Chemotherapy

The literal meaning of the term "chemotherapy" is "to treat with a chemical agent," but the term generally refers to the use of potent cytotoxic (cell-killing) agents that are prescribed for some forms of cancer. These drugs not only kill tumor cells, but can destroy normal cells as well.

The cells that are most vulnerable to cytotoxic agents are those that grow and divide rapidly. Among those affected are cancer cells, hair and intestinal cells, red blood cells, and the white blood cells comprising the immune system.

The rationale for the use of chemotherapy to treat MS stems from the fact that MS is considered to be an autoimmune disease. An abnormal, heightened immune action of certain white blood cells mounts an attack on the myelin of the central nervous system. Destruction of myelin—the fatty sheath that surrounds and insulates nerves—causes nerve impulses to be slowed or halted and produces the symptoms of MS. Since administering chemotherapeutic agents diminishes the numbers of white blood cells, it should theoretically slow down or halt this autoimmune destruction.

Approval of Mitoxantrone (Novantrone®) by the FDA
On October 13, 2000, following a multi-center, randomized, placebo-controlled clinical trial, the FDA approved the marketing of mitoxantrone (Novantrone®) for "reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary-progressive, progressive-relapsing or worsening relapsing-remitting MS." In addition to being the first drug approved in the U.S. for secondary-progressive MS it offered new treatment options for others experiencing worsening of the disease.

Safety and Side Effects
The short-term safety and tolerability of mitoxantrone were found to be acceptable in the initial trials. Among the more common side effects seen were nausea, hair loss, urinary and upper respiratory tract infections, and menstrual disorders. The longer-term safety of Novantrone® in MS is more problematic. Dose-related cardiac toxicity has been reported, primarily in cancer patients. Although no clinically significant cardiac problems were seen in the relatively short MS trials, the FDA recommended that Novantrone® be used only by those with normal cardiac function, *and for no more than a total cumulative dose of 140mg/m2* (once every three months at a dose of 12 mg/m2) because of possible cumulative cardiac toxicity.

In May, 2005, the FDA added a “black box warning” to the labeling of Novantrone®. Post-marketing reports of adverse events have shown that impaired cardiac function can occur at any time, even early in the treatment. The risk of cardiotoxicity increases with each dose of medication, and congestive heart failure can occur during or after treatment. To address this cardiac risk, the FDA now recommends cardiac monitoring—beginning with a cardiac evaluation prior to the start of treatment and again before each subsequent dose.

In addition to cardiac toxicity, acute myelogenous leukemia (AML), a type of cancer, has been reported in MS patients and cancer patients treated with Novantrone.

Results of Earlier Trials of Chemotherapeutic Agents

Some of the many chemotherapeutic agents that have been used to treat MS are described below. The results of many clinical trials—studies to see if a promising drug actually helps people with MS—have not conclusively shown them to be of definite value, and their use in treating MS remains controversial.

Azathioprine (Imuran®)

The use of azathioprine (Imuran®), as a treatment for MS remains controversial. A drug that suppresses the immune system, azathioprine is commonly used to treat autoimmune diseases such as rheumatoid arthritis, and as part of chemotherapy for some cancers.

Research Results Are Mixed

Over the past 20 years, azathioprine has been, and continues to be, the subject of numerous clinical trials—both in the United States and abroad—to see if it is useful as a treatment for MS. The results—using different patient populations, different doses and different protocols—have been mixed. Some benefit, in the form of slowed progression or fewer relapses, was noted in 60% of the trials. There was no apparent benefit in the other trials.

Side Effects Can Be Severe

Some patients have not been able to take azathioprine because of severe nausea. Other potential side effects of azathioprine include severe anemia or or leukopenia (shortage of white blood cells), liver damage, and a long-term increased risk of developing cancers such as leukemia or lymphoma.

The decision to use azathioprine is a complicated one, and should be made by the physician and the patient together, after a discussion of the potential risks and benefits.

Cladribine (Leustatin®)

Cladribine is a medication that has been used to treat hairy cell leukemia. Pilot studies suggested a benefit in both relapsing-remitting and progressive

MS. In a larger, multicenter trial in primary-progressive and secondary-progressive MS, participants experienced no clinical benefit but did show a significant reduction in gadolinium-enhancing lesions on MRI. Side effects have included infections and bone marrow suppression with reduced platelet counts. A large-scale, phase III, multicenter trial of Mylinax, an oral form of Cladribine, is now underway. Mylinax is known to stop the proliferation of certain types of immune cells, called lymphocytes. Of the many types of lymphocytes that exist, some are known to damage myelin, the protective coating around the nerve fibers in the central nervous system. The trial, which involves 1,200 people with MS, will last two years.

Cyclophosphamide (Cytoxan®)

Cyclophosphamide (Cytoxan®) is a potent immunosuppressive drug that is usually given to treat cancer. It has been used for treating MS for many years, mostly in uncontrolled studies, where it was often but not always reported to improve the condition of people with primary or secondary progressive MS. More recent studies have shown that, at best, there is only a modest benefit from cyclophosphamide. A study in people with rapidly progressive disease is currently underway. The drug is currently used only in selected situations. Its use should be discussed with a neurologist and decisions reached on an individual basis.

The side effects of short-term treatment with high doses are hair loss, nausea, occasional bladder injury, and risk of infection. Long-term side effects include sterility, mutations, and the increased risk of cancer.

Cyclosporine-A

Cyclosporine-A first received attention when it was shown to significantly reduce rejection rates in organ transplantation. Unlike most immune suppressing drugs, it appears to have a specific action against primarily one type of white blood cell, the helper T cells. Since there is some evidence that these cells are abnormally active during acute exacerbations of MS, and since it has been shown to be effective in treating other autoimmune diseases in humans and EAE (the animal model of MS), cyclosporine was tried in a double blind, placebo-controlled trial in patients with progressive MS.

The study enrolled almost 600 men and women and followed them for two years. Many variables were studied, such as clinical status, functional abilities, blood, spinal fluid, and MRI scans. Those patients who received cyclosporine had a slightly (but statistically significant) slower rate of disease progression than the placebo group. There were no significant differences in ability to perform activities of daily living, and no change in MRI or spinal fluid test results.

Serious Side Effects Associated with Cyclosporine-A

There were serious side effects associated with cyclosporine use, namely kidney damage and high blood pressure.

Another study done in Germany compared cyclosporine to another immunosuppressive agent, azathioprine. More than 80 patients in each treatment group completed a two-year double blind protocol.

No significant differences between the two groups were apparent at the end of the study, but the cyclosporine group had twice as many side effects as the azathioprine-treated patients.

It has been concluded that the risks of cyclosporine outweigh the benefits for treatment of MS and do not justify its use under most circumstances. It is rarely used today.

Methotrexate

Methotrexate is a synthetic immunosuppressive drug that is highly effective in the short-term against rheumatoid arthritis, an autoimmune disease. It also effectively prevents EAE, the animal model for MS.

Although a clinical trial of methotrexate in the 1970s did not show benefit to MS patients, there has been renewed interest in the drug and a recent controlled trial showed the drug had modest benefit. In this trial, 30 people with primary or secondary progressive MS who were still able to walk received weekly low-dose methotrexate. Deterioration of arm function was slowed, compared to the arm function of those receiving a placebo, but there was no difference in worsening of leg function, or in overall disability.

See also…

Sourcebook

- Autoimmune Disease
- Clinical Trials
- Placebo Response
- Research

Society Web Resources

- Treatments
  www.nationalmssociety.org/Treatments
- Medications Used in MS
  www.nationalmssociety.org/Meds
- Progressive MS
  www.nationalmssociety.org/ProgressiveMS

Book

Coyle P., Halper J. *Meeting the Challenge of Progressive Multiple Sclerosis* (3rd ed.). New York: Demos Medical Publishing, 2001.

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To contact your chapter, call **1-800-FIGHT-MS** (1-800-344-4867) or visit the National MS Society web site: www.nationalmssociety.org.

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