RITUXIMAB

by David G. Maloney, M.D., Ph.D.

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Dr. David Maloney is Professor of Medicine, Division of Oncology, at the University of Washington and Member, Clinical Research Division, the Fred Hutchinson Cancer Research Center. Early in the 1990's, while at Stanford University working with Ronald Levy, M.D., he conducted the initial clinical trials of the antibody rituximab in the treatment of patients with low-grade lymphoma. These initial studies ushered in a new era of treatment for patients with B-cell malignancies.

For our Doctor on Call series Dr. Maloney answers questions posed by the Torch about the drug Rituxan (rituximab, MabThera) – possibly the drug most frequently used to treat WM, both alone and in combination.

What is rituximab and how is it made?

Rituximab (Rituxan) is a monoclonal antibody that binds to a protein named CD20. CD20 is a molecule that is present on the cell surface of normal B-lymphocytes and on most of the malignancies that arise from B-lymphocytes, including most lymphomas and also WM. Rituximab is a chimeric antibody (from a fusion of two cell types) formed from protein sequences of mouse and human antibodies. The binding site that attaches to CD20 is murine (the mouse portion), while the rest of the antibody, which interacts with and attracts support from the immune system, is from a human antibody. Rituximab is produced by a cell line that is grown in tissue culture.

How was the dose and schedule of rituximab determined?

Rituximab was initially identified to have anti-tumor activity in the treatment of patients with indolent B-cell lymphomas based on a series of studies evaluating single doses from 10-500 mg/meter squared body surface area and then 4 weekly doses of 125-375 mg/meter squared. Because the treatment was well tolerated, the highest dose (375 mg) was selected for further study. Anti-tumor effects were observed at each of these weekly doses, and the drug was approved by the FDA in 1997 (using the 375 mg dose, weekly for 4 or 8 doses) for the treatment of relapsed low-grade lymphoma. Approximately 50% of patients had at least a partial remission lasting about 1 year. Subsequent studies have started to evaluate different doses and schedules. There is limited data that indicates some diseases (such as chronic lymphocytic leukemia) may require higher doses or a more frequent dosing schedule. In combination with chemotherapy, rituximab is usually given with each 3-4 week chemotherapy cycle. The usual doses are 375-500 mg/meter squared, but few controlled studies evaluating dosing have been done.

How does rituximab kill tumor cells?

Rituximab kills tumor cells either by interacting with the patient's own immune system or by changes induced in the tumor cells directly by the antibody binding to the CD20 on the cell surface. The immune mechanisms are thought to be the most important. Once the antibody is attached to the

tumor cell, cells of the immune system are attracted to the cell and attach to the other end of the antibody, the FC portion (fragment crystallizable – the stem of the Y-shaped antibody) through specialized receptors (called FC receptors). This may then lead to the destruction of the tumor cells. There is some limited evidence that patients who genetically have cells with higher affinity FC receptors may have better responses to rituximab. Rituximab may also interact with another portion of the immune system, the complement system, that can kill antibody-coated cells by assembling a complex of proteins that poke holes in the tumor cell, leading to its death. Lastly, rituximab binding to the tumor cells may augment the effects of chemotherapeutic agents and other biologic agents used in lymphoma therapy, such as fludarabine and thalidomide.

What are the typical infusion related reactions to rituximab?

Rituximab is given by slow intravenous infusion. The initial doses are often associated with mild to moderate symptoms including fever, low or high blood pressure, allergic type symptoms of rash or wheezing or chills. These reactions are usually managed by slowing or stopping the infusion, or with medications. In some patients, however, the reactions may be severe, including, but very rarely, life-threatening. In most patients the reactions are with the initial infusions, although some patients may continue to react to subsequent treatments. The cause of the reactions is likely in part due to the killing of B-lymphocytes (normal and tumor) in the blood. Subsequent infusions are usually associated with fewer reactions, in part due to the persistence of rituximab in the blood from the prior treatment.

What is HAMA or HACA?

HAMA stands for “human anti-mouse antibody” and HACA stands for “human anti-chimeric antibody.” These refer to the possibility of patients making an immune reaction against the rituximab antibody. Since rituximab has some protein sequences that are from a mouse antibody, it is possible for patients to develop an antibody response against rituximab. This is actually very rare in patients with lymphoma but more common in patients who receive rituximab for other diseases such as rheumatoid arthritis. Several of the “next generation” anti-CD20 antibodies are fully human antibody sequences which may further decrease the risk of immune reactions.

How active is rituximab as a single agent in WM patients?

WM is a malignancy of the B-lymphocyte and typically expresses high levels of the CD20 antigen. This led to clinical trials in WM using the standard dosing approved for low grade lymphoma (one dose each week x 4 weeks). Several studies in previously untreated patients and in patients previously treated with chemotherapy have demonstrated that about 30-40% of patients have at least a partial remission (more than 50% reduction in IgM protein) from the treatment. An additional 15-20% of patients have a minor response (25- 50% reduction). Recent studies suggest that patients who have a minor response also benefit from the treatment with improvement in bone marrow function and symptoms.

What about repeat courses of rituximab?

Treatment with two, four-week courses of rituximab separated by 2-3 months has been well tolerated and appears to improve the response rate and may improve the response duration. It is reasonable to consider repeated courses of rituximab in patients who appear to be responding to the initial course (or to consider “maintenance therapy” as discussed below).

What about "maintenance" therapy with rituximab?

Several large, recent clinical trials in patients with other low-grade lymphomas have demonstrated that treatment with extended doses of rituximab has been associated with a decrease in the risk of tumor progression and an extension of the duration of remission. Two different schedules have been used. The first, and most common, is treatment with one dose of rituximab given every 2-3 months for 2 years following the initial treatment with rituximab or rituximab/chemotherapy combination. The other common schedule is treatment with a 4-week course of rituximab, repeated every 6 months for up to 2 years. Direct comparison of these different schedules has not been done. Studies evaluating courses longer than 2 years are ongoing. Thus far, there have not been any reported randomized trials of maintenance rituximab in patients with WM. However, patients with WM who respond to initial rituximab and then go on to receive maintenance rituximab appear to have had prolonged remissions. Based on the data in indolent lymphoma, maintenance rituximab should be considered for patients with WM. In my clinical practice, in the case of patients not on a clinical trial, I discuss the risks and benefits of maintenance treatment (one dose every 2-3 months for up to 2 years) for all patients who respond to therapy with rituximab or rituximab/chemotherapy combination.

Are there risks associated with "maintenance" rituximab?

Although this has not yet been studied in detail in WM patients, maintenance therapy with rituximab has been fairly well tolerated in other indolent lymphoma patients. The risk of infusion-related symptoms usually decreases over time. There has been a small increased risk of suppression of the immune system and thus an increased risk in minor (upper respiratory or sinus) infections. In some patients this is associated with a decrease in the normal immunoglobulin levels (IgG). In addition, some patients may have drops in their white blood cell counts. Patients on maintenance need to be closely monitored. As discussed below rare patients may have serious complications following rituximab therapy.

Can there be severe reactions during or following rituximab therapy?

There can be rare severe reactions to rituximab-based treatments. These include severe infusion reactions as well as the risk of reactivation of serious viral infections such as hepatitis B or other viruses. Progressive multifocal leukoencephalopathy (PML) is an extremely rare and usually fatal brain condition that has been rarely observed in patients treated with rituximab. It is also seen in patients with cancer treated with other agents. It is not clear what the impact of maintenance rituximab will be on this devastating but, fortunately, at this time rare toxicity. All of these issues impact the risk versus benefit of rituximab therapy and need to be carefully considered with your oncologist.

Are there any factors that may predict how well rituximab will work in WM?

The clinical trials with single agent rituximab in WM have led to the observation that patients with IgM levels less than 4-6,000 have had higher response rates, as have patients with higher normal serum albumin levels. In addition, patients with immune systems with the higher affinity FC receptor variants have had higher response rates. These factors are most important when using rituximab as a single treatment. Combination of rituximab with other agents, such as chemotherapy, appears to overcome some of these limitations.

Why does the IgM level effect the response to rituximab?

This is an area that needs more attention. It is possible that the high levels of IgM either impact the interaction of rituximab with the immune system or possibly alter the levels and persistence of rituximab in the circulation. Additional studies that explore different doses and schedules of rituximab are needed.

What is the IgM "flare" seen in WM patients treated with rituximab?

Early studies using rituximab in WM patients detected the interesting finding that about 50-60% of patients actually had an increase in IgM levels in the first weeks following rituximab treatment. In some patients with high IgM levels (generally greater than 5,000 mg/dl), or in patients with high viscosity, this increase in IgM levels may be associated with severe worsening of symptoms. In most patients, this is a transient rise, with resolution in 2-6 months. There does not appear to be a correlation with the ultimate anti-tumor effect. Patients with high IgM levels or hyperviscosity may require plasmaphereses to decrease the IgM levels or combination therapy with chemotherapy to prevent toxicity associated with the IgM flare. The cause of the IgM flare is unknown, but it is not simply the destruction of tumor cells and the dumping of IgM into the blood. It may be a result of alterations in the tumor cell or the effect of substances (cytokines) released from other cells in the blood and bone marrow, or due to changes in the kinetics of the antibody in the blood.

Why do some patients not respond to rituximab, and why does it stop working in others?

Resistance to rituximab treatment has been observed in two situations. Patients who do not respond to the initial treatment with rituximab have primary resistance. The mechanism of this is poorly understood, but this may be associated with high IgM levels or low affinity FC receptors. Other patients, in whom rituximab works initially, are found to be resistant to a repeat course of treatment. This "acquired" resistance is also poorly understood but may be due to changes in the tumor cells making them less susceptible to antibody-based killing. In low grade lymphoma, approximately 50% of patients who initially respond to rituximab are resistant to the next treatment. Combinations with chemotherapy or other novel agents such as thalidomide may be able to reverse this resistance.

What are the best chemotherapy and rituximab combinations for WM?

Unfortunately this is an area that remains controversial and suffers from a lack of randomized clinical trials. Encouraging activity has been associated with conventional chemotherapy regimens such as rituximab combined with CVP or CHOP chemotherapy or with fludarabine or pentostatin based treatments. Recent trials have incorporated rituximab with newer combinations of agents such as bortezomib or thalidomide along with other agents such as dexamethasone and Cytoxan. The decision of which rituximab and chemotherapy combination to use needs to be individualized for each patient based on many factors such as the presence of neuropathy or other comorbidities.

What about the newer anti-CD20 antibodies?

The success of rituximab has prompted an explosion of next generation anti-CD20 antibodies hoping to improve response rates and outcome in lymphoma patients. Most of these have failed to demonstrate increased activity over what would be anticipated with rituximab alone. The FDA has recently

approved ofatumumab (Arzerra), a human antibody for treatment of patients with relapsed chronic lymphocytic leukemia. Direct comparisons with rituximab have not yet been reported. Several other promising anti-CD20 antibodies are currently in clinical trials.

Can rituximab responses be increased by immune stimulants?

This is an area of very active investigation, but as yet firm conclusions are few. Because rituximab is thought to work in part through interaction with the immune system, it stands to reason that agents that make the immune system better may improve the activity of rituximab. Many agents have been tried, including Neupogen, cytokines such as interleukin-2, or interferon, with no proven benefit. Other agents, such as thalidomide or lenolidomide have had mixed results in the clinic. Randomized trials in patients with WM and other lymphomas are required.

Dr. Maloney received his M.D. and Ph.D. in cancer biology from Stanford University, followed by an internship and residency in internal medicine at Brigham and Woman's Hospital and a fellowship in oncology at Stanford. While at Stanford, Dr. Maloney worked with Dr. Ronald Levy to develop monoclonal antibody treatments for lymphoma and has since participated in several clinical trials studying these agents. His current research focuses on the mechanisms of action of monoclonal antibodies and the use of non-myeloablative allogeneic transplantation for the treatment of hematologic malignancies.

Currently a member of the American Society of Hematology, American Society of Clinical Oncology, American Society of Blood and Marrow Transplantation, the Southwest Oncology Group Lymphoma Committee, and the National Comprehensive Cancer Network (NCCN) Committee on Hodgkin's Disease, Dr. Maloney is also Co-Chair of the Lymphoma Working Committee for the Center for International Blood and Marrow Transplant Research. Throughout his career, Dr. Maloney has authored and co-authored many articles focusing on antibody therapy, lymphoma, myeloma and transplantation that have appeared in publications such as the Journal of Immunology*, the* New England Journal of Medicine*, and* Blood*.*

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