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Monoclonal antibody therapy of T cell lymphoma: single agent trials of anti-CD2 (Siplizumab) and anti-CD4 (Humax-CD4)

Although there has been significant progress in the management of B-cell non-Hodgkin's lymphoma, the treatment of T-cell lymphomas remains unsatisfactory with less than 20% of patients experiencing long term disease control. In addition to their inherent resistance to chemotherapy, the complexity of treating T-cell lymphoma in part resides in the diverse clinical entities encompassed by this diagnosis as well as their less frequent occurrence compared with the more common B-cell lymphomas. The T cell has a wide array of cell-surface receptors that can serve as targets for treatment by monoclonal antibodies. These receptors include broadly expressed antigens, for example CD2 and CD52 present on almost all normal and malignant T cells or their expression may be restricted, such as CD4 or CD8 where only specific populations display the antigen. The advantage of using the broadly expressed antigens as targets for monoclonal antibodies is their applicability to a wide array of T cell neoplasms but the concomitant immunosuppression associated with their use is a major disadvantage. Restricted receptors limit the target cell population depleted by treatment and thus may be better tolerated but this limits the population eligible for treatment. Two monoclonal antibodies evaluated for the treatment of T cell lymphoproliferative disorders are siplizumab which binds to CD2 and zanolimumab which binds to CD4. Two phase I trials of siplizumab demonstrated promising activity in T cell malignancies with partial and complete responses observed in patients with peripheral T cell lymphoma (PTCL), adult T cell leukemia/lymphoma and large granular lymphocyte leukemia but the development of Epstein-Barr virus-related lymphoproliferative disease (EBV-LPD) in five of 51 patients (10%) treated prompted closure of the single agent trials. Siplizumab is being evaluated in combination with rituximab in an attempt to prevent EBV-LPD. Zanolimumab has been evaluated in the treatment of cutaneous T-cell lymphoma (CTCL) and PTCL with responses observed in both groups. Fifty-six percent of patients with CTCL treated with high doses of zanolimumab (980 mg per treatment) responded with a median response duration of 81 weeks. In a separate trial in patients with aggressive T cell lymphomas, three of fourteen patients (21%) achieved objective responses to the same high dose treatment regimen used in the CTCL trial. Zanolimumab therapy was well tolerated with a limited increase in infectious complications; no cases of EBV-LPD were

reported. Zanolimumab is currently being evaluated in patients with CTCL who have progressive disease following bexarotene and at least one other systemic treatment in a licensing trial. Although responses occur with both siplizumab and zanolimumab alone, receptor modulation represents an obstacle to the effective use of these antibodies.

Peripheral T cell leukemias and lymphoma (PTCL) represent post-thymic T cell neoplasms that comprise about 10% of all non-Hodgkin lymphomas.[1] They are classified by the World Health Organization into three major groups by their clinical presentation as either predominantly leukemic, nodal or extranodal.[2] The WHO identifies a fourth group of neoplasms of uncertain lineage and stage of differentiation that has a single entity blastic NK cell lymphoma. PTCL have distinct immunophenotypic characteristics, clinical presentations, geographic distributions and in most cases are highly aggressive with a minority of patients cured with current clinical approaches. In contrast with diffuse large B cell lymphoma where chemotherapy in combination with rituximab has a curative impact in about 50-80% of patients,[3-5] the outcome for those with T cell lymphoma is significantly worse with less than 20% of patients cured.[6-8] At the present time there is no agent with activity similar to rituximab for the treatment of T cell neoplasms. T cells express a rich array of cell surface molecules that can be targeted by monoclonal antibody based approaches and many are undergoing clinical testing. Morris et al. characterized the features of the ideal targets for receptor-directed therapy for T cell malignancy in their review of receptor-directed therapy of T cell lymphoma.[9] These included 1) expression restricted to the malignant T cell 2) a high level target expression 3) a non-modulating receptor target and 4) absence of serious systemic side effects with receptor engagement. Alemtuzumab appears to fulfill these criteria, is commercially available, and has been safely combined with chemotherapy. Alemtuzumab (anti-CD52) is undergoing evaluation in a phase III clinical trial in combination with CHOP chemotherapy based on the high response rates observed in small phase II trials of alemtuzumab alone and in combination with CHOP chemotherapy, although significant concerns about the toxicity of this approach due to immunosuppression exist.[10-13] This review will discuss two monoclonal antibodies, siplizumab, which targets CD2, and zanolimumab, which targets CD4, that are currently in clinical trials for the treatment of T cell lymphoma.

Siplizumab

Siplizumab is a humanized IgG1 class monoclonal antibody that binds to the CD2 receptor found on human T-lymphocytes, natural killer (NK) cells, and thymocytes. It was constructed using molecular techniques to insert the CD2 binding region from the characterized CD2 specific rat monoclonal antibody, BTI-322.[14] CD2 plays a key role in lymphocyte adhesion and cell signaling through binding to its receptor LFA3 (CD58).[15] It is expressed at high levels on the majority of T cell neoplasms although the level of CD2 expression typically differs from that of normal peripheral blood T cells. In most instances, the level of CD2 expression is less than that of normal T cells (Stetler-Stevenson, MA, unpublished data). In rare instances, T cell neoplasms fail to express CD2 and patients with such tumors are not appropriate candidates for siplizimab therapy.[16] Activation of normal T cells is associated with an increased level of CD2 expression and contrary to expectation, dexamethasone increased CD2 expression on transformed T cells.[17-19] Anti-human CD2 monoclonal antibodies inhibit T cell responses to various stimuli. The

inhibitory effect of anti-CD2-directed therapies is most potent during antigen presentation and higher doses result in similar levels of T cell depletion but greater CD2 modulation. *In vitro* studies have shown that siplizumab induces alloantigen hyporesponsiveness and causes deletion of T- and NK-cells in mixed lymphocyte reaction (MLR).[20] CD2 knockout mice produce T cells that have reduced proliferative responses and reduced interferon gamma (IFN-γ) release in response to antigen stimulation compared with CD2-expressing T cells.[21] However CD2 deficient T cells maintain normal cytolytic activity.

These properties have led to its consideration as an immunomodulator in clinical settings where the suppression of T-cell reactivity may have clinical benefits such as psoriasis and other autoimmune diseases, graft-versus-host disease (GvHD), and in solid organ transplantation. Clinical trials of low doses of siplizumab in patients with psoriasis demonstrated that the antibody produced T cell depletion and this led to its testing as a treatment for adult T cell leukemia/lymphoma(ATL) in the MET1 animal model.[22] In this model, animals challenged with tumor develop leukemia that results in death within 100 days of challenge. About 50% of tumor-bearing animals treated with siplizumab on a weekly basis for four weeks survive and the life expectancy of tumor-bearing animals treated on a weekly basis for six months was identical to that of non-tumor bearing littermates. This suggested that siplizumab cures the majority of tumor-bearing animals. The mechanism of action of siplizumab in controlling tumors is primarily through its ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC). This was demonstrated with studies in the Fc receptor knock out mouse. The Fc receptor knock out mouse is incapable of mediating ADCC and the antitumor activity of a rituximab in B cell lymphoma,[23] traztuzumab in breast cancer,[23] and alemtuxumab,[24] daclizumab[25] and siplizumab[22] in the MET1 model of T cell lymphoma is lost.

Based on these animal model studies, siplizumab was evaluated in a phase I trial in patients with CD2-positive lymphoproliferative syndromes. The primary purpose of the trial was to determine the maximum tolerated dose and safety profile of siplizumab in patients with T cell neoplasms. The study also explored the effects of siplizumab administration on CD2 expression on normal and malignant peripheral blood lymphocytes and lymphocytes from lymph node aspirates, the time course of T-cell and NK-cell depletion during treatment and reconstitution of these cells following completion of therapy, serum pharmacokinetics and antitumor activity. Patients infected with human immunodeficiency virus, hepatitis B or C, and patients with evidence of cytomegalovirus reactivation detected by polymerase chain reaction or antigen detection were excluded because of the expected T cell depletion. Twenty-nine patients were entered into the trial with the majority having ATL and large granular lymphocyte leukemia (LGL). The malignant cells were required to express CD2. The initial trial design included 7 cohorts treated with a divided infusion of the antibody, over two or three days, on an every two week schedule (Figure 1A). The dose escalation plan for the trial is shown in Table 1. The first infusion of siplizumab was associated with the infusion reactions, fever and chills, typically observed with monoclonal antibodies particularly when the target cell population is found in the peripheral blood. These infusional reactions were managed by holding the infusion until the side effects had resolved and then resuming the infusion. In all patients the infusions could be completed without recurrence of symptoms. Subsequent cycles of therapy were administered without infusional toxicity in most cases. As anticipated, T cell numbers

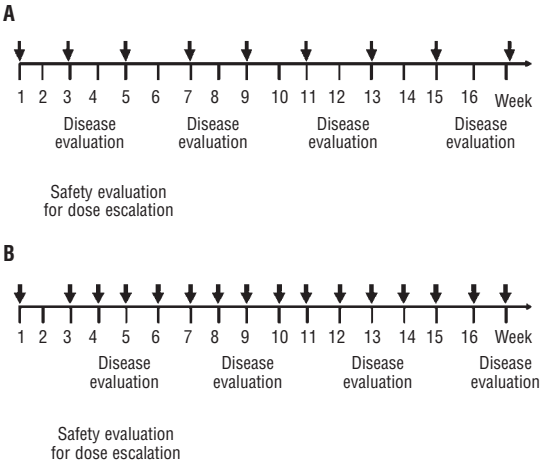

Figure 1. Schema for Phase I trial of siplizumab in T cell lymphoma.

Table 1. Schedule of siplizumab administration cohorts 1-10.

	Siplizumab Doses (mg/kg)			
	Day 1	*Day 2*	*Day 3*	*Patients enrolled*
Cohort 1	0.2	0.2	--	3
Cohort 2	0.2	0.2	0.2	3
Cohort 3	0.4	0.4	--	3
Cohort 4	0.4	0.4	0.4	4
Cohort 5	0.4	0.8	1.2	3
Cohort 6	0.4	1.2	1.8	3
Cohort 7	0.4	1.8	2.6	3
Cohort 8	0.8	--	--	3
Cohort 9	3.4	--	--	3
Cohort 10	4.8	--	--	1

Cohorts 1-7 14 day cycles

Cohorts 8-10 Single dose day 1, 14 and then weekly cycles

declined after siplizumab treatment with about a 90% decrease in both $CD4^+$ and $CD8^+$ peripheral blood T cell populations but B cell numbers were not affected. Decreased numbers of natural killer (NK) cells in peripheral blood were observed but rebounded to near baseline levels despite continued treatment. Objective responses, both partial and complete, were observed in patients with ATL (3 partial responses) and LGL (3 complete responses). These encouraging clinical responses and the low toxicity profile led us to modify the protocol based on other observations that we anticipated would improve the therapeutic benefit. First, modulation of CD2 expression was observed within 24 hours following the first infusion of the antibody during each treatment cycle. Doses as low as 0.4 mg/kg were sufficient to modulate more than 90% of the surface CD2 from both malignant and normal T cells in the peripheral blood and recovery of CD2 expression required 7-10 days to return to pretreatment levels. As a consequence of this antigen loss, patients with high leukemic counts did not experience any additional cytoreduction from infusions given on subsequent treatment days in a cycle, similar to the experience with zanolimumab in patients with Sezary syndrome that will be discussed later. Second, the tumors of some patients increased in size during the second week of each cycle in the absence of treatment. In an attempt to improve the therapeutic benefit, the protocol was amended to administer weekly infusions (Figure 1B) after an initial two week cycle that was incorporated to allow us to examine the effects of siplizumab on CD2 expression. This schedule permitted an opportunity for the malignant cells to re-express CD2 on the cell surface and the more rapid treatment schedule allowed less time for tumor growth between dosing intervals. Three additional cohorts were treated but a significant problem rapidly emerged with this new schedule. Six patients received more than one dose of siplizumab in this second cohort and three developed Epstein-Barr virus lymphoproliferative disease (EBV LPD). The time course of onset of the complication was short with EBV LPD occurring at 55, 147 and 189 days after initiation of treatment. None of the 22 patients treated on the every two week schedule developed EBV LPD during treatment but a review of the post treatment course of these patients identified

one additional case. This patient who had CTCL progressed after two cycles of siplizumab and was subsequently treated with the histone deacetylase inhibitor romidepsin until disease progression and then gemcitabine when she developed EBV LPD 309 days after the start of siplizumab therapy. She was also diagnosed simultaneously with cytomegalovirus pneumonia highlighting the severe immunosuppression associated with her underlying disease and previous treatment. The ability of siplizumab to decrease $CD4^+$, $CD8^+$ and NK cell numbers combined with modulation of CD2 expression without altering B cells results in a situation where B cell proliferation of EBV-infected cells cannot be effectively controlled by innate or immune mechanisms with a high risk for the development of EBV LPD.

To take advantage of the observed synergy between monoclonal antibodies and chemotherapy, a phase I trial has been initiated incorporating dose-adjusted EPOCH infusional chemotherapy and increasing doses of siplizumab for the treatment of patients with chemotherapy naive T cell lymphoma. The treatment schema is shown in Figure 2. Rituximab will be administered on day 5 of each cycle based on its ability to prevent and treat EBV LPD in other settings.[26-28] Peripheral blood EBV DNA levels will be monitored to determine whether this helps to predict the development of EBV LPD in patients treated with siplizumab. If more than one case of EBV LPD occurs in patients treated with this regimen, the trial will be discontinued.

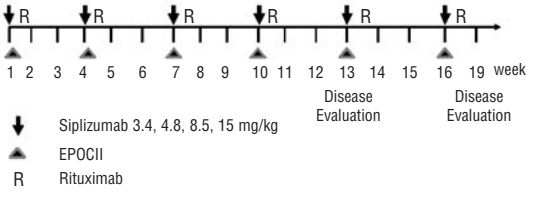

Figure 2. Schema for Phase I trial of siplizumab and dose-adjusted EPOCH-rituximab in T cell lymphoma.

Zanolimumab

Zanolimumab is a fully human IgG1 monoclonal antibody directed at CD429, which is expressed on helper and regulatory T cells and at lower levels on monocytes. Zanolimumab exerts its antitumor activities through several mechanisms.[30] First, it inhibits signaling events associated with T cell activation. T cell proliferation and cytokine production are inhibited in the presence of zanolimumab. Furthermore, this inhibition of CD4-mediated signaling may prevent transmission of the survival signals provided by the interaction of the malignant T cells with Langerhans cells in the Pautrier's microabcesses of patients with CTCL. Second, as with most monoclonal antibodies, depletion of the target population is effected by Fc receptor expressing cells through ADCC. CD45RO T cells (mature) appear to be more sensitive to killing by zanolimumab than CD45RA T cells (naïve). Although capable of fixing complement, zanolimumab does not appear to use this mechanism in patients to eliminate T cells.

Zanolimumab was initially tested in the setting of autoimmunity in patients with rheumatoid arthritis and psoriasis where it demonstrated a low toxicity profile but no significant activity. Similar to the experience with siplizumab, the significant T cell depletion that accompanied zanolimumab therapy led to its use in patients with T cell malignancy. Trials have been now been conducted in patients with CTCL and PTCL with good activity and a phase III registration trial is underway for the treatment of CTCL.

Depletion of $CD4^+$ T cells induced by zanolimumab is dose-dependent. In a phase I trial in normal volunteers, a single intravenous 4 mg/kg dose produced a 75% median reduction

in peripheral blood CD4+ T cells at 12 hours after treatment31. Patients with psoriasis treated with 40, 80 or 120 mg of antibody showed a gradual decline in CD4+ T cell number that reached maximum levels after 6 weeks. CD4+ T cell numbers were reduced to about 40% of baseline levels and were maintained at this level with continued treatment during the last 8 weeks of the trial. Recovery of CD4 counts was observed within two weeks of treatment discontinuation. Two trials of two different dose levels were conducted in patients with early and late stage CTCL32. Patients with early stage disease were treated with 280 or 560 mg of zanolimumab and late stage patients were treated with 280 or 980 mg of antibody. The maximum CD4+ T cell depletion occurred within 2-3 weeks of starting treatment. Zanolimumab produced an 80% reduction in CD4+ T cell number. The T-cell count one week following the last infusion showed dose-dependent declines in CD4+ cell counts of 264, 195, 81 and 42 cells per micoliter at the 280 (early stage), 280 (late stage), 560 and 980 mg dose levels respectively. There was no difference in recovery of CD4+ T cell numbers between the dose groups with a recovery of 137 T cells per microliter per year.

Thirty-eight patients with mycosis fungoides (MF) and 9 with Sezary syndrome(SS) were treated in these studies. The overall response to therapy was 13 of 38 (34%) patients with MF and 2 of 9 (22%) patients with SS. There appeared to be a dose response to therapy in patients with MF with 3 of 20 (15%) patients responding at the 280 mg dose level, 7 of 14 (50%) at the 560 mg dose level and 3 of 4 (75%) at the 980 mg dose level. Only 2 patients with SS responded to treatment despite the fact that most were treated at the highest dose level. The absence of significant activity in SS may reflect the downmodulation of the CD4 receptor that occurs with zanolimumab treatment. As was observed in the trial with siplizumab, loss of the target antigen after antibody administration was also associated with loss of response to subsequent antibody infusions. The time to achieve a response ranged from 2-12 weeks and the duration of response for patients treated with high doses ranged from 8-91 weeks with a median response duration of 81 weeks. In a separate trial zanolimumab was evaluated in patients with relapsed or refractory non-cutaneous PTCL.[33] Zanolimumab was administered intravenously at the high dose used in the CTCL trial, 980 mg weekly for 12 weeks. Twenty-one patients were entered, primarily angioimmunoblastic T cell lymphoma (AILT) (9), PTCL-unspecified (7), and anaplastic large cell lymphoma (ALCL) (4). Objective tumor regressions were obtained in 5 patients; three partial responses (1 ALCL and 2 AILT) and two complete remissions (one each in patients with AILT and PTCL-unspecified). Although therapy was discontinued after 12 weeks responses were durable in two patients lasting 182+ and 252+ days at the time of the report. As in the other studies zanolimumab was well tolerated with infusion reactions as the major toxicity. There were no reports of opportunistic infection in the trials of zanolimumab, perhaps due to the absence of declines in CD8+ T cells and natural killer cells since these populations which are protective against viral pathogens are not targeted with zanolimumab.

Conclusions

Zanolimumab and siplizumab have the potential to modulate expression of their targeted receptors and as a result are not particularly effective in patients with high leukemic blood counts likely due to receptor modulation. The effect of these antibodies in tumor tissues has not been well studied but a similar effect in lymph nodes and other solid tumor

masses could lessen their effectiveness there as well. Agents that prevent modulation of the targeted receptors or that accelerate re-expression could enhance the activity of siplizumab and zanolimumab. Alternatively use of modified antibodies, radionuclides, immunotoxins and antibody drug conjugates (ADC), represent an exciting approach to improving the activity of agents targeting CD2 or CD4. The ADC SGN-35, a chimeric antibody targeting CD30 modified by the addition of monomethylauristatin E, a synthetic analog of the naturally occurring cytotoxic agent, dolastatin,[10] shows excellent results in the treatment of Hodgkin lymphoma.[34] The immunotoxin, BL22, which combines the binding site of a monoclonal antibody directed at CD22 and Pseudomonas exotoxin, produces complete remissions in purine-analog refractory hairy cell leukemia.[35] These results demonstrate the effectiveness of these constructs for cell surface receptors that undergo internalization after antibody binding and provide a rationale for modification of CD2 and CD4 to enhance the effectiveness of targeting these receptors. The successful treatment of PTCL remains challenging due to the large number of disease entities encompassed by this designation, their relative rarity, and the heterogeneity even within the diagnosed subtypes of PTCL. Finally, a fundamental difficulty in the treatment of CTCL and PTCL with monoclonal antibodies is the expression of the targeted antigen on both normal and malignant T cells. This makes it impossible to selectively eliminate malignant cells without affecting at least a portion of the normal T cell populations. Immunosuppression is therefore an expected consequence of this approach. Whether viral infections and EBV LPD can be successfully treated and prevented will be critical to the viability of the use of broadly targeted T cell antigens such as CD2 and CD52 to treat T cell lymphoma.

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