

## **NEW DEVELOPMENTS IN THE THERAPY OF NON-HODGKIN'S LYMPHOMA**



### **John P. Leonard, M.D.**

Richard T. Silver Distinguished Professor of Hematology and Medical Oncology, Center for Lymphoma and Myeloma, Division of Hematology/Oncology, Weill Cornell Medical College and New York Presbyterian Hospital, New York, New York.

The treatment of non-Hodgkin's lymphoma (NHL) remains a complex clinical problem. A major challenge is the fact that there are over 40 different lymphoma subtypes, and tailoring therapy to individual patient subsets is desired but difficult. With some indolent lymphoma subtypes, cure is not expected but a chronic course is typical. Short of eradicating the disease, having tools that can effectively control the disease for an extended period with minimal toxicity and maintain quality of life is essential. In aggressive lymphoma types, a significant proportion of patients can be cured with chemotherapy-based regimens. However, new approaches are needed to further improve cure rates and to reduce toxicity. At Weill Cornell Medical College, we have undertaken several initiatives with the aim of improving outcomes and quality of life for patients affected by the spectrum of lymphoid cancers.

Lymphoid malignancies represent the first area where the use of monoclonal antibody treatments was demonstrated to be effective, and now these tools have been applied to many different tumor types. Monoclonal antibodies are immune proteins that are injected intravenously into the bloodstream and which are engineered to bind to tumor cells in a targeted fashion. While some antibodies are designed to elicit an immune response against the tumor or directly induce tumor cell killing, others are rendered radioactive to deliver lethal radiation to the tumor cell while minimizing the damage to normal cells. We have participated in and led trials with a number of

monoclonal antibodies, including two agents that have since received FDA [Food and Drug Administration] approval. Rituximab, an antibody which binds to the CD20 protein on tumor cells, is an effective single agent treatment for indolent lymphoma (particularly the follicular subtype), and has clinical activity in virtually all other B-cell malignancies. The precise role of rituximab in various treatment settings is currently being defined, either alone or in combination with other therapies. One major area of investigation includes study into the key mechanisms of action of rituximab, as this information as well as the reasons for resistance can lead to new and improved versions which may be better optimized. We are currently studying a “second generation” version of rituximab in clinical trials with promising early results. Our group was the first to use a “combination antibody” treatment approach in lymphoma, without chemotherapy. Rather than using a cocktail of chemotherapy drugs, our hope is to use a combination of targeted antibodies in order to enhance effectiveness while sparing toxicity. Initial results are quite encouraging. One of our regimens is currently under investigation by the Cancer and Leukemia Group B (CALGB), a cooperative group of the National Cancer Institute, which is studying this approach as an initial treatment for follicular lymphoma that could potentially allow patients to avoid or at least delay having to receive chemotherapy. We are also currently exploring a number of other antibodies as treatment for lymphoma, and our group (including Drs. Morton Coleman, Richard Furman, and Peter Martin) is recognized as a leading center in this area of research.

A major translational project led by Dr. Jia Ruan in our group, involves strategies to inhibit angiogenesis, thereby starving lymphomas of their blood supply. It has moved into the clinical arena which identified patients most likely to benefit. Based

on some initial efforts of Dr. Coleman and colleagues, Dr. Ruan is leading a clinical trial of a novel combination of low-dose oral chemotherapy with new biologic therapies that offer patients less toxicity while having impressive anti-tumor activity.

Mantle cell lymphoma remains a significant clinical problem and is an area of intense clinical and translational research. This uncommon form of lymphoma has historically been associated with an unfavorable prognosis and is treated in an aggressive fashion by many centers. Recent data suggest that advances in management have contributed to a significant improvement in survival for mantle cell patients. Our group has appreciated that some patients can have an indolent, less rapidly growing course of disease. Led by Dr. Peter Martin, we have recently analyzed our outcomes and reported that overall survival of our patients treated in a less aggressive fashion is similar to those of other centers which employ much more toxic chemotherapy approaches. This has caused many groups to re-evaluate their management strategy for this disorder. Additionally, we have recently been the first to report results of observation with deferred treatment in selected MCL patients. In addition to these efforts, we are committed to the development of new treatment approaches, particularly those directed at the key biologic pathways associated with MCL. Several agents, including those which target tumor blood vessels, or those which directly interfere with the cell cycle proteins regulating cell division, are actively being investigated in translational studies. Initial efforts have demonstrated proof of concept, and current plans include efforts to rationally combine new targeted therapeutic drugs.

All of these initiatives remain focused on the unmet needs of lymphoma patients. Clinical and translational research has led to breakthroughs in the development of novel

personalized approaches which can more specifically target tumor cells and individual patient subsets while minimizing toxicity. While this work presents many challenges, we are confident that outcomes for patients with non-Hodgkin's lymphoma are likely to improve further in the coming years as a result of these efforts.