



Targeting CD20 in Follicular NHL: Novel Anti-CD20 Therapies, Antibody Engineering, and the Use of Radioimmunoconjugates

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Rituximab (chimeric anti-CD20 monoclonal antibody) is widely employed in the treatment of patients with B cell non-Hodgkin lymphoma (NHL). This agent has activity in both indolent and aggressive disease, alone and in combination with chemotherapy. Unfortunately, however, many patients develop resistant disease. Ongoing efforts to improve outcomes include changes in dose and schedule, as well as the use of other biologic agents or antibodies that may enhance activity when administered together with rituximab. A relatively new focus is the development of engineered anti-CD20 antibodies that are optimized for their capability to mediate antibody-mediated cellular

cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Human or humanized structures have also been employed to potentially improve these attributes, as well as to improve on pharmacokinetics and immunogenicity. Other studies in NHL have clearly demonstrated that radiolabeled anti-CD20 antibodies (such as I-131 tositumomab and Y-90 ibritumomab tiuxetan) may be useful in relapsed and refractory disease, and have potential utility as part of initial treatment as well. Further studies of these modified anti-CD20 antibodies are ongoing in order to optimize their use for maximal clinical benefit.

CD20-directed monoclonal antibodies clearly demonstrate clinical efficacy in patients with B cell non-Hodgkin's lymphoma (NHL). The chimeric anti-CD20 antibody rituximab was first studied in recurrent indolent NHL, and the "standard" regimen of 4 doses administered weekly (375 mg/m²) resulted in an objective response rate of 48% with a median time to progression (TTP) of just over 1 year.¹ In diffuse large B cell lymphoma and in mantle cell lymphoma, response rates are in the 30% range.^{2,3} This degree of activity can be quite meaningful, and is associated with manageable toxicity, but unfortunately substantial numbers of patients do not respond and many relapse. Strategies to potentially improve efficacy include increases in dose (particularly through "maintenance" or "extended induction" schedules), as well as the addition of chemotherapy or novel biologic agents. More recently, several groups have engineered anti-CD20 antibodies to improve their ability to mediate antibody-mediated cellular cyto-

toxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Additionally, antibody structures with human characteristics may potentially augment immune-based anti-tumor activity, improve pharmacokinetics, and reduce immunogenicity (given their similarity to the host). Finally, radiolabeled antibodies not only provide antibody-mediated effects but also deliver targeted radiation, which can overcome resistance and enhance efficacy. Recent data suggest that this approach can be useful in refractory disease and is also promising when used as part of initial treatment.

Rationale for the Development of Second Generation Therapeutic Anti-CD20 Monoclonal Antibodies

Evidence has suggested that prolonged exposure (beyond 4 weekly infusions) may improve efficacy of single agent rituximab therapy (as discussed fully by Dr. Ghielmini in this volume). Pharmacokinetic studies of data from the pivotal trial indicated that 4 doses of rituximab at 375 mg/m² do not generally result in steady state serum concentrations and that the mean serum half-life after the fourth infusion is approximately 200 hours.¹ Antibody clearance can be variable among patients, and better responses have generally been associated with higher serum rituximab levels. While significant efforts have been made in exploration of extended dosing regimens, retreatment at progression or during remission,⁴⁻¹⁰ it is possible that antibody modifications toward a human or humanized structure would result in more favorable pharmacokinetics and enhanced efficacy.

In order to optimize a therapeutic anti-cancer agent, however, it is critical to understand its dominant mecha-

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nisms of action and reasons for resistance. (See “Unique toxicities and resistance mechanisms associated with monoclonal antibody therapy” by Dr. Friedberg in this volume for a full discussion.) Despite the utility of rituximab, the critical pathways in its activity remain under debate. Many investigators believe that ADCC is an dominant part of the process, and this opinion is consistent with findings that polymorphisms in Fc receptors correlate with response.^{11,12} Byrd and colleagues suggested that rituximab-induced apoptosis is important in its activity in chronic lymphocytic leukemia (CLL) and that response can be correlated with caspase activation.¹³ Finally, the role of complement-mediated cytotoxicity (and the complement regulatory proteins CD55 and CD59) has been explored, and some studies support a role for this pathway, though this remains controversial.^{14,15} Currently, it appears that rituximab may have multiple potential mechanisms of action and that the involved pathways may relate at least in part to the histologic subtype of the tumor, host characteristics, and concurrent use of other agents in combination such as chemotherapy. Despite the lack of clarity, however, engineering of novel anti-CD20 antibodies to enhance their anti-tumor immune effects has progressed through preclinical studies and is currently in phase I and II clinical trials in lymphoma patients.

Preclinical and Clinical Data with Engineered Anti-CD20 Antibodies

Teeling and colleagues characterized two novel human anti-CD20 antibodies (2F2 and 7D8) developed from human immunoglobulin (Ig) transgenic mice.¹⁶ Preclinical studies in the presence of complement demonstrated greater CDC than rituximab, presumably relating to slower “off rates” resulting in greater interaction with C1q and enhanced downstream complement activation. Additionally the fully human structure offers potentially favorable attributes with respect to immunogenicity and pharmacokinetics. From this work, the HuMax-CD20 human IgG1 monoclonal antibody (2F2) is undergoing evaluation in three phase I/II clinical trials (in follicular lymphoma, in CLL, and in rheumatoid arthritis) by Genmab A/S. Hagenbeek and colleagues recently reported on 40 patients with follicular lymphoma who were treated with this agent.¹⁷ Subjects were treated with 4 weekly infusions of 300-1000 mg following acetaminophen and diphenhydramine premedication. Median age was 59 years and patients had a median of 2 prior treatment regimens (range 1–5). Circulating B cells were depleted following therapy, and no dose-limiting toxicity was observed. The median half-life of circulating antibody after the fourth infusion was 342 hours. Twelve of 24 subjects demonstrated objective response, including 4 CR and 1 CR unconfirmed. These data suggest that this agent is well tolerated and is associated with meaningful clinical activity. Further studies are ongoing.

PRO70769 is a humanized IgG1 anti-CD20 monoclonal antibody undergoing evaluation by Genentech, Inc.¹⁸

Preclinical studies of a day 1 and day 15 intravenous infusion schedule in cynomolgus monkeys demonstrated circulating, splenic and lymphatic B cell depletion. While human clinical studies are currently focused in autoimmune disorders, it is conceivable that this agent might also have a role in the treatment of B cell malignancies.

IMMU-106 (hA20), also a humanized anti-CD20 monoclonal antibody, has been developed by Immunomedics, Inc. This agent shares the same human IgG framework as epratuzumab, a humanized anti-CD22 monoclonal antibody with clinical activity in B cell malignancies.¹⁹ Preclinical studies have shown that this agent can directly induce apoptosis of B cells and that it mediates both ADCC and CDC.²⁰ Additionally, IMMU-106 has clinical activity in Raji-bearing SCID mouse tumor models, which is enhanced by the addition of epratuzumab. Clinical trials are ongoing with this agent in B cell lymphomas, and objective responses (including complete responses) have been observed. Interestingly, a report noted that IMMU-106 could be administered safely to and provide a response in a patient with resistant systemic lupus erythematosus and human anti-chimeric antibodies due to prior rituximab therapy (which was no longer effective).²¹ Though further study is clearly needed, this provocative report suggests that human or humanized antibodies may have utility in situations where rituximab is contraindicated.

Challenges in the Clinical Development of Novel Anti-CD20 Antibodies

Given that most patients with B cell lymphoma receive rituximab as part of their initial therapy and/or routinely at relapse, establishing the potential benefits of a novel anti-CD20 monoclonal antibody in lymphoproliferative disorders is a challenge. While a new anti-CD20 antibody might have some activity in rituximab-refractory patients, response rates would be expected to relate to whether there are shared mechanisms of resistance between rituximab and other antibodies. The lower response rates to single-agent rituximab in CML (relative to follicular lymphoma, where the bar is high) suggest that this setting may be particularly appropriate for the testing of new molecules. In contrast, some agents have been evaluated in “rituximab sensitive” patients, or at least those who would not be expected to be refractory based on a prior response. Results observed in this population, with mixed histologies and varied previous treatment regimens, are difficult to interpret. Ultimately,

Table 1. Selected novel anti-CD20 antibodies in clinical development.

Agent	Clinical trial setting	Ref.
HuMax-CD20 (Genmab S/A)	Follicular NHL, CLL Rheumatoid arthritis	16,17
PRO70769 (Genentech, Inc)	Rheumatoid arthritis	18
IMMU-106 (hA20) (Immunomedics, Inc)	NHL	20

most new anti-CD20 antibodies will likely require comparative studies to single agent rituximab in B cell malignancies. Ironically, the success of rituximab in lymphoma and its relative lack of immunogenicity in this patient population appears to drive some developers of second generation anti-CD20 molecules toward rheumatologic diseases as a more enticing target, as the routine use of rituximab for treatment of autoimmunity may be less straightforward.²²

Anti-CD20 Radioimmunotherapy (RIT)

The addition of a radioisotope to a therapeutic monoclonal antibody can improve its activity through targeted radiation.²³ Two radiolabeled anti-CD20 monoclonal antibodies are approved by the US Food and Drug Administration, yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab, for use in patients with recurrent low-grade or transformed low-grade lymphoma. The 1-week duration of therapy is generally welcomed by patients and is clearly shorter than alternative treatment options. Reasonably long-term follow-up has been obtained over approximately 10 years in some studies, and the toxicity profile has been generally well characterized. Principal side effects are hematologic and occur from approximately 4 until 8 weeks after treatment, due to radiation effects on the bone marrow. Incidence of neutropenic fever and the need for transfusional or hematopoietic growth factor support is generally low. Additionally, I-131 tositumomab has been associated with low rates of human anti-mouse antibody formation (HAMA) and hypothyroidism in approximately 10% of subjects.

An attractive feature of radioimmunotherapy (RIT) is that in some cases it can provide durable multi-year responses, even in patients with disease that is resistant to chemotherapy.^{24,25} Recent data have also suggested that these drugs can be effective in rituximab-refractory patients, with some patients having remissions for several years despite prior short responsiveness or unresponsiveness to previous unlabeled anti-CD20 therapy.^{26,27} Evidence suggests that RIT can commonly provide remissions that are longer than those observed with previous treatments, a phenomenon that contrasts with usual expectations with chemotherapy.^{24,28} Efforts to predict which patients with lymphoma will respond to RIT and which subjects are most likely to have a durable response (and therefore perhaps should be considered for early use of RIT) have not clearly identified a clear set of characteristics associated with a favorable outcome.

RIT Used Early in Treatment for Lymphoma

As RIT clearly has utility in patients with resistant disease, a logical next step is to employ it early in the course of treatment to attain potentially even better efficacy. A trial which evaluated the use of I-131 tositumomab in indolent or transformed NHL at first or second relapse resulted in a response rate of 76%, with a complete response (CR) rate of 49%.²⁹ Overall duration of remission was a median of 1.3

years, and approximately 25% of subjects were in a continuous remission from 2.6+ to 5.2+ years after RIT at the time of the report. One might hypothesize that initial treatment could provide even better outcomes, as RIT would be administered prior to the evolution of chemoresistance and at a time of even greater bone marrow reserve. Kaminski and colleagues evaluated RIT with single agent I-131 tositumomab as initial therapy for follicular NHL.³⁰ Seventy-six patients with advanced stage follicular lymphoma received a 1-week course of RIT and were observed for safety and efficacy. The overall response rate was 95%, including 75% complete responses, and 80% of Bcl-2 polymerase chain reaction-positive patients (at baseline) converted to negative after therapy. At over 5 years' median follow-up, estimated progression-free survival was 6.1 years. Hematologic toxicity was acceptable, while HAMA formation (which is uncommon in relapsed patients in relation to their immunosuppressed condition) occurred in most subjects. The implications of HAMA formation are unclear, but it could possibly interfere with subsequent treatment with other murine antibodies and rituximab.

These interesting findings have led to additional studies which will ultimately help to determine the role of RIT as a component of initial therapy for indolent lymphoma. The Southwest Oncology Group (SWOG) conducted a trial of CHOP followed by I-131 tositumomab as initial treatment for follicular NHL in 90 subjects. Treatment was well tolerated, with an overall response rate of 90% (67% CR) and a 2-year progression-free survival of 81%.³¹ Fludarabine and CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy have also been employed in studies by our group in sequence with I-131 tositumomab in follicular lymphoma with similarly promising results.³² Initial results from these trials suggest that the upfront chemotherapy plus RIT approach in these regimens may be more active in low- and intermediate-risk follicular lymphoma international prognostic index (FLIPI) subjects. Other studies with Y-90 ibritumomab tiuxetan as initial therapy in combination with either rituximab or with chemotherapy are also ongoing. Currently SWOG and Cancer and Leuke-

Table 2. Settings where the use of radioimmunotherapy (RIT) is under evaluation in non-Hodgkin lymphoma (NHL).

- Chemotherapy-refractory indolent and transformed NHL
- Rituximab-refractory indolent and transformed NHL
- Single agent initial follicular NHL therapy
- Combination chemotherapy + RIT in upfront indolent NHL
- Combination rituximab + RIT in upfront indolent NHL
- Combination chemotherapy + RIT in upfront diffuse large B cell lymphoma
- Combination chemotherapy + RIT in upfront mantle cell lymphoma
- RIT + chemotherapy in autologous stem cell transplantation

mia Group B (CALGB) are performing a randomized trial of CHOP plus concurrent rituximab versus CHOP followed by I-131 tositumomab as initial therapy for follicular NHL. Other studies are evaluating the use of RIT in other clinical situations, including as a component of an autologous stem cell transplant approach, where promising results with poor-prognosis patients have been observed.³³⁻³⁶

Issues in Further Development of RIT

Data clearly suggest that CD20-directed RIT can be a useful treatment option for many patients with B cell lymphoma, yet relatively few patients appear to be routinely receiving it in practice. Logistical considerations (regarding coordination at a treatment site between medical oncology and nuclear medicine staff) will become less of an issue as centers gain experience with administering RIT. Concerns remain regarding the risk of long-term toxicity (including secondary leukemias) that can be associated with the use of radiation. While these risks appear low (and in the range of those observed with conventional modalities),^{37,38} longer term data with larger numbers of patients will be of value. A major question remains whether RIT should be used mainly in refractory, late-stage patients, in first or second relapse, or as part of initial treatment. In particular, patients with responsive disease but with short remissions can benefit from the opportunity for a durable response that can realistically occur following RIT. Additional support for the early use of monoclonal antibody-based treatments is provided by evidence suggesting that monoclonal antibody-based strategies (including RIT) may be improving overall survival.³⁹ Preliminary data also demonstrate that RIT may have limited activity in relapsed and refractory aggressive lymphomas, such as diffuse large B cell and mantle cell subtypes.^{40,41} Sequential chemotherapy-RIT regimens are currently under evaluation as part of initial treatment for these histologies. Difficulty remains in clearly establishing the best settings for the use of RIT and will require randomized trials with long-term follow-up for clarification. Until comparative trial results are available, the choice of RIT among the array of new treatment options will remain a subjective decision for lymphoma clinicians and their patients.

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