The use of rituximab has improved response rates and survival in many histologies of B-cell non-Hodgkin’s lymphoma (NHL). However, it has become clear that some patients have an intrinsic resistance to rituximab, while many other patients develop resistance after an earlier response to rituximab. In most situations, the molecular cause of either innate or acquired resistance has not been elucidated. In some cases, this has been associated with the complete loss of CD20 expression. CD20 does not have a critical biologic function and is not essential for cell survival. Antigen loss and knock-out of the gene in mice has not been associated with a significant phenotype. In most clinical situations, resistant tumors still express CD20. This suggests that resistance must come from either resistance to immune effector mechanisms of complement-dependent cell lysis and antibody dependent cell-mediated cytotoxicity (ADCC), or to the development of resistance to signal transduction from antibody binding. There is some evidence in chronic lymphocytic leukemia (CLL) that resistant cells express higher levels of complement-resistance proteins, however, this was not seen in NHL. Changes in apoptosis-regulating proteins such as BCL2 have been observed in vitro but are of unclear significance.

Methods of overcoming resistance include the generation of antibodies with increased complement- or ADCC-mediated immune activity, or increasing the direct effects of antibody binding. Many of the next generation anti-CD20 antibodies are humanized and feature additional genetic engineering to augment interaction with the Fc-gammaRIIA receptor. This may increase ADCC killing and may either decrease the emergence of resistance or possibly provide antitumor activity in rituximab-resistant patients. The addition of cytokines (such as IL-2 or GM-CSF) has also been proposed to augment ADCC effector cells. Some of the next generation antibodies have better complement-mediated lysis, and others induce greater apoptosis. Arming the antibodies with toxins or radionucleotides also provides increased tumor-cell killing by different pathways and may be an effective strategy in rituximab-resistant patients. Lastly, many chemotherapeutic agents may be combined with anti-CD20 antibodies, and some appear to act synergistically in cell killing. It remains to be seen how to best combine these strategies to prevent and treat the emerging problem of rituximab resistance.

Recent studies have demonstrated a prolongation of survival for patients with indolent non-Hodgkin’s lymphomas (NHL). One major reason is the availability of effective and well-tolerated monoclonal antibodies, such as rituximab, which have reshaped treatment paradigms for patients with B-NHL. However, many patients are not responsive to rituximab-based regimens, while others become resistant during rechallenge or maintenance therapy. Thus, new approaches are needed. Radioimmunotherapy (RIT) (Y90-ibritumomab tiuxetan and I-131-tositumomab) induces responses in 60%-80% of patients; median duration of response is ~1 year and, for patients experiencing a complete remission, response may last several years. Because eligibility criteria for RIT are stringent, other effective drugs are needed. Bendamustine, a purine analogue/alkylator hybrid, has demonstrated impressive activity in rituximab-relapsed and refractory patients with response rates >75%, with one third experiencing a complete remission. Thus, bendamustine has set the standard against which other drugs will have to be compared in this setting. Other new agents in clinical trials include lenalidomide, an immunomodulatory drug (IMiD) with major activity in myelodysplastic syndrome and multiple myeloma. Recent data suggest that ~25% of patients with relapsed or refractory NHL may respond to this single agent; combination strategies are in development, notably with rituximab and bendamustine. Bortezomib is active not only in mantle cell lymphoma, but also follicular and marginal zone lymphomas, but with minimal activity in diffuse large B-cell NHL, CLL/SLL or Hodgkin’s lymphoma. Several small molecules that target apoptotic pathways are also being developed, primarily in combination with other agents. A new generation of monoclonal antibodies in clinical trials includes several human or humanized anti-CD20s and others targeting CD80, CD40, CD22, CD23, TRAIL, as well as bispecific antibodies and small modular immunonopharmaceuticals (SMIPs). The challenge will be to develop rational combinations that will improve the outcome of patients with rituximab-relapsed or refractory NHL. Effective strategies may be rapidly moved to the up-front setting and, as a result, may further prolong the survival of patients with indolent NHL.
GERMAN EXPERIENCE WITH BENDAMUSTINE IN B-CELL LYMPHOMA

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Background: Non-Hodgkin’s lymphoma (NHL) is a challenging disease to treat, due to an inability to achieve a cure with conventional therapeutic regimens and a high likelihood of relapse after treatment. There are many subtypes of lymphoma—some are indolent (follicular lymphoma [FL]), whereas others are aggressive and require aggressive therapies. Many patients with FL may be observed initially until their disease progresses before starting conventional treatment. Standard treatment regimens for lymphomas often include chemotherapy (CHOP-cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab, an anti-CD20 monoclonal antibody. With more aggressive lymphomas, such as mantle cell lymphoma (MCL) or diffuse large cell lymphoma (DLBCL), rituximab with either hyper-CVAD, BEACOPP or ABVD is used. For those who relapse or are refractory to these therapies, chemotherapy with ICE or DHAP with rituximab, radioimmunotherapies, hematopoietic stem cell transplantation, experimental therapies with, eg, proteasome inhibitors or hypermethylating inhibitors, are the options available. Again the choice of therapy depends on the type of disease or the staging of the patient. Bendamustine, a novel agent, a hybrid of nitrogen mustard with a purine antimetabolite, has shown promise in the relapsed/refractory patients with FL and other indolent lymphomas. Several clinical trials have explored and are continuing to explore the effects of bendamustine in combination with other agents. In 2005, a German phase 2 study in low-grade NHL and MCL showed that the combination of bendamustine with a monoclonal anti-CD20 antibody, rituximab, was very effective (with an overall response rate around 90%) in rituximab-naive relapsed or refractory indolent and mantle cell lymphomas. The German Study Group Indolent Lymphoma (StiL) is conducting several trials with bendamustine. One phase 3 study is comparing CHOP plus rituximab to bendamustine with rituximab. Interim results presented at ASH in 2007 showed that the combination of bendamustine and rituximab appears to be as effective as and more tolerable than standard CHOP-R. As a single agent, in a multicenter phase 2 study, it has shown an overall response of 75% in heavily pretreated patients. Conclusions: These studies by the German groups should offer new insights into the utility of bendamustine in the treatment of B-cell lymphomas.

THE US CLINICAL EXPERIENCE WITH BENDAMUSTINE

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Ten years ago, rituximab, the first monoclonal antibody therapy targeting CD20, was approved by the FDA in the United States for use as a single agent for patients with relapsed or refractory follicular non-Hodgkin’s lymphoma. For the first time in over 30 years, preliminary data now suggest a possible survival benefit for patients with follicular lymphoma when monoclonal antibodies are incorporated in the treatment paradigm. However, resistance to rituximab remains a problem, and patients are not cured with standard therapy. Standard approaches to patients with resistance to standard therapies, including rituximab, include radioimmunotherapy, autologous stem cell transplantation, and allogeneic stem cell transplantation. Few clinical trials have been conducted focusing on patients with rituximab resistance. One promising agent that clearly has activity in this group of patients is bendamustine. This alkylating agent, a hybrid of nitrogen mustard with a purine antimetabolite, has shown promise in the relapsed/refractory patients with FL and other indolent lymphomas. Several clinical trials have explored and are continuing to explore the effects of bendamustine in combination with other agents. In 2005, a German phase 2 study in low-grade NHL and MCL showed that the combination of bendamustine with a monoclonal anti-CD20 antibody, rituximab, was very effective (with an overall response rate around 90%) in rituximab-naive relapsed or refractory indolent and mantle cell lymphomas. The German Study Group Indolent Lymphoma (StiL) is conducting several trials with bendamustine. One phase 3 study is comparing CHOP plus rituximab to bendamustine with rituximab. Interim results presented at ASH in 2007 showed that the combination of bendamustine and rituximab appears to be as effective as and more tolerable than standard CHOP-R. As a single agent, in a multicenter phase 2 study, it has shown an overall response of 75% in heavily pretreated patients. Conclusions: These studies by the German groups should offer new insights into the utility of bendamustine in the treatment of B-cell lymphomas.

BIOLOGY AND NEW DIAGNOSTIC TOOLS IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

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In biologic terms, there has been an increased recognition of the probable meaning of mutation status of V genes, expression of ZAP-70 as a diagnostic tool, and the diagnostic utility of IgVH genes. In general, the goal of chronic lymphocytic leukemia (CLL) treatment is to improve outcomes for CLL patients. Bendamustine promises to improve outcomes for CLL patients.

ADVANCES IN CHEMOTHERAPY: BENDAMUSTINE FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: B-cell chronic lymphocytic leukemia (CLL) is a clonal hematopoietic disorder characterized by proliferation and accumulation of aberrant lymphocytes. The management of CLL, determined by the stage and activity of the disease, could include watch and wait for indolent disease, to radiation, chemotherapy, or hematopoietic stem cell transplantation for the more advanced patient. Several randomized studies have indicated that cytotoxic therapy in the indolent phase of disease improves the prolonged survival of patients with CLL. Chlorambucil, with or without steroids, has been for many years the drug of choice for newly diagnosed patients. Purine nucleoside analogs, such as fludarabine and cladribine, used in randomized studies have indicated a higher overall response and a longer response duration than with chlorambucil or cyclophosphamide combination regimens. The monoclonal antibodies directed against CD52 antigen (alemtuzumab) and CD20 antigen (rituximab) have been used in combinations with purine analogs for those failing standard therapies, and they demonstrate significant activity in CLL. More recently, the effect of alemtuzumab in previously untreated patients is being investigated, and results appear encouraging. A multicenter, prospective randomized study comparing alemtuzumab and chlorambucil as first-line therapies is ongoing. Bendamustine is promising, both as a single agent and in combination, for treatment-naïve and relapsed or refractory CLL patients. In vitro studies have demonstrated that bendamustine can induce apoptosis in B-CLL cells as a single agent and in combination with fludarabine. The German CLL Study Group (GCLLSG) has conducted several trials with bendamustine. A phase 1/2 study by the GCLLSG showed that bendamustine has excellent single-agent efficacy for heavily pretreated, relapsed/refractory CLL patients, with an overall response rate (ORR) over 30%. An international phase 3 study showed that bendamustine was significantly more effective than chlorambucil as a first-line treatment for CLL Binet stage B or C patients. Interim results presented at ASH in 2007 from an ongoing GCLLSG phase 2 trial showed that a combination of bendamustine and rituximab is an effective regimen in patients with relapsed CLL, with an ORR of more than 60%. Bendamustine has also shown efficacy when used in combination with mitoxantrone + rituximab in CLL patients, with response rates around 90%, and studies are still investigating these combinations. An ongoing Swiss phase 2 study is also investigating the combination of bendamustine with bortezomib.

Conclusions: Bendamustine appears generally well-tolerated and has minimal cross-reaction with other therapeutics. The development of new regimens that include bendamustine promises to improve outcomes for CLL patients.