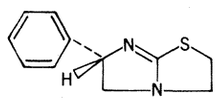
Cancer Immunotherapy: Focus on the Drug Levamisole

For the past few years, clinicians seeking agents to use in cancer immunotherapy have focused mainly on BCG (bacillus Calmette-Guerin), a bacterial preparation thought to increase cell-mediated immunity. But BCG has several disadvantages including its severe and even dangerous side effects. Consequently, investigators are looking at other agents that may stimulate cell-mediated immunity without producing harmful reactions in patients. One of these agents is levamisole,



a drug that is already used in many countries as a deworming agent for both humans and animals.

About four years ago, Gerard Renoux and Micheline Renoux of the University of Tours discovered that levamisole stimulates the immune system of laboratory animals. Since then, a number of investigators have been trying to learn how the drug affects immune responses and whether it will do so in human patients with defective immunity. They hoped that levamisole would boost cell-mediated immunity without affecting antibody production.

Many investigators think that production of antibodies against tumor antigens may actually enhance tumor growth but that cell-mediated immunity helps to prevent cancer (*Science*, 3 May 1974). Thus, enhancement of the latter kind of immunity might prevent a tumor from growing, cause it to regress, or prevent the spread of the cancer to other parts of the body. A current view is that immunotherapy may be most valuable when used as an adjuvant to conventional surgical and chemotherapeutic techniques in order to prevent recurrence of the cancer and metastases following removal of the primary tumor.

The results of a number of studies on the effects of levamisole on immune responses and its use for immunotherapy of cancer and other diseases thought to involve defective immunity were presented at a recent conference.* Two main points emerged from the discussion of the mechanism of levamisole action. The first is that the drug does boost cellular immunity, at least in some assays, although how it does this is still unclear. And the second is that levamisole has this boosting effect only when cell-mediated immunity is depressed. Then the drug may restore it, often to normal, but levamisole does not potentiate cellular immunity to higher than normal values.

The big question is whether this capacity of levamisole to restore cellular immunity in some circumstances will pay off in therapeutic benefits for patients. At present, the results of early clinical trials in cancer therapy could best be described as mixed. Some promising results have been found with breast cancer patients. According to Alexandro Rojas of the Angel H. Roffo Instituto de Oncologia in Argentina, levamisole therapy increased the survival rates of the patients he has studied for a maximum time of 39 months and prolonged the time when the patients were free of tumor following radiation therapy. (These patients' tumors were too far advanced to treat surgically. In all studies with this as yet unproven drug, the patients had advanced or recurrent cancers and poor prognoses with conventional therapies.) J. M. Debois of St. Norberdus Hospital in Duffel, Belgium, also found some improvement in the clinical course of breast cancer treated with levamisole.

On the other hand, J. Leonard Lichtenfeld of the Baltimore Cancer Research Center and Yashar Hirshaut of Memorial Sloan-Kettering Cancer Center could show no effects whatsoever of levamisole on the clinical conditions of cancer patients. Moreover, Hirshaut used a battery of assays to assess both cell-mediated and humoral immunity in the patients. He detected no effect of the drug on any of them, although other investigators have found that levamisole improved certain indicators of cellular immunity in their patients.

These divergent results illustrate the fact that cancer immunotherapy is at present more of an art than a science. Investigators are just beginning to learn how to identify patients who may benefit from it and how to treat them. Many factors may influence how a patient responds to therapy. For example, the timing of drug administration may be critical. Elizabeth Doller of the Milton S. Hershey Medical Center found that levamisole could prevent metastases of a tumor in hamsters, even in the presence of the growing primary tumor, provided that the drug was given before the metastases were established. These results are also encouraging with regard to the idea of using adjuvant immunotherapy to prevent metastases after conventional treatment.

Other factors that may determine a patient's response to immunotherapy with levamisole are the amount of the drug given and the kind and extent of the tumor. Especially important is the immune status of the individual. In order to benefit from levamisole the patient must have cells with depressed immune activity that are capable of responding to the drug. There is also the possibility that levamisole may be effective in restoring cellular immunity depressed as a result of chemotherapy. Michael Chirigos of the National Cancer Institute found that combining levamisole with chemotherapeutic drugs for treating animal leukemias resulted in a greater percentage of cures than did chemotherapy alone.

There are indications that levamisole may be useful in treating conditions other than cancer. For example, Lynn Spitler of the Children's Hospital of San Francisco found that the drug helped control recurrent infections with herpesviruses, especially infections of the cornea. According to Richard O'Reilly of Sloan-Kettering Institute in Rye, New York, the drug decreased the frequency, duration, or pain of recurrent oral or genital infections with these viruses in about half of the 12 patients who received it.

Gerard Renoux and Benjamin Gordon of Kuakini Hospital and Home in Honolulu have also given the drug to a few patients with systemic lupus erythematosus (SLE). This disease is an autoimmune condition characterized by production of antibodies against the body's own tissues and by defective cellular immunity. Although Gordon expressed caution about becoming overly optimistic about the results with one patient, he did find that levamisole completely reversed the symptoms of a woman with SLE after a number of other drugs had failed to do so. He is now beginning to treat additional SLE patients with the drug.

All of the investigators reported essentially the same side effects of levamisole treatment. The most common ones included loss of appetite, nausea, diarrhea, nervousness, irritability, and fatigue. Some patients developed skin rashes while taking the drug. These side effects are relatively mild compared to those associated with most agents used for cancer chemotherapy and to those of BCG. This does not mean that levamisole is nontoxic; an overdose can kill laboratory animals in 15 minutes. But the relative lack of severe side effects plus the fact that levamisole can be taken orally makes levamisole attractive to clinicians—and makes them hope they can get it or a related compound to work.

—JEAN L. MARX

*The Second Conference on Modulation of Host Resistance in the Prevention or Treatment of Induced Neoplasias, which was held in Bethesda, Maryland, on 1 to 3 December, was sponsored by the National Cancer Institute and the John E. Fogarty International Center of the National Institutes of Health.