



CHRONOTHERAPY AND CANCER

by Regina Patrick RPSGT

Cancer, as we know, is a group of diseases in which normal cells begin to proliferate rapidly and uncontrollably. As they proliferate, they progressively replace normal cells in an organ thereby destroying the ability of the organ to perform its normal function. A person is ultimately unable to sustain life as more and more organs are affected. Scientists are not sure what triggers the uncontrolled proliferation of cancer cells but studies indicate that a disrupted circadian rhythm may be a risk factor. Ironically, one's circadian rhythm may be useful as part of the treatment protocol for people undergoing cancer chemotherapy. Studies indicate that chemotherapy drugs have their greatest therapeutic effect at certain points in

Scientists are studying circadian rhythms to improve cancer treatment

a person's circadian rhythm. Scientists are now studying how to use circadian rhythmicity to improve cancer treatment.

A cell's life cycle consists of two major periods: growth (interphase) and

reproduction (mitosis). Cells spend most of their time in interphase performing their unique functions such as synthesizing hormones, growth factors, proteins etc. within an organ. Mitosis takes place in a span of a few hours.

Interphase consists of three steps – G1 (gap1) phase, S (synthesis) phase, and G2 (gap2) phase. During the G1 phase, a cell's genetic material exists within its nucleus as chromatin (a compact mesh-like network of 46 DNA molecule strands). During the S phase, DNA information encoded in the chromatin is replicated resulting in 92 DNA molecule strands. During the G2 phase, the chromatin strands begin to coil and condense and spindle fibers begin to form. The spindle fibers will later play a role in separating the replicated DNA strands apart from each other when the nucleus divides.

Mitosis is a four step process consisting of prophase, metaphase, anaphase, and telophase. The end result of mitosis is the division of a cell's nucleus.

In prophase, the membrane enveloping the nucleus of the cell disintegrates; this will later allow the chromosomes to migrate toward the cell's equatorial plane. The strands of chromatin continue to coil and condense until finally 92 strands (now called chromatids) are visible. However, a chromatid is joined to its duplicate (i.e., sister chromatid) in a small region called the centromere.

In metaphase, the spindle fibers extend the length of the cell from pole to pole. Each of the 46 chromatid pairs travels along the fibers toward the equatorial plane of the cell. The centromere dupli-

cates breaking the bond between the sister chromatids. At this point, they are called chromosomes.

In anaphase, spindle fibers shorten and pull each sister chromosome in opposite directions away from the equatorial plane toward their respective pole. Once the two sets of chromosomes arrive at their poles, each half of a cell has 46 chromosomes containing the exact same genetic information.

In telophase, the chromosomes at each pole begin to uncoil and form masses of chromatin. The spindle fibers disintegrate and a nuclear envelope reappears around each of the masses of chromatin. This ends mitosis.

As mitosis ends, the cell undergoes one final process – cytokinesis. The cell's cytoplasm invaginates at the equatorial plane until the cell is split into two genetically identical and separate (daughter) cells. These daughter cells now enter interphase.

Changes (i.e., mutations) in genetic information encoded in DNA strands can occur at any point during interphase or mitosis. Currently, scientists have identified about 100 genes that when mutated can result in cancer. The mutations can abnormally activate cellular division or can inhibit a cell's tumor suppressor activity allowing unregulated growth to occur.

The aim of chemotherapy for cancer, of course is to stop the uncontrolled growth of cells. Alkylating medications, antimetabolite medications, anti-tumor antibiotics, and mitotic inhibitor medications accomplish this by various means.

Alkylating medications (e.g., cisplatin) block DNA synthesis during either interphase or mitosis. These medications bind with a DNA molecule. When this occurs, a DNA molecule strand may break; the drug may cause cross-links between a DNA strand with its sister DNA strand; or the drug may cause mis-codes in a DNA strand. These alterations impair DNA molecule synthesis and ultimately block a cell's ability to reproduce.

Antimetabolite medications (e.g., 5-fluouracil [5-FU]) are effective only during the S phase when the genetic information in chromatin is replicated. Chemical reactions of cellular enzymes with an antimetabolite medication results in formation of deoxynucleotides (compounds consisting of a deoxyribose molecule, a phosphate group, and either a purine or pyrimidine base). The deoxynucleotides accumulate to excessive levels within a cell which leads to breaks in DNA strands. The broken ends of the DNA strands then activate enzymes that disrupt cellular metabolism causing a cell to die.

Anti-tumor antibiotic medications (e.g., bleomycin) exert their cytotoxic effect during the S or G2 phase. They block the synthesis of enzymes needed for DNA replication. Some anti-

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tumor antibiotic medications bind with the DNA molecule strand resulting in uncoiling and irreparable breaks in the DNA molecule. The cell therefore can not go through mitosis.

Mitotic inhibitor medications (e.g., vinorelbine) block mitosis at metaphase. They do this by interfering with the formation of spindle fibers in early metaphase or by blocking the disintegration of spindle fibers in late metaphase. When a mitotic inhibitor medication blocks spindle formation, the chromosomes can not be pulled toward opposite poles during anaphase. When a mitotic inhibitor medication does not allow spindle fibers to disintegrate, chromosomes can not leave the equatorial plane. Either way, the cell's nucleus can not continue dividing nor can the cell undergo cytokinesis.

The synthesis of proteins, enzymes, and other substances involved in cellular growth and reproduction fluctuates rhythmically in a 24-hour period. This phenomenon is strategically used in chronotherapy. Chronotherapy is the administration of a drug at specific times within one's circadian rhythm in order to achieve the drug's maximal therapeutic effect while minimizing its toxic or other adverse effects.

In 1974, chronotherapy pioneer Franz Halberg et al. reported the successful use of chronotherapy for cancer in a human. The subject was a woman who had a yolk sac tumor on her right ovary. She was 21 years old at the time and given a 10% chance of surviving past two years. Her tumor was removed and she began a 20 month course of chemotherapy. The timing of the administration of the drugs was varied during the first four months. In the first month, the drugs were given between 08:00–11:00; in the second month, between 20:00–22:00 (8:00

pm – 10:00 pm); in the third month, at 4:00; and in the fourth month, at 22:00. Before the drugs were administered, her oral temperature was assessed every four hours for 24 hours to determine her circadian rhythm. The rhythmic rise and fall of one's core temperature parallels that of a tumor. Therefore, increased body temperature indicates increased tumor cell activity (such as mitosis) when the cells would be their most susceptible to a chemotherapy drug. After four months of chemotherapy, the researchers found that the subject's oral temperature was highest at 4:00 a.m. and at its lowest at 22:00. They therefore administered chemotherapy at 04:00. At the end of the 20-month treatment protocol, the subject was cancer-free. In 2006, Halberg et al. wrote an update on the patient who, now in her 50s, has remained cancer-free since her treatment in 1974. They concluded individualizing the timing of the administration of chemotherapeutic drugs led to this success.

Since the Halberg study, some researchers such as Bulgarian scientists Kurteva et al.³ have investigated chronotherapy's efficacy compared to that of other cancer treatment regimen. Kurteva et al. compared chronotherapy to three other treatment regimens in colorectal cancer patients. The patients were separated into four groups. Group 1 received intra-arterial chemotherapy with the drugs 5-FU, mitomycin, and epirubicin. Group 2 received intravenous chronochemotherapy with the drugs 5-FU, leucovorin, and cisplatin; the former two drugs were infused for two hours between 18:00 – 06:00 and the last drug was infused during 10:00 – 18:00. Group 3 served as a control group and was treated with only 5-FU and leucovorin. Group 4 represented the standard colorectal cancer treatment and was treated with 5-FU, vincristine, and CCNU (also known as lomustine). They found that 58% of the intra-arterial group obtained either complete recovery (26%), partial recovery (24%), or stable disease (8%) while 74% of the chronochemotherapy group obtained either complete recovery (10%), partial recovery (36%), or stable disease (28%). Only 10% of subjects in group 3 and 18% of subjects in group 4 experienced partial recovery. They concluded that chronotherapy for cancer could be an effective treatment regimen for cancer patients since its efficacy in response rate was equivalent to that of the intra-arterial chemotherapy.

Cancer accounts for 25% of deaths in America. The National Cancer Institute (NCI) estimates that 1,444,920 Americans will be diagnosed with cancer for the first time and 560,000 people will die from cancer in 2007. These statistics make improving survival rates a chief concern. Chronotherapy may provide another avenue for improving survival rates. Currently, several international multicenter studies are ongoing. For example, the Chronotherapy Group of the European Organization for Research and Treatment of Cancer (EORTC) is investigating the impact of chronotherapy on quality of life; its ability to improve tolerance to certain chemotherapy medications (e.g., vinorelbine); and its impact on different kinds of cancer (in other words is it more effective for one type of cancer than another). A few studies have investigated using a programmable drug delivery pump to administer chemotherapeutic drugs at times that are more in synchronization with a patient's circadian rhythm. Results with the pump have been promising showing increased survival, fewer drug side effects, and in some cases patients are able to continue with their normal activities. Once scientists learn how to effectively utilize one's circadian rhythm in chronotherapy, chemotherapy for cancer may be less toxic and less detrimental to quality of life for people undergoing treatment.

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