause will lead to loss of ovarian function, which can increase risk of osteoporosis and early heart disease. In addition, early menopause can result in infertility, hot flashes, vaginal dryness and weight gain, all of which can have a negative psychosocial, emotional and physical impact on women of childbearing age.

DDC has become a standard of care for the treatment of some high risk lymphomas. Studies are continuing to evaluate DDC used in conjunction with rituximab. Studies have also evaluated using DDC in ovarian cancer, with positive results.

It is clear that there is a benefit to DDC for certain patients. Determining who will benefit is the focus of ongoing studies in these and other types of cancer. In addition, longer follow-up of previously reported studies will give more information on the use of DDC and long-term benefits or complications.