Experimental Hematology

Newer monoclonal antibodies for hematological malignancies

Jorge Castillo, Eric Winer, and Peter Quesenberry

Division of Hematology and Oncology, Rhode Island Hospital, Brown University Warren Alpert Medical School, Providence, RI, USA

Since the approval of rituximab in 1997, monoclonal antibodies have come to play an important role in the therapy of hematological malignancies. Rituximab, gemtuzumab ozogamicin, and alemtuzumab are US Food and Drug Administration–approved for treatment of B-cell lymphomas, acute myeloid leukemia, and chronic lymphocytic leukemia, respectively. Multiple monoclonal antibodies directed against new and not-so-new cellular antigens are undergoing development and investigation all over the world. Most of these new compounds have undergone primatization or humanization, improving their specificity and decreasing their antigenicity when compared to earlier murine or chimeric products. This review will focus on three major aspects of monoclonal antibody therapy: 1) new therapeutic approaches with currently approved agents; 2) preclinical and clinical experience accumulated on new agents in the last few years; discussion will include available phase I, II, and III data on ofatumumab, epratuzumab, CMC-544, HeFi-1, SGN-30, MDX-060, HuM195 (lintuzumab), galiximab, lumiliximab, zanolimumab, and apolizumab; and 3) the role of naked and radiolabeled monoclonal antibodies in the hematopoietic stem cell transplantation setting.   © 2008 ISEH - Society for Hematology and Stem Cells.   Published by Elsevier Inc.

Since the discovery of hybridoma technology in 1975 [1], the production and variety of monoclonal antibodies have been exponentially increasing. Multiple agents have been developed; initially from murine origin, later chimeric between murine and humanized, and now fully human antibodies. This evolution has improved both antigenicity and specificity for the antigens they target. Initially developed for detection of cellular antigens for immunohistochemical diagnosis, the application of monoclonal antibodies has recently broadened to include therapy of multiple diseases.

Development of monoclonal antibodies against cell clusters of differentiation (CD) allows targeted therapy of known present antigens in malignant lymphoid or myeloid cells. Many of these antigens play important roles in signal transduction and ion transportation inside the cell, and after antibody modulation, vital survival pathways for malignant and normal cells are blocked or dysregulated. This effect, along with an immunologic boost, namely antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), promotes apoptosis in the targeted malignant cells [2,3].

Monoclonal antibodies have been used as single-agent therapies (Table 1) or in combination with other antibodies or chemotherapy (Table 2). Different strategies of action have been developed using monoclonal antibodies; these agents have been used naked (without any drug or radioactive material attached to them) or as part of radioimmunotherapy (RIT) or immunotoxins. The purpose of this review is to summarize the initial experience with novel monoclonal antibodies, new therapeutic approaches with already approved agents, and the role of monoclonal antibodies in the transplantation setting.

Monoclonal antibodies directed against lymphoid antigens

Anti-CD20 antibodies
The CD20 antigen is a transmembrane protein of 35-kD molecular weight, which is located mainly on pre-B and mature B lymphocytes [4]. Its function is still unclear, but there is evidence that it may play a role in regulating cell cycle and differentiation processes and act as a calcium ion channel as well [5]. Most B-cell non-Hodgkin's lymphomas (NHL) express CD20, but stem cells, pro-B cells, or plasma cells do not. CD20 is not secreted from the cell surface, and it is not found free in plasma [6,7].

Rituximab (Rituxan). The most commonly used and most vastly studied anti-CD20 antibody is rituximab, which

Offprint requests to: Jorge Castillo, M.D., Division of Hematology/Oncology, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02906; E-mail: jcastillo@lifespan.org

Table 1. Response rates with selected monoclonal antibody single-agent therapy

Antibody	Target	Trials	n	Setting	ORR (%)	CR (%)	PR (%)	SD (%)	Reference
Alemtuzumab (subcutaneous)	CD52	Phase II	41	Untreated CLL	87	19	68		[53]
		Phase III	297	Untreated CLL (vs chlorambucil)	83	24	59		[54]
Epratuzumab	CD22	Phase I/II	56	Refractory/recurrent aggressive lymphoma	10	5			[68]
		Phase I/II	55	Refractory/recurrent indolent lymphoma	18	6			[67]
CMC-544	CD22	Phase I	34	Relapsed/refractory lymphoma	35				[79]
Galiximab	CD80	Phase II	37	Relapsed/refractory FL	11	11		34	[88]
Lumiliximab	CD23	Phase I	46	Refractory/recurrent CLL	0				[81]
Ofatumumab	CD20	Phase I/II	33	Relapsed/refractory CLL	46		46		[51]
		Phase I/II	40	Relapsed/refractory FL	38	18	20		[50]
Zanolimumab	CD4	Phase II	47	Refractory CD4$^+$ CTCL	56				[118]
		Phase II	15	Refractory CD4$^+$ PTCL	27	13.5	13.5		[119]
SGN-30	CD30	Phase II	20	Refractory/recurrent systemic ALCL	20	5	15		[102]
		Phase II	17	Refractory/recurrent cutaneous ALCL	35	6	29		[104]
		Phase II	15	Refractory/recurrent HD	0			50	[103]
MDX-060	CD30	Phase I/II	48	Refractory/recurrent CD30$^+$ lymphoma	11	4	7	35	[106]
HuM195	CD33	Phase II	50	Refractory/recurrent AML	6	4	2		[151]

ALCL = anaplastic large T-cell lymphoma; AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; CR = complete response; CTCL = cutaneous T-cell lymphoma; FL = follicular lymphoma; HD = Hodgkin disease; ORR = overall response rate; PR = partial response; PTCL = peripheral T-cell lymphoma; SD = stable disease.

was the first monoclonal antibody to be approved by the US Food and Drug Administration (FDA) for treatment of a human disease in 1997, and is now considered part of the standard therapies of choice for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

Rituximab combined with CHOP (RCHOP) has improved the overall survival (OS) and event-free survival in newly diagnosed patients with DLBCL in multiple phase III randomized trials [8–11]; the potential advantage of giving RCHOP every 14 days instead of every 21 days is currently being investigated [12]. Rituximab and CVP (cyclophosphamide, vincristine, and prednisone) have proven to improve overall response rate (ORR) and progression-free survival (PFS) when compared to CVP alone in patients with FL, but an improvement on OS was not apparent [13]; but, recently, a meta-analysis showed that the combination of rituximab and any type of chemotherapy improved OS when compared to chemotherapy alone with a hazard ratio (HR) of 0.65 [14,15]. The most common side effects of rituximab include fever, chills, and rigors and are mainly infusion-related. The incidence of these reactions tends to diminish with subsequent infusions. Fatal reactivation of hepatitis B virus has been described in patients undergoing therapy with rituximab [16]; routine hepatitis B virus serologies should be taken prior to, during, and after rituximab therapy to detect some possible late reactivations [17].

Rituximab in chronic lymphocytic leukemia. Rituximab has not been FDA-approved for treatment of chronic lymphocytic leukemia (CLL), but it is the most commonly used monoclonal antibody in this disease. The apoptotic mechanisms of rituximab seem to play a more important role in CLL than in NHL. Single-agent rituximab has limited

activity in previously treated [18,19] or untreated [20] CLL. A potential explanation is the weak expression of CD20 by CLL cells. Dose-escalation [21] and more dose-intensive regimens [22] have been tried and have showed only limited activity. The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is considered by many the standard of care in previously treated or untreated CLL. In relapsed CLL, FCR achieved an ORR of 37% with complete response (CR) rate of 25% and a nodular PR of 12% [23]. Furthermore, FCR reached an ORR of 94% with a 72% CR rate and a 4-year OS of 83% in patients with untreated CLL [24]. Other promising combination is fludarabine and rituximab (FR); in untreated CLL patients, FR has shown an ORR of 90% with a 47% CR rate in the CALGB 9712 study [25], while the CALGB 9011 showed an ORR of 84% with a 38% CR rate [26]. The combination of FCR and alemtuzumab will be discussed later in this review.

Maintenance regimens with rituximab. Two big randomized trials have shown the clinical benefit of adding rituximab maintenance following induction therapy for advanced relapsed or refractory FL. Van Oers et al. [27] showed that maintenance rituximab improved PFS in patients who received induction CHOP with and without rituximab (HR = 0.65). There was also an improvement in OS for patients who responded to induction chemoimmunotherapy and were randomized to maintenance rituximab (HR = 0.52). Forstpointner et al. [28] achieved similar results by randomizing patients with relapsed or refractory FL and mantle cell lymphoma to rituximab and fludarabine, cyclophosphamide, and mitoxantrone (FCM) or FCM alone. Patients treated with RFCM had a better response rate than patients who received FCM alone. Rituximab

Table 2. Response rates with selected monoclonal antibodies combination therapy

Antibody	Target	Trials	n	Regimen	Setting	ORR (%)	CR (%)	PR (%)	SD (%)	Reference
Alemtuzumab	CD52	Phase II	78	Alemtuzumab + FCR	Relapsed/refractory CLL	65	24	41		[55]
		Phase II	177	Alemtuzumab + FCR	Untreated high-risk CLL	73	25	48		[56]
Apolizumab	HLA-DR	Phase I	29	Apolizumab + rituximab	Refractory/recurrent lymphoma	42	21	21		[164]
Epratuzumab	CD22	Phase I/II	15	Epratuzumab + RCHOP	Untreated DLBCL	87	67	20	7	[71]
		Phase II	65	Epratuzumab + rituximab	Refractory/recurrent lymphoma	47	27	20		[70]
		Phase II	23	Epratuzumab + rituximab	Refractory/recurrent lymphoma	61	52	9		[69]
Galiximab	CD80	Phase I/II	73	Galiximab + rituximab	Relapsed/refractory FL	64	31	33		[89]
Lumiliximab	CD23	Phase II	31	Lumiliximab + FCR	Relapsed/refractory CLL	71	48	23		[82]
Gemtuzumab	CD33	Phase II	32	Gemtuzumab + FAC	Relapsed/refractory AML	34	34			[137]
		Phase II	59	Gemtuzumab + FAC	Untreated AML/MDS	47	47			[136]
		Phase II	19	Gemtuzumab + ATRA	Untreated APML	84	84			[139]
		Phase II	8	Gemtuzumab + ATRA + ATO	Relapsed APML	100	100			[140]
HuM195	CD33	Phase III	191	MEC + HuM195	Refractory/recurrent AML	NR	36			[152]

AML = acute myelogenous leukemia; APML = acute promyelocytic leukemia; ATO = arsenic trioxide; ATRA = all-*trans* retinoic acid; CLL = chronic lymphocytic leukemia; CR = complete response; DLBCL = diffuse large B-cell lymphoma; FAC = fludarabine, cytarabine, cyclosporine A; FCR = fludarabine, cyclophosphamide, rituximab; FL = follicular lymphoma; MDS = myelodysplastic syndrome; MEC = mitoxantrone, etoposide, cytarabine; ORR = overall response rate; PR = partial response; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, predisone; SD = stable disease.

maintenance showed a longer response duration (not reached vs 16 months) compared to observation. There are ongoing trials to show if maintenance rituximab following rituximab-containing induction chemoimmunotherapy (PRIMA [Primary Rituximab or MAintenance] trial) or rituximab induction (RESORT [Rituximab Extended Schedule or ReTreatment] trial) would be of benefit in the therapy of untreated FL.

The role of maintenance rituximab in DLBCL is less clear. Habermann et al. [11] reported a longer FFS in patients with untreated DLBCL who received CHOP as induction but not in patients who received RCHOP.

Rituximab in AIDS-related lymphomas. The role of rituximab in AIDS-related lymphomas (ARL) is still unclear. A phase III trial [29] in ARL patients showed a higher but not statistically different response rate for RCHOP when compared to CHOP without a survival benefit. An increased risk of infectious death was also reported, mainly in patients with CD4$^+$ counts <50 cells per mm^3. More recent phase II trials [30] report safer toxicity profiles in patients with ARL with CD4$^+$ counts >100 cells per mm^3 and receiving appropriate prophylactic antibiotic therapy.

Rituximab in autologous stem cell transplantation. Rituximab has been used along with BEAM (BCNU, etoposide, cytarabine, and melphalan) for autologous stem cell transplantation (SCT) in 67 patients with relapsed aggressive NHL [31]. Rituximab was given before and after BEAM and on days 1 and 8 after SCT. The 2-year OS and DFS were 80% and 67%, respectively; these were statistically different than historical controls. There was no increased incidence of infections in the patients receiving rituximab.

Rituximab has also been given as maintenance therapy following autologous SCT in patients with relapsed or refractory B-cell NHL [32]. Four weekly infusions were administered on day 42 and 6 months after SCT. The 2-year OS was 88%. Despite a 54% rate of grade 3 and 4 neutropenia and delayed B-cell recovery, the rate of infections was not increased. The role of post-SCT rituximab is currently being investigated in a phase III randomized controlled trial in patients with relapsed DLBCL [33].

Rituximab in allogeneic SCT. Recently, very encouraging results were reported using FCR as a nonmyeloablative conditioning regimen prior to allogeneic SCT [34]. Forty-seven patients were followed prospectively for a median of 60 months. OS and PFS were 85% and 83%, respectively. The incidence of grade II to IV acute graft-vs-host disease (GVHD) was 11% using tacrolimus and methotrexate as immunosuppressive therapy.

Anti-CD20 RIT
RIT using two different murine anti-CD20 antibodies (Y-90 ibritumomab and ^{131}I tositumomab) has also been approved for the treatment of rituximab-resistant relapsed, refractory

indolent lymphomas. Y-90 ibritumomab (Zevalin, Biogen Inc., Cambridge, MA, USA) achieved higher ORR and CR rates than rituximab in relapsed/refractory FL, but time to progression (TTP) and duration of remission (DOR) were not statistically significant [35,36]. [131]I tositumomab (Bexxar, GlaxoSmithKline, Research Triangle Park, NC, USA) achieved ORR of 60% to 70% in heavily pretreated patients (some were resistant to rituximab); many patients achieved a durable response rate similar or better than rituximab with the obvious convenience of single-dose therapy [37].

Anti-CD20 RIT in autologous SCT. Use of SCT has improved survival in patients with relapsed or refractory lymphomas, but the majority of patients will invariably relapse and a proportion will not be considered suitable candidates for high-dose therapies because of their age, performance status, or comorbidities. Radiation therapy (RT) is one of the most effective therapies for hematological malignancies. Higher doses of RT have been associated with less relapse rates but also with increased toxicities. Using RT directed to tumor cells (i.e., RIT) as conditioning regimen prior to SCT would theoretically allow safer and better responses.

Two major strategies have been developed using RIT as part of conditioning regimens for autologous SCT:

1. High-dose RIT with or without chemotherapy. The Seattle Consortium pioneered the high-dose RIT approach using ^{131}I tositumomab [38]. An encouraging CR rate of 84% was achieved with minimal nonhematological toxicity. In a cohort analysis, high-dose RIT showed longer 5-year PFS and OS when compared to high-dose chemotherapy (48% vs 29% and 67% vs 53%, respectively); RIT was also associated with decreased treatment-related mortality (4% vs 11%) [39]. The same group reported a 3-year PFS of 51% and low incidence of nonhematological toxicity in 24 patients older than 60 years [40]. High-dose RIT has been used in combination with high-dose chemotherapy [41]; this study shows that ^{131}I tositumomab can be safely given in combination with high-dose etoposide/cyclophosphamide. Patients who received RIT and high-dose chemotherapy seemed to have longer PFS and OS than controls treated with total body irradiation and high-dose chemotherapy. High-dose RIT using Y-90 ibritumomab in combination with carmustine, etoposide, cytarabine, and melphalan (BEAM) showed a 3-year OS of 54% in 44 heavily pretreated patients with NHL [42]. In another report [43], 31 patients with relapsed NHL received Y-90 ibritumomab and high-dose etoposide/cyclophosphamide. The 2-year OS was 92% with similar toxicity rates than total body irradiation.
2. Standard-dose RIT plus high-dose chemotherapy. Vose et al. [44] showed that ^{131}I tositumomab could be safely given prior to BEAM and autologous SCT. This

regimen achieved a CR rate of 57%. A subsequent phase II trial [45] showed an impressive 3-year OS of 81% in 40 patients with relapsed but chemosensitive DLBCL. There is an ongoing phase III trial comparing ^{131}I tositumomab-BEAM vs rituximab-BEAM in relapsed DLBCL [33]. In a similar fashion, Y-90 ibritumomab prior to BEAM and autologous SCT has shown to be safe and effective [46]. This regimen achieved a longer PFS and OS than BEAM alone (88% vs 65% and 72% vs 67%, respectively).

Ofatumumab. Ofatumumab is a fully humanized anti-CD20 monoclonal antibody that has been shown, preclinically, to be exceptionally active and produce a stronger CDC by more efficiently binding C1q to the surface of the CD20-positive cell [47]. This newer antibody interacts with a different epitope than rituximab, which is located in the smaller extracellular loop of CD20 [48], giving it a higher binding affinity.

Initial phase I/II clinical data in relapsed/refractory FL was presented by Hagenbeek et al. [49,50]. Forty patients were given escalated doses of ofatumumab from 300 mg to 1000 mg intravenously weekly for 4 weeks, obtaining an ORR of 63% with 57% response in patients previously treated with rituximab without reported dose-limiting toxicity. Coiffier et al. [51] presented the early results of a phase I/II trial of ofatumumab in 33 patients with relapsed/refractory CLL reporting significant depletion of $CD19^{+}CD5^{+}$ cells by all patients and 67% response at the highest dose (2000 mg) by the 4th week. There are ongoing phase III trials of ofatumumab in CLL and FL [33].

Anti CD-52 antibodies
CD52 is a surface peptide expressed in lymphocytes, monocytes, macrophages, and some granulocytes. CD52 is strongly expressed in CLL and some indolent NHL.

Alemtuzumab (Camptah-1H, Genzyme Corporation, Cambridge, MA, USA). Alemtuzumab is a humanized anti-CD52 monoclonal antibody that has shown to induce apoptosis of malignant lymphocytes, CDC, and ADCC in vitro. Alemtuzumab has been approved by the FDA for treatment of fludarabine-refractory CLL. Alemtuzumab is able to eradicate minimal residual disease (MRD) from the bone marrow, even in high-risk CLL patients with del(17p13). Patients who achieved MRD-negative marrow had longer survivals than patients who achieved either MRD-positive CR or PR [52]. On the other hand, patients who had bulky lymphadenopathy had a lower CR rate. The major observed side effects are prolonged myelosuppression and lymphopenia. Prophylaxis against Pneumocystis carinii pneumonia and Varicella zoster virus is mandatory in patients receiving alemtuzumab.

To minimize its toxicity, subcutaneous alemtuzumab has been administered three times a week in 41 untreated CLL

patients [53]. The ORR was 87%, but it was less effective against nodal disease. Some patients needed more than 18 weeks of therapy to achieve the best response. Subcutaneous alemtuzumab has been compared to chlorambucil in the up-front setting [54], achieving higher ORR (83% vs 55%) and CR rate (22% vs 2%). Again, CLL patients with del(17p13) had superior response to alemtuzumab. Cytomegalovirus (CMV) reactivation was seen in 52% of patients receiving alemtuzumab, making the monitoring of CMV mandatory with this therapy.

FCR and alemtuzumab (CFAR) has been studies in 78 relapsed CLL patients [55]. CFAR obtained an ORR of 65% and a CR rate of 24%. Patients received granulocyte colony-stimulating factor (G-CSF) support as well as Pneumocystis carinii pneumonia and Varicella zoster virus prophylaxis. Valganciclovir showed to be more effective than valacyclovir in preventing CMV reactivation. CFAR is being investigated as front-line therapy in 177 patients with high-risk CLL defined by high levels of β2-microglobulin [56]. In this population, CFAR showed an ORR of 71%. All patients in CR and near PR were MRD-negative at the end of therapy. This trial continues accruing.

Alemtuzumab has been used as consolidation therapy after chemotherapy for CLL. The intravenous regimens have shown to be effective at achieving MRD-negative responses following fludarabine [57] or fludarabine/cyclophosphamide [58]; the latter study had to be stopped given the elevated toxicity in the alemtuzumab arm. Subcutaneous alemtuzumab as consolidation therapy has also proven to be effective in untreated CLL, but with a safer toxicity profile [59]. A study using fludarabine and rituximab followed by consolidation alemtuzumab in untreated CLL patients is ongoing [33].

Alemtuzumab in SCT. Its T-cell depletive effects make alemtuzumab a potentially useful agent in conditioning regimens prior to SCT for multiple hematological malignancies. Alemtuzumab could decrease the incidence of acute and/or chronic GVHD following allogeneic SCT, while allowing more effective reduced-intensity regimens by enhancing graft-versus-tumor effect. Combinations of alemtuzumab and fludarabine/busulfan [60] and fludarabine/melphalan [61] have been reported safe and effective with lower rates of GVHD in acute myeloid leukemia (AML)/MDS. The latter combination has also been used prior to SCT in the treatment of CLL [62], but rates of GVHD appeared higher than in the experience reported here. Patients with Hodgkin's disease (HD) who received alemtuzumab-containing regimens seem to experience less acute and chronic GVHD without increasing relapse rates [63].

Anti-CD22 antibodies. The CD22 molecule is a transmembrane glycoprotein that plays a role in cellular adhesion, regulation of B-cell homing and modulation of B-cell activation [64]. B-cell malignancies express CD22 up to 60% to 80% of cases. CD22 is unique in that it is internalized into the cell when bound by antibody. This property makes it an interesting target for RIT or immunoconjugates [65].

Epratuzumab. Epratuzumab (hLL2) is an IgG1 humanized monoclonal antibody that in vitro has shown to bind to CD22 and internalize into the target cell [66]. An initial phase I/II trial was published by Leonard et al. [67]. The population investigated had pretreated indolent NHL with a median of 3.5 prior therapies, including 44% of patients who received prior rituximab. Initially this was a dose-escalation trial; with doses ranging from 120 mg/m^2 to 1000 mg/m^2 over 30 to 60 minutes weekly for 4 weeks, a dose-limiting toxicity was not reached. Epratuzumab had an ORR of 18% with a CR rate of 6% in this heavily pretreated population. In FL, a 43% ORR was achieved with a dose of 360 mg/m^2 weekly. The use of naked epratuzumab was then evaluated in aggressive NHL, mostly DLBCL [68]. This population was heavily pretreated, 25% had previous SCT and >80% had bulky disease. The ORR was 10%, for patients with DLBCL the ORR was 15%. Leonard et al. [69] presented data on 23 patients with previously treated FL and DLBCL who received epratuzumab 360 mg/m^2 along with rituximab 375 mg/m^2 weekly for 4 weeks. All patients were rituximab naïve. In the FL group, an ORR of 67% and a CR rate of 60% were achieved. In the DLBCL group an ORR of 67% and a CR rate of 50% were reported; the incidence of human antihuman antibodies was null. A similar European study by Strauss et al. was published recently [70]. Sixty-five previously treated patients were enrolled, 46 had a diagnosis of indolent NHL (34 had FL) and 19 had aggressive NHL (15 were DLBCL). An ORR of 47% was achieved (64% in FL and 47% in DLBCL patients), with a CR/CRu rate of 22% (24% in FL and 33% in DLBCL patients). Finally, the combination of epratuzumab (E) and RCHOP in newly diagnosed DLBCL has been studied; in a pilot trial, E-RCHOP every 21 days showed feasibility with an ORR of 86% and 87% incidence of grade 4 neutropenia [71]. Epratuzumab is being studied for relapsed/refractory Waldenstrom's macroglobulinemia [71].

Anti-CD22 RIT. Murine and humanized forms of anti-CD22 antibodies have been used in combination with different radionuclides. ^{131}I-radiolabeled murine LL2, an IgG2a monoclonal antibody, was developed to take advantage of the internalizing properties of the CD22 antigen, but it was found to have a very short intracellular life. The compound was cleaved intracellularly and the ^{131}I was exocytosed, not allowing a full destructive effect of the radioisotope [72]. Despite this molecular finding, this study reported an ORR 55% with 27% CR rate and hematological toxicity more prominent in patients with decreased bone marrow reserve prior to begin the study [73]. When used with humanized LL2 monoclonal antibody, Y-90 showed different advantageous characteristics and a more favorable tumor dosimetry compared to ^{131}I

[74]. Y-90 was longer lasting inside the cell, even after the antibody was catabolized, and the lack of γ-emissions will make the compound suitable for outpatient settings but less suitable for follow-up scintigraphy; on the other hand, the β-particle from Y-90 has a much deeper penetration, making it favorable to treat larger lesions [75]. Weekly infusions of Y-90 hLL2 has been used in 16 patients with previously treated NHL [76], obtaining an ORR of 62% (75% in indolent NHL and 50% in aggressive NHL) with 25% CR/CRu rates. Three weekly infusions were feasible in this population with minimal toxicity. The main adverse effects were hematological toxicity, but no patient required platelet transfusions or growth factors. Re-186 radionuclide has been described to have some additional advantages, including having β-particles and minimal γ-emissions high enough for scintigraphic imaging for dosimetry, unfortunately, the life of the radioisotope inside the cell is much shorter compared to Y-90. Re-186 hLL2 was evaluated in a phase I trial in 18 pretreated patients with different types of NHL [77], a maximal tolerated dose of 2.0 GBq/m^2 was reached with transient hematological side effects being the most prominent.

Other anti-CD22 monoclonal antibodies. CMC-544 [78] is an immunoconjugate that combines a humanized anti-CD22 monoclonal antibody (IgG4 type) with calicheamicin, a potent antitumor antibiotic that binds DNA and undergoes structural changes causing double-strand DNA breaks resulting in apoptosis (safety and feasibility of calicheamicin has been established using another monoclonal antibody, gemtuzumab ozogamicin, which will be described below). An initial dose-escalation trial [79] in patients with B-cell NHL showed feasibility with clinically manageable thrombocytopenia being the most common adverse effect.

Preclinical models using a combination of CMC-544 and rituximab demonstrated an increase survival in severe combined immunodeficiency–bearing mice [80]. Further clinical use of CMC-544 is currently being studied in two early-phase multicenter trials investigating the use of this agent alone and in combination with rituximab in indolent and aggressive NHL [33].

Anti-CD23 antibodies
CD23, also known as Fc epsilon RII, is a low-affinity IgE receptor that is expressed in virtually all CLL cells and is involved in allergy and resistance to parasites. The CD23 molecule is also expressed by mature B-cells, activated macrophages, eosinophils and platelets.

Lumiliximab. Lumiliximab (IDEC-152) is a chimeric primate-human anti-CD23 monoclonal antibody that has shown to induce apoptosis in CLL cells. The apoptotic effect of lumiliximab seems preclinically to be increased by fludarabine and rituximab [81]. In a phase I trial [82], escalating doses of lumiliximab were administered to 46 patients with CLL. No complete or partial responses were

observed, but it was well-tolerated. Byrd et al. [83] also presented data on lumiliximab in combination with FCR [83]. Patients who received lumiliximab and FCR attained higher response rates (ORR 71%, CR 48% and PR/PRu 23%) than historical FCR-only controls. The toxicity profile was comparable to FCR. A phase III trial comparing FCR with and without lumiliximab is ongoing [33].

Anti-CD80 antibodies
The CD80 antigen, also called B7.1, is the natural ligand for the T-cell antigen CD28, which mediates T-cell and B-cell adhesion. CD80 is expressed on activated B cells, T cells, and dendritic cells, and is often expressed on the surfaces of FL cells and other lymphoid malignancies, such as mycosis fungoides (MF) [84,85]. This pathway is crucial in the recognition of antigen as well as self-recognition and immune tolerance, and is often called the costimulatory pathway [86].

Galiximab. Galiximab (IDEC-114) is a primatized (human IgG1 constant regions and *Cynomolgous macaque* variable regions) monoclonal antibody that binds to CD80 on lymphoma cells upregulating apoptosis, antiproliferation, and induction of ADCC. The CD80 antigen is highly expressed in T cells of psoriatic lesions [84], and in an initial study in psoriatic patients, galiximab showed a very safe profile without development of anti-galiximab antibodies [87].

A phase I/II trial has been reported by Czuczman et al. [88]; in this study, galiximab was used in 37 patients with relapsed/refractory FL and the dose was escalated from 125 mg/m^2 to 500 mg/m^2 without reaching a dose-limiting toxicity. Most of the side effects were grade 1 or 2 toxicity. No anti-galiximab antibodies were detected. The ORR was 11% (2 CR and 2 PR), but stable disease (SD) was achieved by 34% of the patients. A phase II study combining rituximab and galiximab in relapsed/refractory FL was recently presented by Friedberg et al. [89] showing an ORR of 64% (CR 17%, CRu 14%, and PR 33%). This study used the 500 mg/m^2 dose for all 73 US patients. Comparing these results with rituximab monotherapy, the combination showed similar safety profile, and a longer median PFS (12.2 vs 9.4 months). There are two ongoing phase III clinical trials, one will compare galiximab plus rituximab with rituximab alone in relapsed/refractory NHL; the second study will evaluate galiximab plus rituximab as retreatment in patients who responded to this combination in the Friedberg study [33].

Anti-CD30 antibodies
The CD30 molecule belongs to the tumor necrosis factor receptor family [90] and was initially identified on Reed-Sternberg cells [91]. CD30 overexpression has been described on HD, anaplastic large cell lymphoma (ALCL), and mediastinal B-cell lymphoma, but it has limited expression on otherwise normal tissues (activated B cells, activated T cells, activated NK cells, and some vascular beds) [92].

This characteristic makes CD30 a potentially relevant target for monoclonal antibody therapy. There is an extensive list of anti-CD30 monoclonal antibodies developed throughout the years [93–97]. A murine anti-CD30 was used as part of RIT and showed to be effective (ORR = 27%) but was associated with severe hematotoxicity [98].

HeFi-1. HeFi-1 is a murine monoclonal antibody that has proven to be preclinically effective in ALCL, but with a variable response in HD [95], and is currently being investigated in a phase I trial sponsored by the U.S. National Cancer Institute in patients with cancer showing at least 30% expression of CD30 by immunohistochemistry [33].

SGN-30. SGN-30 is a chimeric monoclonal antibody and has proven to be effective to arrest Reed-Sternberg cells of HD growth in vitro and in preclinical xenograft models [99] and to be synergistic to chemotherapy in $CD30^+$ malignancies [100]. Forero-Torres et al. [101,102] presented preliminary data from a phase I/II trial using SGN-30 in 20 patients with recurrent/relapsed systemic ALCL showing an ORR of 20% (one CR and three PR), the study is still ongoing. Ongoing trials are investigating SNG-30 as a single agent for relapsed/refractory HD [103] and cutaneous ALCL [104], and in combination with gemcitabine, vinorelbine and pegylated liposomal doxorubicin (GVD) for patients with relapsed/refractory HD [33].

MDX-060. MDX-060 [105] is a fully human anti-CD30 monoclonal antibody that induces killing of $CD30^+$ cell lines and has shown to stop growth of HD preclinical models. It has been studied in a dose-escalation phase I/II trial [106] in refractory/relapsed HD and has shown to be clinically active; in 40 patients with HD achieved one CR and two PR, in six patients with ALCL achieved one CR and one PR with a very acceptable toxicity profile. Two clinical trials are currently recruiting patients; one is investigating the effect of MDX-060 in systemic or cutaneous ALCL as single agent, the second trial is a phase II randomized trial and will compare single-agent gemcitabine vs gemcitabine plus MDX-060 vs dexamethasone plus MDX-060 [33].

Anti-CD4 antibodies

The CD4 antigen belongs to the immunoglobulin superfamily, is expressed in helper T cells, regulatory T cells, macrophages, monocytes, and dendritic cells, and acts as the coreceptor of the T-cell receptor [107]. CD4 has four domains (D1–D4); D2 to D4 subdomains share structural similarities with immunoglobulin-constant regions while D1 subdomain, which interacts with major histocompatibility complex class II [108], is similar to immunoglobulin variable regions. CD4 is highly expressed by malignant T cells as well, mainly in cutaneous T-cell lymphomas (CTCL) and noncutaneous peripheral T-cell lymphomas (PTCL).

Different monoclonal antibodies against T-cell antigens have been developed and tried preclinically and clinically in T-cell lymphomas without major success. Initially a murine anti-CD5 monoclonal antibody, T101, was developed and used in CLL and CTCL either as a single agent or as part of immunoconjugates or RIT [109–114]. The major limitation of this agent was the development of human anti-mouse antibodies. Recently, the experience with chimeric and development of fully human anti-CD4 monoclonal antibodies may overcome this initial obstacle. Knox et al. reported results with SK3, a chimeric anti-CD4 antibody, which was tried in seven pretreated patients with MF with some effect, a 28.5% incidence of development of human antichimera antibodies, and a good safety profile, but no significant $CD4^+$ cell depletion could be achieved, even though most of $CD4^+$ cells were coated with antibody [115]. Later, the same group reported clinical experience in eight patients with persistent or progressive MF using M-T412, an anti-CD4 chimeric antibody directed against a different epitope of the CD4 molecule, which demonstrated a higher affinity and was able to induce $CD4^+$ lymphocyte depletion through an Fc-mediated mechanism; the incidence of human antichimera antibodies was lower (12.5%) and showed an ORR of 88% with an average FFP of 25 weeks [116].

Zanolimumab. In 2004, a fully human anti-CD4 monoclonal antibody, zanolimumab (HuMax-CD4), was designated a Fast Track Product by the FDA; initially showed a very safe profile in a psoriasis vulgaris trial [117]. Currently its use is under active investigation for the treatment of $CD4^+$ malignancies, mainly CTCL in early and advanced stages and other noncutaneous PTCL. Obitz et al. reported early results of a phase II trial of zanolimumab in refractory CTCL [118]; a safe profile and a favorable response of 40% were observed. D'Amore et al. presented data from a phase II trial of HuMax-CD4 in non-cutaneous PTCL [119] demonstrating an ORR of 62.5% in the first eight patients enrolled in the trial and only one related case of febrile neutropenia. Two phase II clinical trials are evaluating the efficacy of zanolimumab in early and late-stage CTCL [33]. A blinded, randomized phase III trial comparing two different dosing of zanolimumab (8 mg/m^2 vs 14 mg/m^2) in previously treated MF is ongoing [33].

Monoclonal antibodies directed against myeloid antigens

Anti-CD33 antibodies

The CD33 antigen is a 67-kD protein, which belongs to the sialic acid-binding immunoglobulin-like lectin family [120], and it was cloned and localized in chromosome 19 [121]. Andrews et al. [122] later demonstrated that

precursors of human hematopoietic colony-forming cells were largely $CD34^+$ but $CD33^-$. It was hypothesized that antibodies targeted against CD33 would likely ablate $CD33^+$ leukemic blast cells without affecting $CD33^-$ normal precursor cells, allowing for a full bone marrow recovery after treatment [123]. Initial ex vivo studies reported high efficacy of cytosine arabinoside/etoposide in combination with MY9 (a murine anti-CD33 monoclonal antibody) to achieve bone marrow purification in acute nonlymphocytic leukemia [124]. CD33 is expressed by cells of the myelomonocytic lineage and liver sinusoidal cells, but not by lymphoid cells [125]. Recent reports of CD33 expression in drug-resistant multiple myeloma patients may have interesting clinical implications [126].

Gemtuzumab ozogamicin (Mylotarg, Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA). Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody linked to a derivative of calicheamicin, a potent cytotoxic antibiotic that gets released inside the myeloblast by hydrolysis causing DNA breaks and subsequent cell death [127]. Myelosuppression and thrombocytopenia are the most common hematological toxicities seen with regular doses of GO (9 mg/m^2), while hepatic veno-occlusive disease has been reported in the allogeneic transplant setting.

Single-agent GO. As front-line therapy for AML, single-agent GO has shown moderate activity with ORR ranging between 17% and 27% [128,129] and a therapy-related mortality of up to 17%.

In the relapsed setting, the Mylotarg Study Group presented data on 142 AML patients in first relapse treated with single-agent GO in three different phase II trials [130,131] and reported an ORR of 30%, including patients who achieved CR and CR with incomplete recovery of platelets (CRp); an ORR of 26% was reported in patients older than 60 years old, with similar survival rates between the CR and CRp groups and a good tolerability but with 23% grade 3/4 hyperbilirubinemia and few but life-threatening bleeding events likely secondary to thrombocytopenia. GO got approval by the FDA in 2001 based on these studies for patients older than 60 years old with AML in first relapse who will not be suitable for intensive chemotherapy; the ORR was used as a surrogate likely to predict clinical benefit [132]. The role of GO in the pretransplant setting and as maintenance therapy in elderly population is under current investigation [33].

GO used in combination with chemotherapy. In patients with untreated AML, GO has been used followed by mitoxantrone, etoposide, and cytarabine [133]. This combination showed a response of 54% and is currently being investigated in a phase III trial [33]. Lower doses of GO (3 mg/m^2) in combination with daunorubicin and cytarabine or fludarabine, cytarabine, G-CSF, and idarubicin showed ORR up to 91% [134]. The thioguanine-containing regi-

mens showed an increased rate of venooclusive disorder (VOD) of the liver. This study set the background for the randomized MRC AML 15 trial; a total of 1115 patients (92% of patients had untreated AML) were randomized to three different GO-containing chemotherapy regimens and two consolidation regimens. A preliminary report [135] showed an ORR of 85%; GO-containing regimens were associated with reduced relapse rates and longer DFS, but no difference in OS has been observed. GO has also been used in combination with fludarabine, cytarabine, and cyclosporine in the front-line [136] and relapsed settings [137]; the combination showed an ORR of 48% and 34%, a median survival of 8 and 5.3 months, and an incidence of VOD of 7% and 9%, respectively.

Trials evaluating GO in combination with standard induction chemotherapy for patients with AML are under investigation [33].

GO in acute promyelocytic leukemia. Acute promyelocytic leukemia (APML) is a distinct subtype of AML characterized cytogenetically by t(15;17), which transcribes PML/RAR-α, molecule involved in myeloid differentiation and apoptosis. The APML blasts express high levels of CD33.

Single-agent GO showed to be very active in APML. In patients with molecularly relapsed APML, GO achieved molecular remission in 91% of patients after two doses and in 100% of patients after three doses [138]. Estey et al. [139] evaluated the combination of GO and all-*trans*-retinoic acid in 19 untreated APML patients and reported a CR rate of 84% without increased hepatotoxicity. Twelve patients achieved a PCR-negative response. The combination of GO, all-*trans*-retinoic acid and arsenic trioxide was tried in APML patients in first relapse [140]; most of the patients achieved molecular remission and remained in a second response that was longer than their first response.

Interestingly, no VOD or significant hepatotoxicity has been reported with GO in APML patients. A potential explanation is the binding of GO to circulating APML cells, decreasing binding to hepatic cells.

Other anti-CD33 monoclonal antibodies
M195 is a murine IgG2a anti-CD33 monoclonal antibody and was initially used as a diagnostic marker [141]. Later, the same group reported a phase I trial using ^{131}I -M195 demonstrating rapid and specific uptake by the bone marrow and subsequent internalization into the target cells [142]. A dose-escalation trial followed in 1993 [143]. Twenty-four patients were treated, 96% had decreased blood cell counts, and 83% had decreased blast cells in the bone marrow.

In order to counteract the immunogenicity of M195, a humanized compound was developed. HuM195 is an IgG1 computer-modeled version of M195 showing higher binding avidity compared to the parent compound but

with similar immunologic effects and increased ADCC mediated by mononuclear cells [144]. A phase IB trial [145] using I-131-HuM195 showed a safe side effect profile. To further decrease unwanted cytotoxic effects M195 has been linked to Bi-213, α-particle radioisotope, which might be helpful in eradicating minimal residual disease. Bi-213-HuM195 was used in 18 patients with relapsed AML [146], 93% of the patients had circulating blast response and 78% had reduction in the number of bone marrow leukemic cells with pancytopenia being the most common adverse effect. Mulford et al. [147] presented data on cytarabine followed by Bi-213-HuM195 in 25 patients with newly diagnosed or relapsed/refractory AML, CML in accelerated phase or RAEB/RAEB-T achieving an ORR of 28% with two CR, three CRp, and two PR, as expected all patients developed febrile neutropenia.

The combination of interleukin (IL)-2 and HuM195 was studied based on the finding that IL-2 may potentiate HuM195 effect by increasing the NK-cell dependent ADCC [148]. In a phase I trial, this combination showed modest antileukemic activity, but also significant toxicity was reported, mostly IL-2–related [149].

Unlabeled antibody has been used as consolidation therapy for APML to induce molecular remissions with moderate success [150]. A randomized phase II trial comparing two different doses of HuM195 in 50 patients (25 patients in each arm, 12 mg/m^2 vs 36 mg/m^2) with AML [151] reported minimal activity represented by two CR and one CRp of short duration. The same group reported a phase III trial [152] of HuM195 in combination with chemotherapy vs chemotherapy alone in refractory or first-relapsed AML showing a safe administration of the regimen but no real advantage of the addition of the antibody (CR + CRp 36 vs 28%; $p = 0.28$). A dose-escalation trial using HuM195 alone in AML/MDS patients at higher doses than previously used is ongoing [33].

Immunotoxins using HuM195 have been developed, conjugating the antibody with gelonin, a plant extract known to block ribosomal production [153] and later with a recombinant form of gelonin (rGel) [154]; both compounds have shown antileukemic efficacy in preclinical models. A phase I trial of HuM195-rGel in advanced AML is undergoing accrual [33].

Monoclonal antibodies directed against immune-related antigens

Anti-HLA-DR antibodies

Human leukocyte antigen (HLA)-DR is a HLA class II molecule and it is involved in presentation of exogenous antigens. It is expressed in monocytes, macrophages, and B cells, so-called professional antigen-presenting cells. They present these antigens to CD4$^+$ helper T cells to initiate humoral and facilitate cellular immune responses [155].

Apolizumab (Hu1D10; Apo). Apo is a humanized IgG1 anti-HLA class II monoclonal antibody, which binds to 1D10, a variant of the HLA-DRβ chain. HLA-DR is expressed in normal and malignant cells, mainly in the B-cell population [156]. Apo has been shown to induce ADCC, CDC, and apoptosis of B cells in preclinical studies [157,158].

Apo was used in a dose-escalation phase I trial in patients with relapsed, 1D10$^+$ NHL [159,160] and in patients with previously treated CLL/small lymphocytic leukemia [161] and showed minimal toxicity, feasibility, and some response of delayed onset (median time to response 106 days) in this population. However, results from the phase II trial were disappointing [162,163]. When the combination of Apo and rituximab was investigated in previously untreated patients with B-cell NHL and CLL, surprisingly an increased incidence of hemolytic-uremic syndrome was observed, likely secondary to endothelial damage induced by the immunotherapy. The regimen was switched to Apo on day 1 followed by rituximab on day 2 and no hemolytic-uremic syndrome was observed [164]. G-CSF has been reported to increase cell killing by Apo in preclinical studies, Rech et al. [165] presented data in a small group of patients with relapsed/refractory 1D10$^+$ NHL using Apo on a three times weekly schedule showing feasibility. Recently, multiple phase I (ALL, AML, ARL, and Waldenstrom's macroglobulinemia) and phase II trials (relapsed CLL, relapsed HD, and relapsed NHL) using Apo with and without rituximab have been completed with results not yet available [33].

Conclusion

The future in management of hematological malignancies likely will imply the ability of institute personalized therapeutic approaches. In this regard, monoclonal antibody therapy may allow us to put in practice, what we call the art of medicine. Nonetheless, there is an imperative need of more effective therapeutic strategies using combinations of chemotherapeutic agents, naked and radiolabeled monoclonal antibodies, anti-idiotype vaccines, and the new-coming antiangiogenic (i.e., bevacizumab) and immunomodulatory agents (i.e., thalidomide). Ideally, our goal would be to improve the cure rate with these regimens but the achievement of long periods of nonprogression should be considered as secondary objectives of the treatment of incurable conditions such as CLL, FL, or mantle-cell lymphoma. Radioimmunotherapy approaches and vaccines will help eradicate MRD and consolidate the benefits obtained by our induction regimens while maintenance regimens will keep malignant progression at bay, allowing, hopefully, for prolonged drug-free and relapse-free periods of time.

Everyday we accumulate clinical experience with the use of these monoclonal antibodies, and they are an excellent resource in our armamentarium against hematologic malignancies. Although binding to target antigens appears important in most instances where monoclonal antibodies

are therapeutically effective, the actual mechanisms of tumor response remain poorly understood. Whether these responses are due to direct effects on lymphoma cells or whether they facilitate preexisting cytotoxic mechanisms is still an open question. Further progress in understanding these responses should enhance the therapeutic usefulness of monoclonal antibody therapy.

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