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Antibody Therapy for CLL

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Abstract

The introduction of the monoclonal antibodies rituximab (anti-CD20) and alemtuzumab (anti-CD52) has revolutionized the treatment of chronic lymphocytic leukemia (CLL). Both antibodies were first studied as single agents in relapsed CLL, but rituximab is increasingly used in combination chemoimmunotherapy regimens in previously untreated patients. Phase II studies demonstrated that the addition of rituximab to fludarabine-based chemotherapy improves complete response (CR) rates and progression-free survival (PFS), but long-term survival benefit has not been shown. Alemtuzumab is less commonly used, due to its greater infusion, hematologic and immune toxicity. Subcutaneous (SC) administration significantly reduces infusion toxicity, but hematologic and infectious complications, most notably cytomegalovirus (CMV) reactivation, still occur with SC dosing. Alemtuzumab's unique clinical properties include its clinical activity in relapsed CLL patients with del(17p13) and its ability to eradicate minimal residual disease (MRD) in bone marrow. Its use as consolidation therapy to eradicate MRD after nucleoside analog therapy is under active study. Several investigational monoclonal antibodies are in preclinical or clinical studies, most notably lumiliximab (anti-CD23) and ofatumumab (HuMax CD20), and are briefly discussed in this review.

Introduction

Indolent B-cell lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) are ideal targets for monoclonal antibody therapies. In contrast to acute leukemias or aggressive lymphomas, which are characterized by uncontrolled growth and a high proliferative index, failure to undergo programmed cell death, or apoptosis, constitutes the primary cellular defect in CLL. Furthermore, the inherent resistance of CLL to chemotherapy arises from this defective apoptosis. Anti-apoptotic proteins such as Bcl-2, Mcl-1 and X-linked inactivator of apoptosis (XIAP) are over-expressed in CLL, and high levels of Mcl-1 are associated with failure to achieve complete response (CR) to initial therapy with fludarabine (1). While antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are potential mechanisms of action (2,3), monoclonal antibodies exert their anti-cancer effects in CLL, at least in part, by directly inducing apoptosis (15,16). The success of monoclonal antibodies in CLL may depend upon multiple mechanisms of action, and the relative importance of ADCC, CDC and induction of apoptosis may differ *in vivo* among individual antibodies.

The introduction of monoclonal antibodies such as rituximab and alemtuzumab revolutionized the treatment of CLL. However, the optimal use of monoclonal antibodies in the treatment of

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CLL is an area of vigorous, ongoing clinical research. As this chapter will review, monoclonal antibodies have modest response rates when used alone and have limited activity against bulky lymphadenopathy. Therefore, much current clinical research in CLL focuses on the most effective use of monoclonal antibodies in combination with nucleoside analog-containing chemotherapeutic regimens. In addition, monoclonal antibodies such as alemtuzumab are being studied as a potential consolidation therapy to eradicate minimal residual disease (MRD) after induction cytotoxic chemotherapy. Finally, several investigational monoclonal antibodies under pre-clinical and clinical study will be discussed briefly.

RITUXIMAB

Rituximab (Rituxan, Mabthera), a chimeric murine-derived monoclonal antibody that recognizes the CD20 antigen on the surface of normal and malignant B cells, is the best studied and most widely used monoclonal antibody in CLL and indolent B-cell non-Hodgkin's lymphomas (B-NHL). CD20, a calcium channel that interacts with the B-cell immunoglobulin receptor complex, is expressed on virtually all CLL and B-NHL. However, there are several differences in CD20 and rituximab between CLL and B-NHL. In contrast to B-cell lymphomas, which uniformly express CD20 strongly, CD20 expression on CLL cells is weak. *In vitro* and *in vivo* data indicate that rituximab exerts its anti-cancer effects through more than one mechanism of action, and the relative importance of these mechanisms may differ between CLL and B-NHL. Rituximab induces both ADCC and CDC, but caspase 3 activation and induction of apoptosis appear to play a more important role in CLL than in B-NHL (2–5). Complement activation may be important, as increased expression of complement inhibitors CD55 and CD59 resulted in resistance to rituximab in B-NHL cell lines and CLL cells (3,6).

A dosing schedule of 375 mg/m^2 IV weekly for 4 doses was empirically established by initial studies of rituximab in indolent B-NHL. In the pivotal phase II trial of rituximab in 166 patients with relapsed or refractory indolent B-NHL, only 4 of 30 patients with small lymphocytic lymphoma (SLL) or CLL responded (13%), in contrast to an overall response rate (ORR) of 60% in follicular B-NHL (7). Several other studies obtained similarly modest results in CLL/SLL (8–10). Only 7 of 28 patients (25%) in a German CLL Study Group (GCLLSG) achieved partial response (PR) with a median duration of only 20 weeks (11). Similarly, a Nordic study of 24 CLL patients observed ORR 35% with short remission duration (12). One explanation for the limited activity of weekly rituximab in relapsed CLL/SLL may be the weak expression of CD20 on CLL cells.

To improve clinical activity, rituximab 375 mg/m^2 weekly for 8 doses was administered to 31 patients with Rai stage 0, I and II CLL with beta-2 microglobulin levels ≥ 2.0 mg/dl (median 3.6), without other indication for therapy (13). ORR was 90%, but only 19% of patients achieved CR. A similar study demonstrated an ORR of 51% (CR 4%) in 44 previously untreated CLL/SLL patients after 4 weekly doses (14). Twenty-eight patients with stable or responsive disease received additional 4-week courses of rituximab every 6 months for up to 4 cycles, which modestly increased ORR (58%) and CR (9%). The median PFS of 19 months in this study was comparable to that attained by single agent fludarabine in the upfront setting (15). These studies are summarized in Table 1.

These disappointing response rates led to two trials that attempted to improve the clinical activity of rituximab by dose escalation. The MD Anderson maintained weekly dosing but escalated the rituximab dose to 2,250 mg/m^2 in 50 patients with previously treated CLL (n=40) or other B-cell leukemias (n=10). ORR was 40%, and median response duration was 8 months (16). A dose-response relationship was observed; ORR was 22% at 500–850 mg/m^2, compared to 75% at 2,250 mg/m^2. In an alternative approach, 33 patients with relapsed or refractory SLL/CLL received thrice weekly rituximab for 4 weeks (17). To minimize the increased infusion-

related toxicity resulting from circulating tumor CLL cells in peripheral blood, "stepped up" dosing giving 100 mg over 4 hours on day 1 and 375 mg/m^2 thereafter was utilized. ORR was 45% (CR 3%), and median response duration was 10 months. Thirteen patients developed transient, cytokine-associated infusion toxicity that resolved by the third infusion. As in previous studies, rituximab demonstrated greatest activity against peripheral blood disease, with less activity in bulky nodal disease, and complete responses remained rare. Furthermore, thrice weekly rituximab failed to achieve a single response in patients with del(17p13) corresponding to loss of the p53 tumor suppressor gene (18). Thus, these studies showed that, while rituximab is active in CLL, administration as a single agent will not change the long-term prognosis in CLL.

RITUXIMAB AND CHEMOIMMUNOTHERAPY

Fludarabine and rituximab (FR)

The combination of rituximab and nucleoside analogs has proven to be tolerable and clinically active, and the development of so-called chemoimmunotherapy has changed the upfront therapy of CLL in the United States (Table 2). The CALGB 9712 study randomized 104 previously untreated CLL patients to sequential or concurrent fludarabine and rituximab (FR) therapy (19). Patients received standard fludarabine 25 mg/m^2 days 1–5 every 28 days for 6 cycles, with or without concurrent rituximab 375 mg/m^2 on day 1 of each cycle, with an additional dose on day 4 of cycle 1. Patients in both arms received rituximab 375 mg/m^2 weekly for 4 doses beginning 2 months after completion of fludarabine. Superior CR (47% vs. 28%) and OR (90% vs. 77%) rates were observed in the concurrent FR arm, compared to patients in the sequential arm. While patients with high-risk disease, defined as having unmutated IgVH, del(11q22) or del(17p13), were as likely to achieve CR as patients without high-risk features, they relapsed faster and had an inferior median progression-free survival (PFS, 32 months vs. 43 months) (20). A retrospective comparison to 179 previously untreated patients who received single agent fludarabine in the CALGB 9011 study showed that patients who received FR attained superior ORR (84% vs. 63%), CR (38% vs. 20%), 2-year PFS (67% vs. 45%) and 2-year overall survival (OS, 93% vs. 81%) (21).

A multi-center European phase II study administered fludarabine 25 mg/m^2 days 1–5 every 28 days for 6 cycles, and rituximab 375 mg/m^2 on day 1 of cycles 3–6, to 31 evaluable CLL patients. ORR and CR were 87% and 32%, respectively, with similar outcomes in previously treated (ORR 91%, CR 45%) and untreated patients (ORR 85%, CR 25%). Sixteen patients developed a total of 32 infections, and 1 patient died of cerebral hemorrhage resulting from prolonged thrombocytopenia (22).

Fludarabine, Cyclophosphamide, and Rituximab (FCR)

The most promising phase II results with chemoimmunotherapy in both previously treated and untreated CLL have been attained by the MD Anderson with its combination regimen of fludarabine, cyclophosphamide and rituximab (FCR). Fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 2–4 of cycle 1 and days 1–3 of cycles 2–6, and rituximab 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2–6, was given every 28 days for 6 cycles to 177 patients with relapsed CLL (23). Toxicity was acceptable, and infectious complications were manageable. ORR was 73%, with 25% CR and 16% nodular PR, and 12 of 37 patients (32%) in CR achieved molecular remission. FCR was then administered to 300 previously untreated CLL patients; ORR was 94%, with 72% CR, 4-year relapse free survival (RFS) 77%, and 4-year overall survival (OS) 83% (24). The ability to achieve ≤ 1% residual CLL by two-color flow cytometry significantly affected RFS and OS. Five of 138 patients (4%) whose post-FCR bone marrow flow cytometry demonstrated ≤ 1%

residual CLL developed relapse, in contrast to 17 of 62 patients (27%) with > 1% residual CLL. The activity of FCR in patients with poor prognostic factors was not assessed.

Pentostatin, cyclophosphamide and rituximab (PCR)

While FR and FCR achieved excellent results, median age of patients in these studies was 63 and 58 years, respectively. There are limited data on the toxicity profile and efficacy of chemoimmunotherapy regimens in patients > 70 years of age, who comprise the majority of patients in community practice but a minority of patients in clinical studies. A phase II study of pentostatin, cyclophosphamide and rituximab (PCR) in 64 previously untreated CLL patients, including 18 who were ≥ age 70, indicated that PCR is effective in and well-tolerated by older patients (25). Median age was 62.5 years, and 71% of patients had unmutated IgVH. Patients received pentostatin 2 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1, and rituximab 375 mg/m^2 on day 1 (100 mg/m2 on day 1 and 375 mg/m^2 on days 3 and 5 of cycle 1) every 21 days for up to 6 cycles. Filgrastim was administered beginning on day 3. PCR was well tolerated, and OR, CR and nPR (define nPR) rates were 91%, 41% and 22%, respectively. Median PFS was 33 months. The ability to achieve CR/nPR was independent of high-risk genetic or biological factors, with the exception that all 3 patients with del(17p13) failed to achieve CR or nPR.

Patients ≥ age 70 tolerated PCR as well as patients < age 70, except that older patients were more likely to require a dose delay > 1 week (28% vs. 7%, p=0.03) (26). Grade 3–4 hematologic (61% vs. 48%), infectious (6% vs. 11%) and other non-hematologic toxicities (22% vs. 28%) were similar in older and younger patients. OR and CR rates were similar in older and younger patients (83% vs. 93%, 39% vs. 41%). Event-free survival (EFS) was identical for both groups (p=0.98). Thus, PCR is a therapeutic option for previously untreated CLL patients ≥ age 70, who constitute more than half of patients requiring initial CLL therapy. Prophylactic antibiotics and filgrastim should be used as prescribed in this study. Table 2 summarizes the major clinical studies of chemoimmunotherapy regimens which included rituximab.

ALEMTUZUMAB

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody against CD52 (27–30). CD52 is a 21–28 kD cell surface glycopeptide expressed on virtually all human lymphocytes, monocytes and macrophages, a small subset of granulocytes, but not erythrocytes, platelets or bone marrow stem cells. CD52 is expressed on all CLL cells and indolent B-NHL cells (29, 31). Cross-linking of CD52 on B-cell and T-cell lymphoma cell lines inhibited cell proliferation (32). In CLL cells, alemtuzumab induced apoptosis, CDC and ADCC *in vitro.* The ubiquitous expression of CD52 on normal lymphocytes and monocytes predicted the increased neutropenia, lymphopenia and infectious complications that accompany clinical use of alemtuzumab.

Phase I studies established a safe dose of 30 mg IV three times per week for 4–12 weeks in relapsed CLL. Alemtuzumab induced significantly more infusion toxicity than rituximab, but stepped-up dosing diminished infusion toxicity and made administration feasible and tolerable. Phase I studies administered 3 mg on day 1, 10 mg on day 2, and 30 mg on day 3 and thrice weekly thereafter. The role of alemtuzumab in CLL was established by several studies, which are summarized in Table 3 (33–36). A multi-center, European phase II study gave alemtuzumab 30 mg thrice weekly for up to 12 weeks to 29 recurrent and refractory CLL patients. ORR was 42%, and 1 patient (4%) achieved CR (36). Alemtuzumab cleared peripheral blood CLL cells in 97% of patients, but was less effective at eliminating marrow (36%) or nodal disease (7%).

The pivotal CAM211 trial administered the same regimen to 93 fludarabine-refractory CLL patients. Prophylactic anti-bacterial and anti-viral antibiotics were given, and toxicity was

manageable. ORR was 33%, and 2% of patients achieved CR (34). Median time to progression for responders was 9.5 months; median OS was 16 months for all patients and 32 months for responders. The median peripheral blood CLL count decreased by more than 99.9%, but the antibody was markedly less effective in patients with bulky lymph nodes greater than 5 cm in diameter. While 90% of patients with lymph nodes measuring less than or equal to 2 cm responded, with 64% achieving resolution of their adenopathy, only 12% of patients with lymph nodes greater than 5 cm responded with no patients attaining nodal resolution. Patients with poor performance status did markedly worse, with increased hematologic and infectious toxicity, and only patients with ECOG performance status 0–1 responded to treatment. The activity of alemtuzumab in CLL was confirmed by a multi-center, compassionate use study in 136 fludarabine-refractory patients (37).

Eradication of MRD

In sharp contrast to rituximab, alemtuzumab is able to eradicate MRD in the bone marrow. A British study administered alemtuzumab 30 mg IV thrice weekly for up to 16 weeks (median 9 weeks) to 91 relapsed CLL patients (38). ORR was 54%, and 18 patients achieved a flow negative bone marrow after alemtuzumab. With a median follow-up of 36 months, median treatment free survival was significantly longer (not reached) in patients with MRD negative marrow than in patients who achieved MRD positive CR (20 months) or MRD positive PR (13 months). Five-year OS was 84% for the 18 MRD negative patients. Thus, the ability to achieve an MRD negative bone marrow translated into improved long-term survival. However, this study also illustrated alemtuzumab's limited activity as a single agent against bulky nodal disease (38). ORR was 87% in 33 patients with no lymphadenopathy (CR 72%), compared to only 9% (CR 0%) in 11 patients with lymph nodes greater than 5 cm. Similarly, median OS was 30 months for patients with all lymph nodes less than 5 cm, compared to 9 months for patients with a lymph node greater than 5 cm.

Activity in del(17p13) and other high-risk CLL

Another feature which distinguishes alemtuzumab from rituximab is the former's clinical activity in patients with del(17p13). While only 5% of CLL patients have del(17p13) at diagnosis, up to half of patients acquire this abnormality as their disease progresses over time. Patients with relapsed CLL with del(17p13) are resistant to most standard therapies and constitute the worst prognostic group in CLL (39,40). A retrospective analysis of 36 relapsed CLL patients who received alemtuzumab revealed that 6 of 15 patients (40%) with del(17p13) responded to therapy (41). Alemtuzumab is also active in other high-risk groups; the same study demonstrated responses in 3 of 11 patients (27%) with del(11q22) corresponding to loss of the AMT tumor suppressor gene. Thus, alemtuzumab is able to eradicate MRD and achieve clinical responses in high-risk relapsed patients, including those with del(17p13) (42). These positive attributes make alemtuzumab an important anti-CLL agent, despite its infusion, hematologic and infectious toxicity.

Subcutaneous (SC) administration

In order to diminish infusion toxicity associated with IV alemtuzumab, the German CLL Study Group administered alemtuzumab 3, 10 and 30 mg IV during week 1, followed by 30 mg SC thrice weekly for 4–12 weeks (43). Forty-six relapsed CLL patients, with a median of 4 prior therapies, received a median of 838 mg (of 1123 planned mg) of alemtuzumab. Although infusion toxicity was reduced, treatment was interrupted in 29 patients due to neutropenia (15), infection (8) or other cytopenias (3). Alemtuzumab was discontinued early in 26 patients due to lack of response (12), infection (4) or neutropenia (3). ORR (36%), CR (2%), median PFS (9.7 months) and median OS (13.1 months) were similar to results achieved with IV alemtuzumab in the CAM211 study. Furthermore, responses were observed in 7 of 13 patients

(54%) with del(17p13) and in 5 of 13 patients with del(11q22). Thus, SC administration of alemtuzumab appeared to be as effective as IV dosing, particularly in high-risk patients, suggesting that SC administration may be able to replace the more cumbersome IV dosing schedule.

Single agent alemtuzumab in previously untreated patients

A phase II clinical trial administered alemtuzumab 30 mg SC thrice weekly for up to 18 weeks to 41 previously untreated patients with CLL. Except for transient grade 1–2 fever, first-dose reactions were minimal. ORR was 81%, and 87% of patients (n=38) who received at least 2 weeks of treatment responded (44). Alemtuzumab effectively cleared peripheral blood (CR 95%) and bone marrow (CR + nodular PR 66%), but was less effective against nodal disease (CR 29%). Some patients who achieved CR in the marrow required 18 weeks of therapy to do so, suggesting that prolonged SC administration may be necessary to attain maximal clinical benefit. Median time to treatment failure was not reached at publication (18+ months). Based on these promising results in the upfront setting, the CAM307 study prospectively randomized 297 previously untreated CLL patients to oral chlorambucil 40 mg/m2 every 4 weeks for 12 cycles or alemtuzumab 30 mg IV three times per week for up to 12 weeks (45). All patients in the alemtuzumab arm received prophylaxis for pneumocystis carinii pneumonia (PCP) and VZV (define VZV), and a median of 11.7 weeks of antibody was delivered. Alemtuzumab achieved superior ORR (83% vs. 55%), CR (22% vs. 2%), and PFS. Additionally, this trial prospectively demonstrated that patients with del(17p13) had a superior response to alemtuzumab than to chlorambucil, with a median PFS of 10.7 months compared to 2.2 months. Grade 3–4 hematologic toxicity was not different in the two treatment arms, but 52% of patients in the alemtuzumab arm reactivated CMV, in contrast to only 3% of patients who received chlorambucil. Thus, close monitoring of CMV is mandatory, even when alemtuzumab is given in the upfront setting.

Alemtuzumab and Chemoimmunotherapy

There have been fewer studies of alemtuzumab-based chemoimmunotherapy than of rituximab-based regimens, partly due to the greater hematologic and infectious toxicity of this antibody compared to rituximab. A small study of CLL patients, refractory to fludarabine alone and alemtuzumab alone, suggested that synergy might exist clinically between these two agents (46). Fludarabine 25 mg/m^2 IV on days 3–5 and alemtuzumab 30 mg IV thrice weekly for 8 to 16 weeks were administered to 6 patients. Five patients responded, with 1 CR, and 2 patients achieved MRD negative disease by flow cytometry. Patients received prophylaxis for PCP and VZV, and no serious adverse events were noted. A German study confirmed these findings in a phase II study of 36 relapsed CLL patients, who received fludarabine 30 mg/m^2 IV and alemtuzumab 30 mg IV for 3 days every 28 days for 4–6 cycles, based on toxicity and response (47). ORR was 83%, with 30% CR, median time to progression (TTP) 13 months, and median OS 36 months. One heavily pre-treated patient died of fever of unknown origin, but infectious toxicity was otherwise tolerable. Median CD4 counts did not return near normal for 14–18 months, so prolonged PCP and VZV prophylaxis was given.

FCR + Alemtuzumab (CFAR)

The MD Anderson added alemtuzumab to its FCR regimen, to determine whether alemtuzumab would add clinical activity with tolerable toxicity. Seventy-eight relapsed CLL patients received fludarabine 25 mg/m^2 on days 2–4, cyclophosphamide 250 mg/m^2 on days 2–4, rituximab 375 mg/m^2 (cycle 1) or 500 mg/m^2 (cycles 2–6) on day 2, and alemtuzumab 30 mg IV on days 1, 3 and 5 every 28 days for up to 6 cycles (48). Patients received pegfilgrastrim, as well as prophylaxis for pneumocystis carinii pneumonia (PCP) and cytomegalovirus (CMV). Grade 3–4 neutropenia and thrombocytopenia were observed in 89% and 59% of patients,

respectively. The incidences of major infections (11%), minor infections (28%), and fever of unknown origin (36%) were similar to that observed with FCR in the relapsed setting. However, prophylactic valganciclovir was significantly more effective in preventing CMV reactivation (3 of 30 patients, 10%) than prophylactic valacyclovir (25 of 48 patients, 52%). ORR was 65% (CR 24%); median PFS was 27 months for the 19 patients achieving CR, compared to only 10 months for the 32 patients attaining PR. CFAR was more active in patients who were sensitive to their last fludarabine regimen (ORR 74%, CR 36%) than in fludarabine refractory patients (ORR 49%, CR 6%). Given these promising results, the MD Anderson is conducting an ongoing phase II study of CFAR in previously untreated patients.

Alemtuzumab as Consolidation Therapy after Chemotherapy

Given the ability of alemtuzumab to eradicate MRD in the bone marrow, several studies have examined alemtuzumab as consolidation therapy after initial induction therapy with fludarabine. The MD Anderson administered alemtuzumab 10 or 30 mg IV thrice weekly for 4 weeks to 58 patients who had responded to their most recent therapy but still had residual disease (49). ORR was 53%, and the response rate was dose dependent; 65% of patients at the 30 mg dose responded, compared to 39% of patients who received 10 mg. Eleven of 29 patients (38%) achieved an MRD negative marrow. TTP was not reached after a median follow-up of 24 months and was significantly longer in patients who became MRD negative. In a similar study, the GCLLSG randomized 21 eligible patients, who had responded to fludarabine or Flu/Cy but still had persistent CLL, to observation (n=10) or alemtuzumab 30 mg IV thrice weekly for up to 12 weeks (n=11). The study was discontinued early due to increased toxicity in the alemtuzumab arm; 6 of 11 patients developed grade 4 hematologic toxicity, and 7 patients developed grade 3–4 infections, including 4 patients with CMV (50). However, 5 of 6 tested patients achieved MRD negative bone marrow after alemtuzumab. With a median follow-up of 48 months, median PFS favored the alemtuzumab arm (not reached vs. 20.6 months), and only 3 of 11 patients who received alemtuzumab relaped (51). Based on these promising results, the GCLLSG FLL2i study is evaluating the optimal dose and schedule of alemtuzumab consolidation after initial fludarabine based therapy.

SC alemtuzumab has also been examined in the consolidation setting. The CALGB 19901 study administered fludarabine 25 mg/m2 IV daily for 5 days every 28 days for 6 cycles, followed by alemtuzumab 30 mg SC thrice weekly for 6 weeks, to 28 patients (24 evaluable) with previously untreated CLL (52). ORR after fludarabine induction was only 36% (CR 4%), and 18 patients with stable or responsive disease received alemtuzumab consolidation. Twelve of these 18 patients responded, and 4 of 8 patients converted from PR to CR, for a final intent-to-treat ORR of 50% (CR 18%). Treatment was well tolerated, and only 3 of 18 patients reactivated CMV. The CALGB 10101 study is currently examining a phase II regimen of concurrent fludarabine and rituximab for 6 cycles, followed by SC alemtuzumab for 6 weeks as consolidation therapy.

Toxicity: Why use alemtuzumab?

Due to the ubiquitous expression of CD52 on lymphocytes and monocytes, alemtuzumab causes significantly more infusion, hematologic and immune toxicity than does rituximab, and careful monitoring of and prophylaxis for potential infections is required for any administration of alemtuzumab. Infusion toxicity to IV alemtuzumab is reduced with a stepped-up dosing schedule, and infusion toxicity usually diminishes with subsequent administration (34). SC administration markedly reduces infusion toxicity, but hematologic and infectious complications still exist (44,53). However, infectious complications are manageable with adequate antibiotic prophylaxis and careful monitoring for CMV reactivation and other potential infections (34,45).

Despite its limitations, alemtuzumab is the only approved therapy for CLL that has clinical activity in relapsed patients with del(17p13), a cytogenetic abnormality that is found in up to half of all relapsed and refractory patients (41,42). In addition, alemtuzumab is superior to rituximab in eradicating MRD in the bone marrow, thereby improving long-term survival (38). Thus, alemtuzumab continues to play an important role in the treatment of high-risk CLL, although care should always be used when administering the drug. Ongoing studies continue to examine the use of alemtuzumab in combination with fludarabine and as consolidation therapy for eradication of MRD after fludarabine induction therapy.

INVESTIGATIONAL MONOCLONAL ANTIBODIES

Lumiliximab

CD23, a 45-kDa low affinity IgE receptor, is expressed on almost all CLL cells. Lumiliximab (IDEC-152), a chimeric macaque-human anti-CD23 monoclonal antibody, induced apoptosis in primary CLL cells *in vitro*, and this apoptosis was enhanced by fludarabine and rituximab (54). In an initial phase I study, 46 patients with relapsed CLL received lumiliximab 125–500 mg/m^2 IV weekly or thrice weekly for 4 weeks (55). Toxicity was observed in 89% of patients, but only 15% developed grade 3 or 4 toxicity. A decrease in peripheral lymphocytosis was observed in 91% of patients, 28% experienced more than 50% reduction of the peripheral lymphocyte count, and nodal reduction occurred in 52% of patients. The same investigators subsequently examined the combination of lumiliximab and FCR (56). Thirty-one relapsed CLL patients received fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 on days 2–4 of cycle 1 and on days 1–3 of cycles 2–6, rituximab 50 mg/m^2 and 325 mg/m^2 on days 1 and 3 of cycle 1 and 500 mg/m^2 on day 1 of cycle 2–6, and lumiliximab 50 mg/m^2 and 325 or 450 mg/m^2 on days 2 and 4 of cycle 1 and 375 or 500 mg/m^2 on day 1 of cycle 2–6, every 28 days for up to 6 cycles. Grade 3 or 4 toxicity, primarily hematologic, was observed in 65% of patients. ORR was 71%, and 52% of patients achieved CR. Based on these promising results, a randomized phase III study comparing FCR alone to the combination of FCR and lumiliximab is ongoing.

Ofatumumab

HuMax CD20 (Ofatumumab) is a fully humanized, high-affinity monoclonal antibody whose epitope on CD20 is distinct from rituximab's target. Ofatumumab has higher affinity for CD20 and activates CDC more effectively than rituximab. Twelve of 26 relapsed CLL patients responded (1 nPR, 11 PR) in a phase I/II study; median time to TTP was 161 days in responders, and median time to next therapy was 366 days (57). The area under the curve (AUC) correlated with both TTP and time to next therapy, and clearance of ofatumumab (median 10 mL/h; range 3–42) correlated inversely with clinical outcome. Grade 1–2 infectious toxicity was seen in 48% of patients, but 1 patient developed grade 4 interstitial pneumonitis. A phase III registration study of ofatumumab in alkylator, fludarabine, and alemtuzumab resistant CLL is nearing completion, and a phase II study of ofatumumab in combination with cyclophosphamide and fludarabine in previously untreated patients is ongoing.

Other antibodies

Several other monoclonal antibodies have been studied or are in preclinical or clinical development in CLL; these antibodies are mentioned only briefly due to space limitations and are summarized in Table 4. Epratuzumab (hLL2) is a humanized anti-CD22 antibody against Leu-14, the ligand for CD45RO which is expressed on normal B lymphocytes and B-cell malignancies including CLL (58). A dose-escalation phase I/II study in 55 heavily pretreated patients with indolent B-cell NHL, including 13 with CLL/SLL, found a tolerable dose of 1000 mg/m2 for 4 weeks. Nine patients had an objective response with 3 CRs; however, all responses were observed in patients with follicular NHL (59).

Apolizumab (Hu1D10) is a humanized murine IgG monoclonal antibody which recognizes a polymorphic determinant on the MHC class II HLA-DR beta chain (60,61). The 1D10 antigen is present on normal and malignant B lymphocytes, dendritic cells, macrophages, some activated T lymphocytes, 50% of acute lymphocytic leukemia, 50% of diffuse large cell NHL, 50–70% of follicular NHL, and 80–90% of CLL (62). Hu1D10 induces ADCC, CDC and apoptosis *in vitro* (60). Pharmacokinetic data indicated a median serum half life of approximately 11 days, although profound inter-patient variability was observed. Phase I/II studies in relapsed NHL and CLL gave apolizumab by both weekly and thrice weekly dosing (63). Infusion-related toxicity was common but manageable, and most toxicities were grade 1 or 2. While 4 of 8 follicular NHL patients responded (64), only modest clinical activity was observed in phase I/II studies of thrice weekly apolizumab in relapsed CLL (65). Finally, the humanized anti-CD40 antibody CHIR-12.12 blocks activation by CD40 ligand, and a phase I study examining a weekly dosing schedule in relapsed CLL is nearing completion.

CONCLUSIONS

Monoclonal antibody therapy is one of the most significant advances in the treatment of CLL in the last two decades. The best studied and most widely used monoclonal antibodies in CLL are rituximab and alemtuzumab. Both antibodies are used as single agents and in combination regimens, although less research has been conducted on chemoimmunotherapy regimens utilizing alemtuzumab due to the antibody's greater infusion, hematologic and immune toxicity. Rituximab, while not used as commonly as a single agent in CLL, significantly improves CR and PFS when combined with nucleoside analog based chemotherapy. However, it is unclear whether the addition of rituximab necessarily improves long-term overall survival. Alemtuzumab is active in relapsed CLL with del(17p13) and is able to eradicate MRD in bone marrow, but careful attention must be paid to potential infectious complications, most notably CMV. Nonetheless, the use of alemtuzumab as consolidation therapy to eradicate MRD after nucleoside analog therapy is an active area of ongoing research. There are a myriad of investigational monoclonal antibodies in preclinical or clinical studies. Of these agents, lumiliximab (anti-CD23) and ofatumumab (HuMax CD20) are perhaps furthest along in development. Thus, monoclonal antibody treatment in CLL remains an area of vigorous clinical investigation, and the next decade should hopefully see further understanding of the best way to give current antibodies and the introduction of new antibodies.

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Table 1

Selected phase II trials of weekly Rituximab in CLL/SLL

Reference (Authors / year)	Doses	Prior therapy	Evaluable patients	Response rate (ORR)
McLaughlin et al., 1998	4	Yes	30	13%
Nguyen et al., 1999	4	Yes	10	10%
Winkler et al., 1999	4	Yes	9	11%
Ladetto et al., 2000	4	Yes	7	0%
Huhn et al., 2001	4	Yes	28	25%
Itala et al., 2002	4	Yes	24	35%
Hainsworth et al., 2003	4	No	44	51%
Thomas et al., 2001	8	No	21	90%

Table 2

Combination regimens with concurrent Rituximab in CLL/SLL

Reference (Authors / year)	Prior therapy	Rituximab dose (mg/m2)	Cycles	Other agents	Evaluable patients	ORR (CR)
Byrd et al., 2001	Yes	375 q4wks	6	Flu	51	90% (47%)
Schulz et al., 2002	Yes	375 q4wks	4	Flu	31	87% (32%)
Wierda et al., 2005	Yes	500 q4wks	6	Flu/Cy	177	73% (25%)
Keating et al, 2005	No	500 q4wks	6	Flu/Cy	300	94% (72%)
Wierda et al, 2006	Yes	500 q4wks	6	Flu/Cy/A	78	65% (24%)
Kay et al, 2007	No	375 q3wks	6	Pent/Cy	64	91% (41%)

Abbreviations: Fludarabine (Flu), Cyclophosphamide (Cy), Alemtuzumab (A), Pentostatin (Pent)

Table 3

Selected phase II trials of thrice weekly Campath-1H in CLL/SLL

Reference (Authors / year)	Weeks	Route	Prior therapy	Evaluable patients	ORR (CR)
Osterborg et al., 1998	12	IV	Yes	29	42% (4%)
Rai et al., 2001	12	IV	Yes	136	40% (7%)
Keating et al., 2002	12	IV	Yes	92	33% (2%)
Lundin et al., 2001	18	SC	No	38	87%
Stilgenbauer et al, 2004	12	SC	Yes	46	46% (2%)
Moreton et al, 2005	16	IV	Yes	91	54%
Hillmen et al, 2007	12	IV	No	149	83% (24%)

Abbreviations: Intravenous (IV), Subcutaneous (SC)

Table 4

Summary of monoclonal antibodies available in CLL/SLL

Antibody	Antigen	Description	Clinical status
IDEC-C2B8 (Rituximab)	CD20	Chimaeric	FDA approved
Campath-1H (Alemtuzumab)	CD52	Chimaeric	FDA approved
Ofatumumab (HuMax CD20)	CD20	Humanized	Clinical trials
Lumiliximab (IDEC-152)	CD23	Chimaeric	Clinical trials
Epratuzumab (hLL2)	CD22	Humanized	Clinical trials
Hu1D10 (Apolizumab, Remitogen)	1D10 (HLA-DR β)	Chimaeric	Clinical trials
CHIR-12.12	CD40	Humanized	Clinical trials