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Monoclonal Antibody Therapy of T-Cell Leukemia and Lymphoma

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1. Introduction

T-cell leukemias and lymphomas are a heterogeneous group of uncommon tumors that account for 7-15% of lymphomas. [1] They represent approximately 6,500 new cases annually in the United States. Typically patients with malignant T-cell disorders present with high-grade lesions, advanced stage disease and have systemic or “B” symptoms at diagnosis. Until relatively recently these diseases were treated with the same anthracycline-based chemotherapy regimens used to treat B-cell lymphomas. With few exceptions, the outcomes are poorer with lower response rates, shorter times to progression, and shorter median survivals compared to B-cell lymphomas. A number of new agents have recently entered the clinic for the treatment of T-cell lymphomas. [2] These include the histone deacetylase inhibitors voronostat (Zolinza®) and romidepsin (Istodax®) approved for treatment of previously treated cutaneous T-cell lymphoma (CTCL), the antifolate, pralatrexate (Fotolyn®) indicated for the treatment of relapsed or resistant peripheral T-cell lymphoma (PTCL), and the immunotoxin brentuximab vedotin (Adcetris®) for the treatment of relapsed anaplastic large cell lymphoma (ALCL). These newer agents join a handful of drugs approved for the treatment of T-cell lymphomas including beraxotene (Targretin®) and the interleukin-2-diphtheria toxin fusion protein, denileukin diftitox (Ontak®).

The introduction of the chimerized anti-CD20 monoclonal antibody, rituximab (Rituxan®), was a major advance in the treatment of B-cell lymphoma improving the survival of patients with B-cell lymphoma. Unlike B-cell lymphomas no monoclonal antibody has received a similar indication for treatment of T-cell neoplasms. Presently an expanding number of antibodies targeting T-cells are being studied for the treatment of T-cell leukemia and lymphoma. The current status of monoclonal antibody therapy of T-cell leukemia and lymphoma will be the focus of this chapter.

Target Antigen	Description	Monoclonal Antibody
CD2	LFA-3 (CD58)	Slipizumab (MEDI-507)
CD3 (CD3 ζ)	TcR signaling chain	muromonab-CD3 (Orthoclone [®] , OKT3)
CD4	TcR co-receptor	Zanolimumab (HuMax-CD4 [®])
CD5	Scavenger receptor family member	Anti-Leu1 T101
CD25	IL-2 receptor α -subunit	Daclizumab (Zenapax [®])
CD30	TNF receptor family member	Brentuximab vedotin (Adcetris [®])
CD52	GPI-anchored glycoprotein	Alemtuzumab (Campath [®])
CD122	β -subunit of the IL-2 and IL-15 receptor	Mik- β 1
CCR4	Chemokine receptor-4	KW-0761

Table 1. Monoclonal antibodies for the treatment of T-cell leukemia and lymphoma.

2. Characteristics of the ideal target for antibody-directed therapy

Delivering maximum therapeutic benefits with minimal or no toxicity have been the main objective of any therapeutic strategy including antibody therapy. The choice of therapeutic target for antibody therapy is one of the most important variables in achieving this goal. The ideal target for antibody-directed therapy should have following characteristics: Including restriction of the target antigen expression to malignant T-cells. Toxicity and unintended effects of a ubiquitously present target is a significant hindrance in development of antibody therapy, an ideal target should have its expression restricted to malignant T-cell or if the target is expressed on other hematopoietic cells, the loss of these cells or their function should not result in serious complications such as life-threatening immunosuppression. If the target is broadly expressed on other T-cells or hematopoietic cells, treatment will not only eliminate the tumor cells, it will also cause depletion of functional T-cells allowing reactivation or susceptibility to a variety of serious infections. Alemtuzumab (Campath[®]), a monoclonal antibody directed against CD52 is an effective therapy against B-cell chronic lymphocytic leukemia (CLL); however, since CD52 is also expressed on T-cells, treatment results in the depletion of both CD4⁺ and CD8⁺ T-cell populations and an increased risk of opportunistic infections. [3]

The target antigen ideally should be expressed at high density on the malignant T-cells. Most antibodies deliver their therapeutic effect by binding to the target on the cell surface, activating complement, antibody dependent cellular cytotoxicity (ADCC) or inducing signals activating apoptosis. The target receptor must be present in significant numbers on the cell surface to provide an adequate number of binding sites for the antibody. Down modulation and mutations in surface receptors can reduce binding of monoclonal antibodies interfering with

their therapeutic efficacy. Modulation of surface receptor expression is an important physiological characteristic used by normal and malignant cells to control responsiveness to cytokines and other receptor ligands. For unmodified monoclonal antibodies ideally the antibody target should be non-modulating so that adequate target antigen is always available for antibody to exert its therapeutic effect. Modulating receptors internalize antibody-receptor complex leaving limited numbers of surface receptors causing relative resistance. Modulation; however, can be used to an advantage with immunotoxins and ligand-toxin fusion proteins that need internalization to exert their action, but in general, modulation reduces the effectiveness of monoclonal antibodies.

Other characteristics of the ideal monoclonal antibody should include that the targeting of the antigen by the antibody should not lead to serious side effects. In addition to their immunogenicity causing infusion reactions and serum sickness, some monoclonal antibodies can stimulate the systemic release of inflammatory cytokines with serious consequences. A phase 1 dose-escalation trial testing an anti-CD28 monoclonal antibody (TGN1412) with 'super-agonist' effects on T-lymphocytes caused near-lethal acute systemic inflammation requiring hospitalization in six volunteers treated in a phase I study. [4]

3. Qualities of the antibody

Ideally the targeting antibody itself should be non-immunogenic, should act through several mechanisms of antitumor activity and have patient friendly dosing schedules and pharmacokinetics. [5] Current technologies has made it possible to engineer majority of antibodies in clinical use so that most of the molecule except for the receptor-binding domains is identical to that of a human antibody to reduce immunogenicity and the risk of neutralizing responses against the antibody. [6, 7]

3.1. Mechanism of action

Mechanisms of actions of monoclonal antibody action include induction of antibody-dependent cellular cytotoxicity (ADCC). A monoclonal antibody binds to its antigen target and recruits other components of cellular immune system such as NK cells, neutrophils, and eosinophils. These stimulated cells then attack and destroy the tumor cell. Some antibodies will directly bind to Fc receptors on effector cells such as macrophages and cytolytic T-cells causing destruction of the target cell through ADCC. [8]

Complement-mediated cytotoxicity (CMC) is another Fc-mediated mechanism of monoclonal antibody action. [9] It has been shown to play a roll in the antitumor activity of a number of antibodies including alemtuzumab. [10] In addition to CMC, complement fixation is also involved in inflammation, chemotaxis and opsonization, all of which may aid in tumor cell killing.

Monoclonal antibodies can also engage tumor cell surface receptors resulting into release of an apoptotic signal inducing tumor cell killing. Many of the cell surface markers including

those of the tumor necrosis factor receptor (TNFR) family, Fas, and the receptors for TNF-related apoptosis-inducing ligand (TRAIL) when engaged by their ligand deliver an apoptotic signal promoting apoptosis. Monoclonal antibodies can mimic the physiologic ligand of these receptors and can agonistically bind to receptor family members eliciting apoptotic responses on engagement. [11] A number of monoclonal antibodies are known to induce tumor cell apoptosis at least partially through direct engagement of their target receptor including SGN-30 a chimeric anti-CD30 antibody, and alemtuzumab (anti-CD52). [12, 13]

Monoclonal antibodies can also hinder cell growth and regulation through blocking critical ligand-receptor interactions necessary for tumor survival and inducing receptor and down-modulation reducing pro-growth signaling. Daclizumab, the anti-CD25 antibody, exert its main cytotoxic effect by blocking the binding of IL-2 to its receptors depriving T-cells of a necessary growth factor resulting in cell death. [14]

3.2. Immunogenicity of monoclonal antibodies

3.2.1. Non-human monoclonal antibodies

Scientists have attempted to produce single specificity monoclonal antibodies for therapy for more than a century now. Despite early optimism the development of monoclonal antibodies as therapeutic modality remained elusive due to the immunogenicity of monoclonal antibodies. It was only with the introduction of hybridoma technology in 1975 the promise of selectively targeting cancers using monoclonal antibodies became a reality. [15] Early therapeutic monoclonal antibodies were derived primarily from rodents. These antibodies can be produced in large amounts and have greater specificity to their single antigenic determinant compared to polyclonal antisera used for therapeutic purposes. Unfortunately early attempts to use these mouse or rodent antibodies for therapeutic purposes were unsuccessful in large part due to the dissimilarity between the rodent and human immune systems. Initially developed non-human antibodies, as foreign glycoproteins, had several issues hindering their effectiveness and development. These rodent hybridoma-derived antibodies exhibited short *in vivo* half-lives, were highly immunogenic in man often inducing neutralizing human anti-mouse antibodies (HAMA), and they could not engage Fc receptors expressed on human effector cells resulting in their inability at inducing ADCC making them relatively weak cytotoxic agents. Due to the foreign protein sequences serum sickness, infusion reactions and anaphylaxis were also common with these antibodies. In addition, many of these early non-human monoclonal antibodies were not directed against cell surface targets that were accessible to the antibody limiting their efficacy. First FDA approved monoclonal antibody in 1986 for treatment of allogeneic transplant rejection, Muromonab-CD3 (Orthoclone® OKT3), an anti-CD3 monoclonal antibody, is a non-human monoclonal antibody. [16]

3.2.2. Chimerized antibodies

Rapid neutralization of therapeutic antibodies due to formation of immune complexes between the non-human monoclonal antibody and induced host antibodies can severely limit tumor response and may alter antibody distribution and binding resulting in undesired side

effects. Engineering of non-human monoclonal antibodies with human constant domains, so called chimerized or humanized monoclonal antibodies, or the generation of fully human monoclonal antibodies using transgenic or phage display technology has helped overcome many of these issues of immunogenicity. [17-19]

Chimeric monoclonal antibodies are generated by linking the rodent light and heavy chain variable domains to the human immunoglobulin constant domains using recombinant DNA technology. [20] This results in an antibody that contains approximately 65% human sequences that exhibits reduced immunogenicity and an increased serum half-life. Although the immunogenicity of chimeric monoclonal antibodies is significantly reduced, they are occasionally still capable of eliciting a human anti-chimera response (HACA) in some patients.

3.2.3. Chimerized monoclonal antibodies

Second generation monoclonal antibodies were further improved by incorporating the six complementarity-determining regions (CDR) of the rodent antibody-antigen binding site onto a human IgG antibody framework. Further improvements in maintaining the structure of the antigen-binding site and high affinity binding to the target were made by incorporating small number of amino acids in the murine antibody not directly involved in the CDR. [21] Alemtuzumab is one such example. Although the binding between humanized antibodies and the dissociation constants (K_d) of humanized and the parental monoclonal antibody target is weaker than the murine parent, the differences between these are usually small enough to not be significant. [22, 23] Polymorphisms located in the constant regions, or to anti-idiotypic recognition of the variable domain can rarely result in human anti-human (HAHA) antibody responses. [24, 25]

3.2.4. Fully human monoclonal antibodies

To further enhance efficacy, "fully human" monoclonal antibodies have been generated using transgenic mice expressing human immunoglobulin genes. Vaccination of these mice using the desired antigen induces B-cells producing a fully human antibody by the mouse. Panitumumab (Vectibix®) an anti-EGFR monoclonal antibody [26], and ofatumumab (Azerra®), an anti-CD20 monoclonal antibody, were generated using such an approach. Phage display technology has also made it possible to develop fully human monoclonal antibody with significant clinical activity. Phage display techniques have the added benefit of also allowing the enhanced selection of therapeutically relevant features of antibodies. [27]

3.3. Fully human monoclonal antibodies

Most antibodies in clinical use exert their antitumor effect through direct antibody-mediated killing. In an effort to increase cytotoxic effect of monoclonal antibodies other modifications were made to enhance their affinity or cell toxicity by combining the antibody with a toxin or radioisotope.

The antibody Fc region mediates effector function and may be altered to augment binding to FcRIII, a stimulatory receptor and reduce binding to FcRII, an inhibitory receptor, to enhance

ADCC. One strategy is to engineer Fc portions that exhibit reduced fucose glycosylation. [28] Alternatively, the Fc region may be engineered to reduce or enhance CMC by substituting antibody isotypes such as IgG4 that exhibit little complement activation or Fc receptor binding. An additional interaction of the Fc region is with the neonatal receptor FcRn that is involved with immunoglobulin turnover. This receptor interacts with IgG Fc in a saturable and pH dependent manner, this allows FcRn to bind IgG from acidic endosomes generated during pinocytosis, and recycle the IgG back to the cell surface where it is released in the slightly basic pH of the blood. This allows for an extended antibody half-life. This approach holds much promise for favorably altering the pharmacokinetics of monoclonal antibodies ultimately leading to the potential for less frequent administration of these expensive treatments.

3.4. Immunotoxins

Immunotoxins are conjugations of monoclonal antibodies with toxins that result in highly specific cytotoxicity. In this approach it is desirable for the target antigen to be internalized upon antibody binding delivering the toxin into the cell. These toxins, often derived from bacteria or plants sources, are extremely potent. Bacterial toxins such as diphtheria toxin (DT) and *Pseudomonas* exotoxin A inhibit cellular protein synthesis by the irreversible ADP ribosylation of elongation factor-2 (EF-2), while plant toxins such as ricin inactivate ribosomes. [29] Disadvantages of this approach include the increased immunogenicity of most of these toxins because of their microbial or plant origins. In addition, many immunotoxin conjugates are non-specifically taken up by pinocytocytosis by endothelial cell resulting in a vascular leak syndrome with edema and weight gain. In 2011, Brentuximab vendotin (Adcetris®), an immunotoxin composed of an anti-CD30 monoclonal antibody (SGN-30) and the potent anti-microtubule agent monomethylauristatin (MMAE) was approved for previously treated anaplastic large cell lymphoma and Hodgkin's lymphoma. [30] Denileukin difitox (Ontak®) approved for the treatment cutaneous T-cell lymphoma is often categorized as an immunotoxin; however, this agent is not antibody-based, but rather represents a fusion protein between the receptor binding domain of interleukin-2 and diphtheria toxin linked by short peptide sequence. [31]

3.5. Radioimmunotherapy

Radioimmunotherapy combines the specificity of monoclonal antibodies with the tumor killing effects of radiation, in theory sparing non-target cells from exposure to high doses of radiation. The choice of an appropriate antigen target and hence the specific monoclonal antibody is critical, as off target killing needs to be avoided. One consequence of this is the "bystander" or "cross-fire" effect, as radiation can also kill adjacent tumor cells that may not express the target antigen. The greatest clinical experience with radioimmunotherapy is in CD20-expressing lymphomas using radionuclides such as yttrium-90 (⁹⁰Y) and iodine-131 (¹³¹I) labeled anti-CD20 monoclonal antibodies.

4. Antibody therapy for T-cell leukemias and lymphomas

4.1. Anti-CD2 antibodies

CD2 is a surface glycoprotein that plays a key role in lymphocyte adhesion and signaling. [32] It is expressed on human T-lymphocytes, natural killer (NK) cells, and thymocytes, and its stimulation results in T-cell activation and antigen co-stimulation. It also potentiates the physical interaction between T-cells and antigen presenting cells, as well as between T-cells and NK-cells. In the cell membrane, CD2 associates with the T-cell receptor (TcR) and appears to enhance CD3 signaling during low affinity interactions with the major histocompatibility complex (MHC) molecules enhancing class I and class II-restricted antigen recognition. [33]

Siplizumab is humanized IgG1 monoclonal antibodies that binds to CD2 and inhibits T-cell responses and induced severe T-cell lymphopenia. It has primarily been studied as treatment for refractory psoriasis and treatment for graft-versus-host disease occurring during allogeneic bone marrow transplant. It has shown to increase disease-free survival of mice inoculated with human MET-1 adult T-cell leukemia cells. [34] In a phase I/II trial [35], 29 patients with various T-cell malignancies including HTLV-1-associated adult T-cell leukemia, peripheral T-cell lymphoma, cutaneous T-cells lymphoma, T-cell chronic lymphocytic leukemia, and T-cell large granular lymphocyte leukemia were treated with siplizumab. Twenty-eight patients experienced a marked decline in circulating CD4+ and CD8+ T-cells, and NK-cells and there were two complete and nine partial responses. Unfortunately, four patients (13.7%) developed Epstein-Barr virus-related B-cell lymphoproliferative disease (EBV-LPD). [36] This complication has significantly hindered the development of siplizumab. A Phase I trial of siplizumab combined with rituximab and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) for T- and NK cell lymphoma is currently ongoing at the National Cancer Institute, where the rituximab is used to prophylaxis against the risk of EBV-LPD.

4.2. Anti-CD3 antibodies

CD3 represents a series of intermediate molecular weight polypeptide chains (CD3 γ , CD3 δ , CD3 ϵ and CD3 ζ) closely associated with α and β -subunits of the T-cell receptor (TcR) that recognizes antigen-peptide epitopes presented by MHC molecules in a class-restricted manner. [37] The intracellular regions of the CD3-subunits represent the signaling domains of the TcR complex that mediates T-cell activation. CD3 is expressed on most T-cells throughout development and thus represents a pan-T-cell antigen. The vast majority of T-cell neoplasms express CD3, although its expression may be reduced or lost in some lesions. [38]

Muromonab-CD3 (Orthoclone®, OKT3; Janssen Pharmaceutica, Ltd.), a murine IgG_{2a} monoclonal antibody directed against the 20 kDa CD3 ζ -subunit is approved for the reversal of acute allograft rejection in patients undergoing cardiac, hepatic and renal transplants. [39] It has also been used for the depletion of T-cells from stem cell and bone marrow allografts to treat or reduce the risk of serious GvHD. [40] Administration of muromonab-CD3 results in the rapid disappearance of CD3+ T-cells from the peripheral circulation and

lymphoid tissue through complement-mediated lysis, ADCC, apoptosis and the re-direction of T-lymphocytes to other compartments. [41] Binding of muromonab-CD3 to its target receptor also stimulates TcR signaling, activation and proliferation of T-cells with increased expression of HLA-DR and CD25.

In one report, a patient with refractory T-cell acute lymphoblastic leukemia that received muromonab-CD3 experienced a dramatic, albeit transient decline in circulating lymphoblasts and a reduction in splenomegaly. [42] Muromonab-CD3 therapy is made difficult because engagement of the antibody with CD3 ζ increases TcR signaling and can result in the release of inflammatory cytokines that can cause life-threatening cytokine release syndrome. In addition, muromonab-CD3 is also mitogenic for T-cells and its use may risk increasing the proliferation of malignant T-cells. Muromonab-CD3 therapy is also associated with profound suppression of cell-mediated immunity and increased risk of opportunistic infections and secondary malignancies including EBV-LPD, lymphoma, skin cancer and Kaposi's sarcoma.

4.3. Anti-CD4 antibodies

CD4 is a 55 kDa membrane glycoprotein with four immunoglobulin-like domains, a hydrophobic transmembrane domain and a long cytoplasmic tail. [43] CD4 acts as a co-receptor for the TcR complex. It is expressed on helper and regulatory T-cells, and it recognizes antigens presented by MHC class II molecules in association with the TCR. CD4 represents an attractive target since the majority of the post-thymic T-cell malignancies manifest a CD4+ phenotype.

In phase I study, seven CTCL patients were treated with a chimeric antibody composed of the IgG $_1$ κ human constant regions and the mouse variable regions directed against CD4 (anti-Leu3a). [44] Patients were dosed in cohorts of 10, 20, 40 or 80 mg intravenously twice a week for three weeks. At the 80 mg dose, the antibody was detected in skin lesions and also coating circulating CD4+ T-cells in the peripheral blood; however, with no significant depletion of CD4+ cells was observed. In a second study, this group administered a single intravenous dose of another chimeric murine anti-CD4 monoclonal antibody, cM-T412 (Centocor, Inc.), to eight previously treated CTCL patients. [45] Following the antibody infusion there was a significant suppression of peripheral blood CD4+ cells in seven of eight patients. Seven patients responded and the median duration of response was 25 weeks. One patient developed a neutralizing anti-chimeric antibody response. Toxicity was grade 2 or less and usually manifested as infusion reactions, myalgias, and rashes.

More recently, zanolimumab (HuMax-CD4®; Genmab, Inc.), a fully human IgG $_1$ κ anti-CD4 monoclonal antibody was shown to deplete CD4+ T-cells from the skin, reduce dermal inflammatory infiltrates and induce remissions in psoriasis patients. [46] Zanolimumab was evaluated in two separate phase II trials in a total of 47 CTCL/Sezary syndrome patients. [47] Patients received between 280 and 980 mg weekly for up to 17 weeks. Zanolimumab resulted in a dose-dependent and profound CD4+ lymphocytopenia; however, the recovery of CD4+ cells. Overall 13 of 38 (34.2%) CTCL patients and 2 of 9 (22.2%) patients with Sezary cell leukemia responded to the antibody. Adverse events included nine infections attributed to therapy. In a second phase II study, 21 adult patients with relapsed or refractory CD4+ PTCL of non-cutaneous type were treated in a single-arm multicenter study, with

weekly intravenous infusions of zanolimumab 980 mg for 12 weeks. [48]. Objective tumor responses were observed in 24% of the patients with two complete responses and three partial responses. In general, the drug was well tolerated with no major toxicity. Zanolimumab at a dose of 980 mg weekly demonstrated clinical activity and an acceptable safety profile in this poor-prognosis patient population, suggesting that the potential benefit combining zanolimumab with standard chemotherapy in the treatment of PTCL should be investigated.

4.4. Anti-CD5 antibodies

CD5 (Leu-1) is a 67 kDa cysteine-rich scavenger receptor family glycoprotein expressed on T-cells and the B1a subset of B-cells. [49, 50] CD5 acts as a co-receptor and appears to regulate the signaling strength of the TcR signaling response. It may also play a similar role in modulating B-cell receptor signaling. [51] Current evidence indicates that CD5 is a key regulator of immune tolerance. Two small clinical trials have examined the use of anti-CD5 antibodies in patients with T-cell lymphoma. In one trial, 7 patients with refractory Leu-1+ (CD5+) T-cell lymphoma, six with CTCL and one with PTCL, were treated with murine anti-Leu-1 monoclonal antibody at doses of 0.25 to 100 mg administered 2-3 times per week. [52] A decrease in circulating T-cells was observed. The decline in T-cells was short-lived with a return to baseline occurring within 24-48 hours. The target antigen demonstrated down-modulation suggesting that CD5 might be a less suitable target for an unmodified antibody strategy. Five short-lived responses were reported and not surprisingly the majority of patients treated developed neutralizing antibodies. In another trial, T101, a murine IgG_{2a} anti-CD5 monoclonal antibody was administered to eight patients with CD5+ T-cell malignancies, four of which had CTCL. [53] Short-lived clinical improvements were noted in two CTCL patients. Again, the induction of neutralizing antibodies was limiting. More recent trials of CD5-targeted therapy have focused on treatment of B-cell-induced autoimmune diseases and purging of T-cells from bone marrow to prevent GvHD and have used immunotoxin conjugates of anti-CD5. [54-56]

4.5. Anti-CD25

CD25 (IL-2R α) is the 55 kDa subunit of the interleukin-2 (IL-2) receptor, and plays a critical role mediating immune-modulatory function of IL-2 in the activation of T- and B-lymphocytes, NK-cells and macrophages. [57, 58]. Less than 5% of un-stimulated peripheral blood T-cells expresses the IL-2R α ; however, it is highly expressed on activated T-cells and on many B- and T-cell neoplasms such as ATL, ALCL, CTCL, hairy cell leukemia, and on the Reed-Sternberg cells of Hodgkin's lymphoma. [59]

In 1981, Uchiyama and coworkers generated murine anti-Tac that defined the human IL-2R α (CD25). [60] Daclizumab (Zenapax®; Hoffmann-La Roche, Inc.) is a recombinant monoclonal antibody where murine antigen-binding regions of the anti-Tac molecule were joined to a human immunoglobulin framework, approximately 90% of the murine IgG_{2a} has been replaced with a human IgG_{1k} sequence. [61] Daclizumab has the advantages of a low frequency neutralizing antibodies, a significantly prolonged serum half-life compared to murine anti-

Tac, and the ability to mediate ADCC through its humanized Fc-domain. [62] It inhibits IL-2-induced activation of T-cells and it is approved for the prophylaxis of renal allograft rejection in combination with other immunosuppressive drugs.

Daclizumab up to 8 mg/kg was administered to ATL patients in one phase I/II trial. [63] Cohorts of patients were treated with daclizumab 2 mg/kg on days 1 and 2, or 4, 6, or 8 mg/kg as a single intravenous dose every 2 or 3 weeks to complete six doses. Although Daclizumab showed modest clinical activity (2 partial response and 3 patients with improvement of their skin disease), flow cytometry analysis of the peripheral blood 72 hours after the first dose and at weeks 2, 5 and 14 showed that $\geq 95\%$ saturation of IL-2R α on circulating ATL cells could be achieved and maintained. In six patients that underwent lymph node fine needle aspiration, receptor saturation was documented in only half and it was not maintained suggesting that the impeded access of large antibody molecules into tumor is a potential blockade to receptor-directed therapy.

4.6. Anti-CD30 antibodies

CD30 is a cellular membrane protein member of the tumor necrosis factor receptor (TNFR) family expressed on activated T- and B-cells. It is highly expressed on HL Reed–Sternberg (RS) cells, in anaplastic large cell lymphoma (ALCL), embryonal carcinomas, and select subtypes of B-cell derived, non-Hodgkin's lymphomas and mature T-cell lymphomas. The immunotoxin brentuximab vedotin (Adcetris®, SGN-35) was approved by the FDA in 2011 and became the first new treatment for HL in 30 years. Brentuximab vedotin is an antibody-drug conjugate between the antitubulin agent monomethylauristatin E (MMAE) and the anti-CD30 monoclonal antibody cAC10. Clinical studies with unconjugated anti-CD30 antibodies have shown disappointing clinical activity. [64] Objective responses were observed in 6% of patients with HL who were treated with MDX-060 and in none of those treated with cAC10 (SGN-30). However, the results of a pivotal phase II study of brentuximab vedotin in relapsed or refractory HL were impressive [65]. In this study, 102 patients with refractory or relapsed classical HL received brentuximab vedotin every 3 weeks for a median of 27 weeks. Almost all patients exhibited a reduction in tumor volume with 34% complete response and 40% partial response. A phase II multicenter trial evaluated the efficacy and safety of brentuximab vedotin in relapsed or refractory systemic anaplastic large-cell lymphoma (ALCL) patients as CD30 is uniformly expressed in ALCL. [66] Fifty-eight patients received brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks and 50 patients (86%) achieved an objective response, 33 patients (57%) achieved a complete remission (median duration 13.2 months) and 17 patients (29%) achieved a partial remission. Grade 3 or 4 adverse events observed in $\geq 10\%$ of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral neuropathy (12%). Based on these studies, brentuximab vedotin received accelerated approval for the treatment of Hodgkin lymphoma that has relapsed after autologous stem cell transplant and for the management of relapsed ALCL. Currently multiple studies are evaluating combination of brentuximab vedotin combined with standard chemotherapy options in management of both newly diagnosed and relapsed refractory ALCL patients.

4.7. Alemtuzumab (anti-CD52)

CD52 is a glycosylphosphatidylinositol (GPI)-anchored antigen expressed at high density on normal and malignant T- and B-cells, NK cells, monocytes, macrophages, eosinophils and epithelial cells of the male genital tract. It is not expressed on hematopoietic stem cells, granulocytes, erythrocytes, platelets, or plasma cells. Alemtuzumab (Campath®) a humanized rat monoclonal antibody targeting CD52 was approved by FDA for the treatment of relapsed/refractory B-cell chronic lymphocytic leukemia (CLL). [67] Due to the presence of CD52 on T-cells and the antibody's ability to activate several mechanisms of cell death including ADCC, CMC and apoptosis it is an attractive agent to study in T-cell malignancies.

T-cell prolymphocytic leukemia (T-PLL) carries a worse prognosis than CLL and has no established standard therapy and thus constituted a fitting model to study alemtuzumab. An initial trial in 39 T-PLL patients showed an overall response rate of 76%, including 60% complete responses to alemtuzumab. [68] A subsequent study reported the experience with alemtuzumab in 76 T-PLL patients. [69] The objective response rate was 51% with almost 40% patients achieving complete response with median response duration of 8.7 months. The most common treatment-related adverse events were acute infusion reactions. There were 2 treatment-related deaths, 15 infectious episodes in 10 patients during active treatment, and 8 patients experienced late-onset infections due to the long lasting lymphopenia associated with alemtuzumab treatment.

These promising results in T-PLL lead to additional trials of alemtuzumab in both cutaneous T-cell lymphoma and other systemic T-cell malignancies either as a single agent or combined with chemotherapy. Single agent alemtuzumab is active in a variety of T-cell malignancies; however, responses are not durable and the risks of immunosuppression and development of opportunistic infections in patients poses a significant problem. In a phase II trial, alemtuzumab was administered to 22 patients with advanced mycosis fungoides/Sézary syndrome (MF/SS). The overall response rate was 55%, with 32% of patients achieving a complete remission. [70] Remarkably after treatment, Sézary cells were undetectable in blood in 6 of 7 (86%) SS patients and pruritis significantly improved in responding patients. Patients with erythroderma responded better than patients with thick plaque disease or skin tumors.

In a pilot study, 14 patients with heavily pretreated peripheral T-cell lymphoma (PTCL) that received alemtuzumab for a maximum of 12 weeks showed a response rate of 36%. [71] Toxicity included cytomegalovirus (CMV) reactivation in 6 patients, pulmonary aspergillosis in 2 patients, and pancytopenia in 4 patients. Another trial reported on the efficacy of the combination of alemtuzumab combined with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) as initial therapy for 24 PTCL patients. [72] The overall complete response rate was 71% (17 patients) and 1 patient had partial remission. Grade 4 neutropenia and CMV reactivation was frequent. JC virus reactivation, invasive pulmonary aspergillosis, staphylococcal sepsis and pneumonia were also seen. In a recently reported phase II trial by the Dutch-Belgian HOVON group, 20 T-cell lymphoma patients were treated with 30 mg of alemtuzumab three times per week with every two week CHOP for eight courses. [73] The overall response was 90% and the median overall survival and event-free survival were 27 and 10 months, respectively. Although alemtuzumab-intensified CHOP achieved a high number of responses,

many patients ultimately still relapsed, and this treatment was associated with frequent serious infection-related adverse events.

The combination of intravenous alemtuzumab 30 mg three times weekly and weekly pentostatin 4 mg/m² was studied in 24 patients with a variety of T-cell leukemias and lymphomas. [74] This trial showed an overall response rate of 54% with 11 complete responses and median response duration was 19.5 months. As with other trials opportunistic infections due to severe T-cell dysfunction were common in spite of antimicrobial prophylaxis.

4.8. Anti-CD122 (Mik-β1) antibodies

CD122 (IL-2R/IL-15Rβ) is a 75 kDa glycoprotein that constitutes the β-subunit shared by the IL-2 and IL-15 receptors. During signal transduction, CD 122 and CD132, the common γ-chain of type I cytokine receptors, recruit janus kinase (JAK), that in turn activates the signal transducer and activator of transcription (STAT). Activated STAT transcription factors enhances specific gene expression after translocation to nucleus. T-cell large granular lymphocyte (T-LGL) leukemia commonly presents with anemia, neutropenia and less frequently thrombocytopenia. IL-2 and IL-15 can stimulate T-LGL and NK cells and it is thought that the clinical cytopenias seen in T-LGL leukemia are a result of the enhanced NK activity of the leukemic cells. The Mik-β1 antibody (anti-CD122), directed against the IL-2R/IL-15Rβ, can inhibit IL-15-mediated effects *in vitro*. [75]

In a phase I trial, 12 patients with T-LGL leukemia received the murine Mik-β1 antibody and showed no responses in terms of decreases in T-LGL cell counts or improvement in their cytopenias. [76] Greater than 95% saturation of CD122 on circulating T-LGLs was achieved in all patients and down-modulation of CD122 was observed in seven patients. The lack of response may be the result of the short half-life of the murine antibody. In addition, down-modulation of CD122 after binding of the antibody reduced the amount of the receptor on the surface of the LGL cells and might have impacted the efficacy of the Mik-β1 antibody. A phase I safety and pharmacokinetic study of the humanized form of the antibody, HuMik-β1, in T-LGL leukemia patients was recently completed, but the results are not available.

4.9. KW-0761 (anti-CCR4)

Chemokine receptor-4 (CCR4) is over expressed on several T-cell neoplasms in addition to its normal expression on T-helper type 2 and regulatory T-cells. [77]. KW-0761 is a humanized IgG1 monoclonal antibody with a defucosylated Fc region that markedly enhances ADCC due to its increased binding affinity to the Fcγ receptor on effector cells. [78]. In a Phase I trial in 16 patients with relapsed CCR4-positive adult T-cell leukemia/lymphoma (ATL) or PTCL received KW-0761 once a week for 4 weeks by intravenous infusion. Toxicities included infusion reactions and skin rashes. The objective response rate was 31% with two complete and three partial responses. [79] Recently a multicenter phase II study conducted on 28 patients with relapsed ATL showed overall objective response rate of 50%, including eight complete responses, with a median progression-free and overall survival of 5.2 and 13.7 months, respectively. [80] The most common adverse events were infusion reactions (89%) and skin

rashes (63%), which were manageable and reversible in all cases. Based on these results, a multicenter randomized phase II trial is ongoing comparing KW-0761 with standard second-line therapy according to investigator's choice of pralatrexate, gemcitabine and oxaliplatin, or dexamethasone, cisplatin and cytarabine in previously treated relapsed ATL.

5. Conclusions

T-cell leukemias and lymphomas represent a heterogeneous group of uncommon diseases that often present with advanced stage disease and systemic symptoms. Historically they have been treated with combination chemotherapy similar to high-grade B-cell lymphomas; however, outcomes have been poorer. One of the reasons for this may be the lack of effective monoclonal antibody therapy for these diseases comparable to that of rituximab for the B-cell disorders. A number of antibodies targeting surface receptors on T-cells are being clinically studied. Alemtuzumab, a CD52-directed monoclonal antibody has demonstrated antitumor activity as a single agent and in combination with chemotherapy, but with increased risk of serious opportunistic infections. Zanolimumab and KW-0761 directed against CD4 and CCR4 expressed on T-cells, have also show an activity against CTCL and ATL, respectively and are being studied in ongoing clinical trials and offer hope for the future for patients with T-cell malignancies.

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