

## Dual Purpose: Some Cancer Therapies Used to Treat Autoimmune Diseases

In July 1917, when German forces first used mustard gas (sulfur mustard) as a chemical warfare agent against British troops in Ypres, Belgium, no one would have predicted that any good would come of it. The first hint came in 1919, when E.B. and H.D. Krumbhaar reported that victims of mustard gas



**Dr. Bruce Chabner**

poisoning had low white blood cell counts and atrophy of the bone marrow and lymphatic tissues. These observations and subsequent research on the closely related

nitrogen mustards ultimately led to clinical studies in the early 1940s showing that the nitrogen mustard compound mechlorethamine had beneficial effects in patients with Hodgkin disease and other lymphomas. The introduction of mechlorethamine into clinical practice launched the modern era of cancer chemotherapy.

Because of its immunosuppressive properties, nitrogen mustard was also one of the first cancer chemotherapy drugs used for treating other diseases—in particular, those that appeared to involve heightened or abnormal immune system activity. Whereas suppressing the immune system “is not desirable in treating cancer, it happens that the same action is beneficial for people with autoimmune disease,” said Bruce Chabner, M.D., clinical director of the Massachusetts General Hospital Cancer Center in Boston.

### Established Therapies

The goal of chemotherapy in the treatment of autoimmune and inflammatory disorders is to dampen the activity of the immune system rather than to kill abnormal cells. To achieve this goal and minimize side effects, the

doses used are lower than those used in treating cancer. Among the most widely used drugs is methotrexate, an antimetabolite that interferes with various aspects of normal cellular metabolism. Methotrexate has become the standard therapy for moderate to severe rheumatoid arthritis. And, said Michael Weinblatt, M.D., co-director of clinical rheumatology at Boston’s Brigham and Women’s Hospital, rheumatologists often use methotrexate in combination with other drugs for treating rheumatoid arthritis—a concept that “was essentially lifted from the oncologists” and has proved to be successful.

Methotrexate also plays a role in the management of numerous other autoimmune diseases, including psoriatic arthritis, polymyositis, Crohn disease, and certain types of vasculitis (blood vessel inflammation). It is also used for severe cases of psoriasis—a disorder marked by inflammation and abnormally rapid turnover of skin cells. Azathioprine (Imuran), an immunosuppressive antimetabolite that is a derivative of the cancer drug 6-mercaptopurine, is also used to treat many autoimmune and inflammatory diseases and was one of the first drugs used to prevent organ transplant rejection.

Another example is cyclophosphamide (Cytoxan)—a more stable, orally active form of nitrogen mustard. It is considerably more toxic than methotrexate and azathioprine, so its use outside of oncology is not as widespread. However, this drug has played a seminal role in reducing the mortality of some particularly serious nonmalignant diseases. It is used in combination with corticosteroids for inducing remission and preserving kidney function in people with severe lupus nephritis (kidney inflammation)—one of the most serious complications of systemic lupus erythematosus (lupus)—and for inducing remission of Wegener granulomatosis, a rare and once-lethal form of vasculitis.

Many autoimmune and inflammatory diseases have traditionally been treated with high-dose, long-term corticosteroid therapy, which has serious side effects, said Michael Lockshin, M.D., director of the Barbara Volcker Center for Women and Rheumatic Disease at New York's Hospital for Special Surgery. "Most physicians desperately want to find something to lower the dose of corticosteroids, [and] the immunosuppressive agents have been the usual answer to that," he said.

In most cases, chemotherapy drugs are used off-label for treating autoimmune and inflammatory diseases. "Companies simply never sought approval from the Food and Drug Administration for other indications once these drugs were approved for cancer," said John H. Klippel, M.D., president and chief executive officer of the Arthritis Foundation. Markets are small for relatively rare diseases, and a drug will be used off-label anyway, he explained. In addition, once the patent on a drug has expired, companies have no incentive to seek FDA approval.

### New Research Directions

Until 5 years ago, this story would have ended here. But today the treatment of autoimmune disease and cancer is in transition as researchers are developing new, more targeted therapies in place of or as adjuncts to broad-acting cytotoxic and immunosuppressive drugs. Many of these therapies are so-called biologics—monoclonal antibodies and other molecules that are derived from or resemble naturally occurring molecules in the body. And some new and still-experimental cancer therapies, including biologic agents, are showing promise for treating autoimmune diseases.

FDA's approval of several biologic therapies that inhibit the actions of inflammation-causing cytokines, starting in 1998, began transforming the way doctors treat autoimmune diseases. These and other biologic agents block specific components of the immune response, "so that you don't see the general suppression of the immune system that occurs with immunosuppressive drugs," Klippel explained. "As



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a consequence, the side effects tend to be substantially less."

Various biologics initially developed for treating cancer are also being investigated as potential therapies for autoimmune diseases. One prominent example is rituximab (Rituxan), a monoclonal antibody approved by the FDA in 1997 for treating B-cell non-Hodgkin lymphoma. Rituximab targets CD20, a protein found exclusively on the surface of B lymphocytes, and causes rapid and specific B-cell depletion. B cells are thought to play a central role in the pathogenesis of many autoimmune diseases, and preliminary findings from a number of small, investigator-initiated clinical studies suggest that rituximab may be effective for treating diseases including lupus and rheumatoid arthritis.

A more rigorous randomized, double-blind, placebo-controlled clinical trial of rituximab for rheumatoid arthritis was sponsored by corporate partners Roche, Biogen Idec, and Genentech. The results, which have been submitted for publication, provide evidence of improved efficacy with rituximab in combination with methotrexate compared to methotrexate alone, said Arturo Molina, M.D., senior director of global medical affairs in oncology/hematology for Biogen Idec. Other clinical trials to further evaluate the role of rituximab therapy in rheumatoid arthritis are in the works. And in a

March 2004 announcement, Genentech, which collaborated with IDEC Pharmaceuticals (now Biogen Idec) in developing rituximab, said that it has advanced the drug into clinical development for a number of other indications, including lupus and multiple sclerosis.

At the National Institutes of Health, researchers are studying a monoclonal antibody originally developed to treat T-cell leukemia as a possible therapy for several autoimmune diseases. The antibody, daclizumab (Zenapax), is a humanized version of a mouse monoclonal antibody to the interleukin 2 (IL-2) receptor developed by Thomas Waldmann, M.D., chief of the metabolism branch at the National Cancer Institute. The receptor for IL-2 is expressed on activated helper T cells, which normally help fight infection but also turn out to play a central role in initiating the autoimmune response in uveitis (a potentially blinding inflammation of tissues in the eye). This last finding suggested that daclizumab, "which blocks the growth factor IL-2 from 'seeing' its receptor, can be used anywhere where activated T cells cause disease," Waldmann said. Daclizumab is now in phase II clinical trials for uveitis, multiple sclerosis, Wegener granulomatosis, and aplastic anemia.

Agents that inhibit angiogenesis—the formation of new blood vessels—may also find a place in the treatment of some autoimmune and inflammatory diseases. In rheumatoid arthritis, angiogenesis plays a key role in the abnormal proliferation of cells in inflamed joints that leads to invasion and destruction of cartilage and bone.

"There is great interest in inhibitors of angiogenesis in rheumatoid arthritis," and clinical trials of various agents are in progress or in the planning stages, Weinblatt said. Angiogenesis inhibitors, particularly those that inhibit vascular endothelial growth factor (VEGF) activity, may also be helpful for treating psoriasis. Research shows that new blood vessel growth in the skin plays a role in psoriasis and that VEGF levels are elevated in psoriatic lesions.

Not all emerging cancer therapies that also have potential for treating

autoimmune disease are biologics. Histone deacetylase (HDAC) inhibitors are a group of naturally occurring and synthetic compounds that alter gene expression by modulating chromatin structure. Several of these compounds, which induce growth arrest and apoptotic cell death in tumor cells, are in clinical trials for various solid and hematologic cancers. Studies by Wake Forest University rheumatologist Nilamadhab Mishra, M.D., and his colleagues, which show that HDAC inhibitors can downregulate expression of inflammatory cytokines and reduce signs of kidney disease in a mouse model of lupus, suggest that these compounds might also be of benefit for treating lupus. Preclinical studies are still in progress, but Mishra and his colleagues hope to move one of these compounds, trichostatin A (TSA), into clinical trials for lupus.

### Future Trends and Challenges

Although many of the more targeted therapies now being developed for autoimmune and inflammatory diseases are biologic agents, Weinblatt said “a large interest [for the future] is to look at small molecules that may have similar effects on the inflammatory response ... if for no other reason than the economics of the biologics.” Not only are biologic therapies costly, but they also must be administered intravenously or by injection.

In the meantime, Weinblatt said, “what we are looking at now is trying to develop better regimens that can induce remission, which we have not traditionally talked about in our diseases.” In rheumatoid arthritis, for example, “we are looking at taking our available drugs and dosing them better, or hoping that some of the newer agents under development when given in combination with drugs we’re already using ... will induce a better clinical response,” he said.

In fact, several recent studies show that combining biologic therapies with traditional chemotherapy drugs is more effective than either type of therapy alone—in particular for rheumatoid arthritis.

The challenge, Weinblatt said, is to predict which patients could benefit from particular therapeutic approaches. “That’s where we could learn from the oncologists—we can learn how to stage our diseases better.” In rheumatology, researchers are just beginning efforts to identify biological markers of disease that could be used for this purpose. In addition, as in cancer research, much work is ongoing in the area of pharmacogenomics to identify which patients are likely to respond to certain therapies.

As Mass General’s Chabner noted, the initial finding that cancer drugs could also be used to treat autoimmune diseases was due simply to the fact that cytotoxic drugs inhibit the immune system as part of their action. However, certain commonalities in the pathogenesis of autoimmunity and cancer could be of relevance in the

development of new therapies. As Lockshin, of the Hospital for Special Surgery, sees it: “In the autoimmune diseases, it’s a failure to control a benign class of cells”—namely cells that normally function to fight infection—whereas “in cancers, it’s failure to control a malignant class of cells. In both cases, the method of control is to kill the cells by apoptosis, and the control system isn’t working correctly.”

Thus, some of the more targeted therapies developed in the future that will be useful for both cancer and autoimmune disease may act through common pathways. “A lot of chemotherapy right now is just killing cells,” Lockshin said. “If we get out of the business of killing cells, but instead block their activities, we’re likely to achieve better outcomes with less toxicity.”

—Elia T. Ben-Ari