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Immunotherapy with epratuzumab in B-cell non-Hodgkin's lymphoma

During the past decade, the anti-CD20 antibody rituximab has become virtually omnipresent in the management of B-cell lymphomas. With ten years of experience comes not only a greater appreciation for the impact that the drug has had on cancer therapy, but also a greater understanding of its limitations. One strategy to improve on the successes of rituximab has been to engineer novel anti-CD20 antibodies. Although these new agents are likely to be at least as effective as rituximab, they face the challenge of proving their superiority. A second approach, which has the advantage of producing a drug that might join rituximab rather than supplant it, has been to develop antibodies to novel target antigens.

The CD22 antigen a member of the immunoglobulin superfamily and is expressed on most follicular, mantle zone and marginal zone B-cells.[1,2] Its distribution and putative role in signal transduction and cell-cell adhesion make CD22 an attractive target for therapeutic antibodies.[3] Less attractive is its property of rapid internalization upon binding of antibodies since this may limit the capacity of therapeutic antibodies to participate in antibody-dependent cell mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[4] Conversely, antigen internalization is well suited to antibodies capable of directly inducing apoptosis, as well as toxin or radioimmunoconjugates.

Epratuzumab is a humanized IgG1k antibody directed against CD22. Preclinical studies suggested a primarily immunomodulatory effect of epratuzumab on malignant B-cells, with only modest ADCC and no CDC.[5] Two phase I/II clinical trials have been performed with epratuzumab in patients with relapsed B-cell lymphoma. In the first of these trials, 55 patients with relapsed indolent lymphoma were treated with doses ranging from 120-1000 mg/m^2 weekly for four weeks.[6] In the second, 56 patients with recurrent aggressive lymphoma were treated in the same fashion.[7] In both trials treatment was well tolerated, with no dose-limiting toxicity being observed; infusions were often completed within one hour. Serum antibody levels persisted for 12 weeks following therapy and human anti-human antibody (HAHA) formation was rare. Objective responses were demonstrated in 24% of patients with follicular lymphoma, including three complete responses, and 15% of patients with diffuse large B-cell lymphoma; some responses persisted over several years.

Preclinical studies demonstrated that the combination of

epratuzumab with anti-CD20 antibodies was superior to anti-CD20 alone.[8] A potential for synergy was suggested by the observation that rituximab may increase expression of CD22.[8] Based on these data, two trials of combination therapy were performed. The first of these was a pilot study in which 23 patients with relapsed indolent or aggressive lymphoma were treated with epratuzumab 360 mg/m^2 plus rituximab 375 mg/m^2 weekly for four weeks.[9] The toxicity of the combination was comparable to that of rituximab alone and the overall response rate was 67% among patients with either follicular lymphoma or diffuse large B-cell lymphoma. In the second trial, 65 patients with relapsed indolent or aggressive lymphoma were treated at multiple centers in Europe.[10] Fifteen patients had received prior rituximab. 47% of patients responded, including 64% of patients with follicular lymphoma and 47% of patients with diffuse large B-cell lymphoma. The median progression-free survival was 10.9 months for follicular lymphoma and 5.7 months for large cell lymphoma. As encouraging as these data are, they are difficult to interpret in the absence of a control group. Moreover, rituximab-naïve patients, who made up the majority of patients treated in these trials, are increasingly hard to find. Nonetheless, the results were sufficiently positive to justify the currently ongoing study of the combination in patients with untreated follicular lymphoma. The results of this study, which employs several correlative measures, are expected to offer greater information on the potential additive mechanisms of action, and will provide a contemporary benchmark for combination studies.

The combination of rituximab plus epratuzumab is also being studied in combination with CHOP chemotherapy in patients with untreated, CD22-positive diffuse large B-cell lymphoma. Following a pilot study in which the feasibility and efficacy of the regimen were evaluated in 15 patients, a multicenter trial was undertaken in several centers throughout the United States.[11,12] Forty-seven of seventy-six evaluable patients achieved a complete response with a 12-month event-free survival of 85% in thirty-four evaluable patients. Grade 4 neutropenia was common, reflected by the 20% rate of grade 3-4 febrile neutropenia. Only one patient, however, has died from infection while on study. Longer follow-up of these patients will be helpful but at least one phase III study will be required before the combination can be recommended for routine clinical use.

Finally, to take advantage of the property of internalization of CD22, epratuzumab has been conjugated with radioisotopes. Similar to ^{90}Y-ibritumomab tiuxetan, single doses up to 20 mCi of ^{90}Y-epratuzumab have been administered with good response and limited, primarily hematologic toxicity.[13] Capitalizing on the less immunogenic properties of humanized antibodies, fractionated ^{90}Y-epratuzumab has been evaluated.[14] The strategy has produced response rates varying from 41% in patients receiving at a total dose of 5-10 mCi/m^2 over two weeks, up to 90% in patients receiving a

Table 1. Phase I-II clinical trials of epratuzumab.

Study author	*Lymphoma subtype*	*Phase of trial*	*N*	*Prior treatment*	*Treatment*	*Outcome*
Leonard[6]	Indolent	I/II	55	Yes	E[a]	RR:18%
Leonard[7]	Aggressive	I/II	56	Yes	E[a]	RR:10%
Leonard[9]	Indolent/ Aggressive	II	23	Yes	E[b]+R	RR:61%
Straus[10]	Indolent/ Aggressive	II	65	Yes	E[b]+R	RR:47%
Micallef[11]	DLBCL	II	15	No	ER-CHOP	CR:50%
Micallef[12]	DLBCL	II	76	No	ER-CHOP	CR:62%
Kraeber -Bodere[14]	Indolent/ Aggressive	I/II	58	Yes	^{90}Y-DOTA-E	RR:41-90%

N = number of patients; E[a] = epratuzumab 120-1000 mg/m^2 weekly x 4; E[b] + R = epratuzumab 360 mg/m^2 plus rituximab 375 mg/m^2 weekly x 4; E R-CHOP = epratuzumab 360 mg/m^2, rituximab 375 mg/m^2, cyclophosphamide 750 mg/ m^2, doxorubicin 50 mg/m^2, vincristine 1 mg/m^2, prednisone 50 mg/ m^2 every 21 days for six cycles; ^{90}Y-DOTA-E = ^{90}Y-DOTA-conjugated epratuzumab 5-15 mCi/m^2 weekly x 2-3; RR = response rate; CR = complete response; DLBCL = diffuse large B-cell lymphoma.

total dose of 45 mCi/m^2 over three weeks. Longer follow-up in a greater number of patients will be required to adequately assess the safety and efficacy of the approach.

As a single agent, in combination with rituximab, and as a radiolabeled immunoconjugate, epratuzumab has demonstrated safety and efficacy in patients with relapsed indolent and aggressive B-cell lymphomas (Table 1). The major challenge over the next decade will be to quantify the impact of new antibodies and to determine how best to integrate new antibodies into standard practice-phase III trials will play a major role in this process.

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