Combinations of biological agents in non-Hodgkin's lymphomas

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The traditional approach to patients with indolent non-Hodgkin 's lymphomas (NHL) has included a single alkylating agent, a combination of drugs, such as cyclophosphamide, vincristine and prednisone (CVP), or with adriamycin (CHOP), or CHOP, without evidence of an advantage among these approaches.[1] However, the availability of active monoclonal antibodies for the treatment of non-Hodgkin's lymphomas (NHL) has revolutionized the treatment of patients with these disorders. Rituximab, a chimeric anti-CD20 monoclonal antibody, induces responses in about 50% of patients with relapsed/refractory follicular and low-grade NHL.[2] The response rate increases to about 70% in previously untreated patients.[3-5] Nevertheless all patients eventually relapse and require alternative therapies. Increasing the dose or dose intensity or number of infusions has failed to achieve more than a few transient partial responses.[6-8] A variety of maintenance approaches have prolonged the time to progression of select populations of previously treated and untreated patients, but not others,[9-12] still with no clear prolongation of survival 9,10. Related molecules, such as humanized antiCD20s, are in development.[13]

Because of its activity, favorable safety profile, and ability to enhance the activity of other agents, rituximab serves as an excellent foundation on which to construct new, innovative regimens. Combinations of rituximab with any one of number chemotherapy regimens results in responses in 60-100% of previously untreated patients with follicular lymphomas, with complete remission rates ranging from 20% to more than 60%.[14-17]

As a result of the availability of agents such as rituximab and radioimmunotherapies, several recent analyses have provided evidence that, after many decades, the survival of patients with follicular and low-grade NHL is finally being prolonged. How can this occur if patients are not being cured? First of all, the response rates, and particularly complete response rates, are significantly higher with antibody based combinations. Second, there are a number of effective treatment options that can be used sequentially. In contrast to the repetitive use of chemotherapy where subsequent response rates are lower and less durable than previous responses, response rates to antibody based therapies are often higher and more durable than the previous treatment.

A number of observations supports an approach that is biologically based for the treatment of patients with indolent NHL. First, despite the durable responses to chemotherapy alone or with rituximab, there is no evidence for cure. Moreover, many patients are not candidates or do not want to be treated with chemotherapy. In a number of preclinical models and early clinical trials, rituximab appears to act in an at least additive fashion with a number of biological agents.[18-23] Several recent reports have suggested that β-glucans, which are naturally occurring glucose polymers, enhance the activity of rituximab by augmenting complement mediated cytotoxicity.[24] SCID mice treated with this combination experienced a longer survival than with the individual agents. It is within this context that there has been interest in developing combinations of biological agents for the treatment of lymphomas.

Combinations of monoclonal antibodies

The most obvious group of agents with which to combine rituximab includes other monoclonal antibodies. Of the available monoclonal antibodies that might be combined with rituximab, alemtuzumab (Campath-1H) is perhaps the most widely studied. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, expressed on the surface of all lymphocytes, monocytes, macrophages and eosinophils, but whose exact function remains unknown. Although alemtuzumab appears to be very active in chronic lym-

Table 1. Biological Agents for Combinations in B-Cell Lymphomas.

Agent	Target	Status
Rituximab	CD20	Commercial
Alemtuzumab	CD52	Commercial
Epratuzumab	CD22	On hold
Galiximab	CD80	Phase II
Apolizumab	1D10	Phase I/II
hCD20s	CD20	Phase II
Bevacizumab	VEG-F	Phase II
Lumiliximab	CD23	Phase I
Anti-CD40	CD40	Phase II
Apo2L/TRAIL	Death receptors	Phase I
Oblimersen	Bcl-2	Phase III
GX15-070	Bcl family	Phase I
Lenalidomide	Angiogenesis	Phase III

phocytic leukemia (CLL) as well as T-cell lymphomas, its activity in B-cell NHL is disappointing with partial responses in 14% of treated patients.[25] Rituximab has been combined with alemtuzumab in 48 patients with CLL, prolymphocytic leukemia, RIchter's transformation, and mantle cell lymphoma (MCL).[26] The overall response rate was 52% including 4% complete remissions (CRs), 4% nodular partial responses (PRs) and 40% PRs. The median time to progression was 6 months. However, the regimen was very immunosuppressive as shown by the 52% infection rate including reactivation of cytomegalovirus in 27% of patients. Combinations of rituximab with IFN appear at least comparable to rituximab alone in relapsed indolent NHL.[27,28]

Epratuzumab is a humanized IgG1 monoclonal antibody directed against the CD22 antigen, expressed on a variety of lymphomas. The function of CD22 is unclear. In a dose escalation phase I/II study of epratuzumab in 55 patients with indolent NHL, no dose limiting toxicities were identified with doses ranging from 120 to 1000 mg/m^2.[29] The overall response rate in the 51 assessable patients was 18%, but was 24% in patients with a follicular histology. The median duration of response was 79.3 weeks with a median time to progression of 86.6 weeks. A subsequent report included 56 patients with an aggressive NHL, including 35 with DLBCL, who had received a median of 4 prior therapies, including 25% who had undergone an autologous stem cell transplant.[30] As in the study in patients with follicular NHL, there were no dose-limiting toxicities. The overall response rate was 10%, including 3 complete remissions. However, in those with DLBCL, the response rate was 15%. The median time to progression for responding patient was 26.3 weeks. Several lines of evidence support the potential benefit of the combination of epratuzumab and rituximab. First, both exhibit single agent activity. Second, rituximab appears to upregulate the expression of CD22.[19,20] Third, SCID mouse model studies suggest at least additive benefit with the combination compared with either agent alone 19,20. Thus, a phase II trial of the combination was conducted in 23 patients including 15 patients with follicular NHL and 7 with diffuse large B-cell lymphoma.[31] Those with an indolent histology had received a median of 1 prior regimen (ranging from 1 to 6), with 31% refractory to their last therapy. Patients with DLBCL had received a median of 3 prior regimens (1-8), 14% were resistant to their last treatment and 71% had high intermediate or high risk disease. Ten (67%) of those with an indolent histology responded to the combination, as did 4 of 6 patients with DLBCL including 37% and 67% CRs, respectively. The median time to progression for the patients with an indolent histology was 17.8 months, with 3 of the 6 responders with diffuse large B-cell NHL still in remission as of the time of the publication. The combination was well tolerated and the adverse effects were primarily mild to moderate in severity and occurred during the infusion of the antibodies. The response rate and durability were somewhat disappointing suggesting the possibility that the optimal dose and schedule of the agents had not been used. In *in vitro* models, epratuzumab has also been combined with a humanized anti-CD20 with encouraging results.[13] Nevertheless, the future of this antibody is uncertain at the present time.

Apolizumab is a monoclonal antibody directed against a polymorphic determinant of HLA-DR. This antigen is present on both normal and on malignant B-cells from about half of patients with lymphoid malignancies. This antibody has been evaluated in phase I and II trials in patients with relapsed or refractory indolent NHL,[32,33] with activity noted in the phase I trial, but with disappointing results in the phase II study. The combination of Hu1D10 and rituximab is being evaluated at the National Cancer Institute.[34] Of the patients screened, 77% were positive for 1D10

expression. Toxicities have included infusional and allergic reactions, whereas the dose-limiting toxicities were hemolytic uremic syndrome and arterial thrombosis. The response rate was 42% with 21% CR and CRu. The future of this antibody is uncertain.

Based on the possible role for angiogenesis in NHL, bevacizumab has been tested in patients with relapsed aggressive disease, but with limited activity to date.[35] Several anti-CD40 monoclonal antibodies are early in clinical development.[36]

Lumiliximab, a primatized anti0CD23 monoclonal antibody, is currently in clinical trials for patients with small lymphocytic lymphoma/chronic lymphocytic leukemia, with *in vitro* data suggesting at least additive activity when combined with rituximab.[37,38]

Apoptosis targeting agents

Apoptosis may be an important target in lymphoid malignancies. There are two major apoptotic pathways; the extrinsic pathway involves the death receptor domains, and the intrinsic pathway includes mitochondrial based mechanisms related to the bcl family of genes. A number of agents in development target one or the other of these pathways. Oblimersen sodium (G3139; Genasense) is a bcl-2 antisense oligonucleotide that acts on the intrinsic pathway. Antisense oligonucleotides are chemically modified single-strand DNA molecules with a nucleotide sequence that is complementary to the target mRNA and, therefore, are capable of inhibiting expression of the target gene. The Bcl-2 gene is a potentially important target because it is overexpressed in most follicular B-cell non- Hodgkin's lymphomas and chronic lymphocytic leukemias, and in about a quarter of large B-cell NHL. Bcl-2 upregulation is thought to be responsible for maintaining the viability of tumor cells as well as inducing a form of multidrug resistance. Elevated Bcl-2 also correlates with poor response to therapy in NHL.[39]

The extrinsic pathway is modulate by the death receptor domains, which bind molecules such as APO2L-TRAIL.[40] Other small molecules directed at the Bcl-2 family are in phase I trials.[41]

Cancer and Leukemia Group B (CALGB) clinical trials

It is within this environment that the Cancer and Leukemia Group B Lymphoma (CALGB) Committee has elected to move to a more biologically oriented approach to the treatment of patients with NHL, especially those with an indolent histology. The program for the initial treatment of patients with follicular NHL involves phase II testing of a series of doublets of biological agents. The first of these is the combination of rituximab with galiximab, and anti-CD80 monoclonal antibody. CD80 is an immune costimulatory molecule present on the surface of NHL cells. Galiximab (IDEC-114) is a macaque-human chimeric anti-CD80 antibody with *in vivo* anti-lymphoma properties that was actively studied in patients with refractory NHL. In the initial phase I trials, the antibody dose was escalated from 125 mg/m^2 to 500 mg/m^2, and was well tolerated with no dose-limiting toxicities. The major adverse events were mild to moderate fatigue, nausea, and headache. The response rate was 11% (2 CRs and 2 PRs); however, an observation of interest was that the responses tended to occur late, some as delayed as a year after therapy.[42] Based on preclinical data suggesting synergy with rituximab,[43] a phase I/II study of the combination of galiximab and rituximab has recently been completed in patients with relapsed or refractory follicular NHL.[44] The response rate at the highest dose level was 68.2%, which is higher than would be expected from either agent alone in this patient population. Moreover, there were no dose limiting toxicities. This combination is now the initial treatment for newly diagnosed follicular NHL in the CALGB. Following a series of 4 weekly infusions of these antibodies, there will be a continuation phase during which doses will be repeated four additional times at 2 month intervals.

The second of these doublets will be the combination of rituximab with oblimersen. G3139 (oblimersen sodium; Genasense, Genta Incorporated, Berkeley Heights, NJ, USA) is the first antisense molecule to be widely tested in the clinic for the treatment of human tumors. G3139 is a phosphorothioate oligonucleotide consisting of 18 modified DNA bases (i.e., 18-mer) that targets the first 6 codons of Bcl-2 mRNA to form a DNA/RNA duplex. In order to inhibit the target mRNA, antisense oligonucleotides must first be incorporated into cells by endocytosis. The oligonucleotide then inhibits gene expression by hybridization with the mRNA, followed by cleavage of the mRNA by recruitment of RNAse-H and other endonucleases. Single agent oblimersen has demonstrated activity in patients with indolent NHL and MCL.[45,46] In the first phase I study of G3139 in 21 patients with NHL,[45] one patient with low-grade lymphoma who had progressive disease in nodes and bone marrow after 2 prior regimens attained a complete response, which has been maintained for longer than 3 years. Subjective improvement was also noted in the majority of patients who entered the study with tumor-related symptoms. Side effects primarily include neutropenia, thrombocytopenia, and fatigue. Although the response rate to the single agent is modest, it augments the activity of other agents, such as rituximab, fludarabine and cyclophosphamide, and, therefore, this drug will have its greatest impact in combination strategies.[22] In a randomized phase III comparison of fludarabine and cyclophosphamide alone or with

oblimersen, the combination of oblimersen and chemotherapy was superior to chemotherapy alone in CLL.[47] *In vitro* data also suggest that oblimersen exhibits at least additive activity with rituximab.[48] These observations, and others, have stimulated interest in exploring this combination in NHL.

In a small phase II study in a heterogeneous population of 29 patients with relapsed or refractory NHL and a median of 2 prior therapies, the response rate to this combination was 38%, including 2 patients with rituximab refractory disease.[49] This study is ongoing. However, it is clear that both agents are considerably more active earlier in the course of the disease. Thus, the next CALGB follicular NHL study will include a combination of these two agents. It will be activated once the galiximab-rituximab trial is completed. As part of this study as well as the subsequent follicular NHL studies, FCRgamma RIII polymorphisms will be evaluated in an attempt at predicting those patients most likely to respond to the combination.

Novel agents for future trials are under discussion will be selected based on scientific rationale, with either clinical data or preclinical models, drug availability, and feasibility. After several of these doublets have been studied, the most promising will be compared in a randomized phase III trial.

A similar concept is also being evaluated in patients who have progressed after prior therapy. The first trial to be activated will be a randomized phase II study in patients who have relapsed, but were not refractory to, a rituximab-chemotherapy combination as their initial or subsequent treatment. Although the activity or single agent rituximab has been well described in patients with relapsed and refractory follicular and low-grade NHL who had not been treated with prior rituximab,[2,50] or as a single agent in patients progressing after single agent rituximab,[51] results with rituximab in patients who have progressed after a chemotherapy combination including this monoclonal antibody are poorly characterized. In the first trial, the activity of rituximab as a single will be compared with a single novel drug and with the combination of the two agents. The first drug to be studied in this manner will be lenolidamide.

This immunomodulatory derivative of thalidomide has shown impressive activity in patients with myelodysplastic syndrome and the 5q- abnormality[52] and in chronic lymphocytic leukemia,[53]with a suggestion of activity in other lymphoid malignancies. It is more active than thalidomide in vitro, with a somewhat different toxicity profile. Interest in the combination with rituximab stems from data in patients with relapsed and refractory MCL. Mantle cell lymphoma presents a major therapeutic challenge. Although response can be induced in the majority of

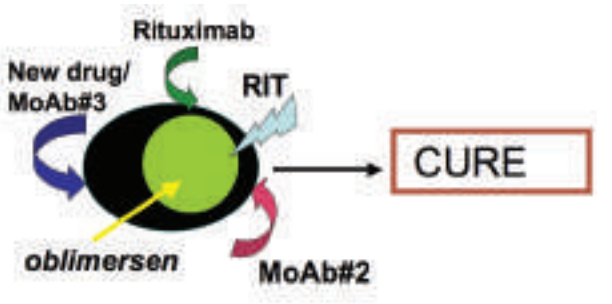

Figure 1. New strategy for treatment of indolent B-cell malignancies.

patients with a variety of chemotherapy regimens, relapse is universal.[54] Salvage therapies have also been disappointing.[55-57] Data with thalidomide in NHL are sparse. However, in a study conducted by the CALGB, single agent thalidomide demonstrated disappointing activity in patients with relapsed and refractory indolent NHL.[58] Rituximab has been reported to have a modest response rate in MCL.[59] The combination of thalidomide and rituximab induced responses in 81% of patients with relapsed and refractory MCL, of which 31% were complete.[60] Subsequent combinations under discussion in the CALGB include rituximab and APO2L-TRAIL, and oblimersen and APO2L-TRAIL.

Summary

The treatment of patients with indolent NHL has entered into a new and exciting phase. Particularly in patients with a low tumor burden, biological approaches provide an attractive, active and less toxic alternative to chemotherapy. Rituximab has revolutionized our approach to patients with B-cell malignancies. However, an important goal of clinical research is to enhance the activity of this agent. One novel approach is to pursue combinations of biological agents which, by themselves may be effective therapy, and which may also augment the activity of chemotherapeutic regimens in appropriate patients. There is an ever expanding menu of novel and active biological agents, including monoclonal antibodies, antisense molecules, apoptosis inducing agents, and other cytokines. A series of combinations of these agents attacking different targets are being developed, which may result in even more effective therapeutic strategies. With the rational development of these regimens may come not only prolongation of survival but, perhaps, the ability to cure patients with indolent lymphoid malignancies (Figure 1).

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