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Contextualizing the Use of Moxetumomab Pasudotox in the Treatment of Relapsed or Refractory Hairy Cell Leukemia

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

Hairy cell leukemia (HCL) is an indolent B-cell malignancy characterized by high initial sensitivity to purine analog chemotherapy, minimal residual disease (MRD) frequently accompanying complete remission (CR), and relapses requiring additional treatment. Repeat chemotherapy shows decreasing efficacy and increasing toxicity with each course. Newer therapies targeting BRAF/MEK or Bruton's tyrosine kinase are effective but generally leave MRD. Rituximab has modest activity as a single agent and can achieve MRD-negative CR in combination with purine analogs, but there is significant toxicity from the chemotherapy. Moxetumomab pasudotox-tdfk (Moxe) is a biologic containing an antibody fragment (Fv) binding to CD22, attached to a portion of *Pseudomonas* exotoxin A. Binding to CD22 enables the toxin to enter and kill cells. Moxe is administered by 30-minute infusions on days 1, 3, and 5 of up to six cycles spaced 4 weeks apart. In phase I testing, 64% of 33 patients at the highest dose level achieved CR, most without MRD. Lack of MRD correlated with prolonged CR duration; of 11 MRD-negative CRs, 10 were still in CR after a median of 42 months of observation. In pivotal testing, 75% of 80 patients had a hematologic response, 41% with CR; 82% (27/33) of CRs were MRD-negative, and only 4 of the 27 MRD-negative patients relapsed during the follow-up period. Hemolytic uremic syndrome and capillary leak syndrome were each observed in 9% of patients, all reversible. In September 2018, the U.S. Food and Drug Administration approved Moxe for the treatment of relapsed/refractory HCL after ≥2 prior therapies. Moxe is undergoing further development in combination with rituximab. ***The Oncologist*** 2020;25:e170–e177

Implications for Practice: Hairy cell leukemia (HCL) has effective treatments including purine analogs with and without rituximab, and oral inhibitors of BRAF, MEK and Bruton's tyrosine kinase (BTK). Despite these therapies, relapse occurs, and moxetumomab pasudotox has an important role in relapsed and refractory HCL because of its ability to achieve high rates of complete remissions (CRs) without chemotherapy; most of these CRs are without minimal residual disease (MRD). CR duration is enhanced in patients who achieve eradication of MRD. To improve the efficacy of this recombinant immunotoxin, a phase I trial is underway in combination with rituximab to reduce tumor burden and decrease immunogenicity.

Introduction

Hairy cell leukemia (HCL) is a rare chronic B-cell malignancy that composes ∼2% of leukemias [1], translating to ∼1,240 HCL cases of the expected 61,780 new cases of leukemia in the U.S. in 2019 [2]. Classic HCL is characterized by pancytopenia, splenomegaly, and increased susceptibility to infection and bleeding (bruising). Circulating malignant cells have hair-like projections, which are cytoplasm extensions, and the cells are most accurately detected by flow cytometry. Characteristically, they have high expression of B-cell markers CD20 and CD22, are positive for CD19 and surface immunoglobulin, and display characteristic antigens CD11c, CD103, CD25, and CD123. By immunohistochemistry of the bone marrow or spleen, HCL cells express tartrate-resistant acid phosphatase (TRAP) and Annexin 1A (Anxa1) [3–5].

Perhaps the most important HCL marker is the BRAF V600E mutation, reported in 2011 and 2012 to be present in 85%–100% of classic HCL cells, detectable by either polymerase chain reaction or immunohistochemistry [6, 7]. In the normal mitogen-activated protein kinase (MAPK) pathway, BRAF promotes phosphorylation of MEK, which in turn promotes phosphorylation of ERK, which leads to cell proliferation. BRAF carrying the V600E mutation is constitutively active and leads to increased proliferation and the HCL phenotype. This mutation is also seen in 50% of melanomas

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and lower percentages of other malignancies, including anaplastic thyroid cancer, lung cancer, and gliomas. It confers sensitivity to BRAF inhibitors [8, 9].

An HCL variant (HCLv) also has cytoplasmic projections and strongly displays B cell antigens, but its clinical course is more aggressive than classic HCL, with a poor response to purine analogs [10–12], although it had good response to concurrent cladribine-rituximab [13]. HCLv, as defined by the World Health Organization, lacks CD25, TRAP, and Annexin 1A [14, 15]. HCLv also lacks the BRAF V600E mutation [16–18] and usually lacks CD123 [19]. Although HCLv has previously been reported to be only 10% as frequent as HCL [20], the World Health Organization in 2016 reported 1,100 new cases of HCL and 810 new cases of HCLv in the U.S. [21]. Compared with HCL, HCLv has fewer cytopenias, more lymphocytosis, and a higher disease burden, including massive splenomegaly.

In 2009, a molecularly defined variant was reported, expressing unmutated IGVH4-34 as the immunoglobulin rearrangement [22]. These patients can appear phenotypically like HCL or HCLv but, like HCLv, have a poor response and outcome after single-agent chemotherapy and lack BRAF V600E [16]. This variant is becoming well recognized as the cause of a more aggressive presentation of HCL [23, 24].

HCL was first described as a distinct neoplasm by Bertha Bouroncle and colleagues in 1958, when survival was 2 years or less from diagnosis [1]. In 1976, when treatments included mainly splenectomy and steroids, a median survival of 4 years was reported [25]. Treatment with purine analogs cladribine or pentostatin, introduced in the late 1980s, has substantially improved the response rate, with 75%–90% of patients achieving complete remission (CR), and about 50% still in remission at 15 years, based on conservative follow-up including blood counts [26]. Follow-up with routine bone marrow biopsies in younger patients showed a median CR duration under 5 years [27]. Despite the high CR rates, minimal residual disease (MRD) often persists and is thought to lead to eventual disease relapse. Classification as a CR requires HCL to be absent by morphologic staining, but MRD can often be detected by bone marrow biopsy immunohistochemistry or flow cytometry of the blood or bone marrow aspirate (BMA) [5].

Current Treatment Approaches

Guidelines for the diagnosis and management of HCL have been published by the U.S. National Comprehensive Cancer Network [12], the European Society for Medical Oncology (ESMO) [11], and the international HCL Foundation [5].

The need for treatment in HCL is defined as cytopenia of at least one type, symptomatic splenomegaly, enlarging lymph nodes, or frequent infections [10, 28]. Cytopenias requiring treatment include neutrophils $<1 \times 10^9$ per L, hemoglobin <10 g/dL, or platelets $<100 \times 10^9$ per L. Patients with these indications may be asymptomatic, but delaying treatment is not appropriate, because cytopenias will worsen and place patients at a higher risk for myelosuppressive toxicities.

Historically effective therapies included splenectomy and interferon. Splenectomy improves normal blood counts, because enlarged spleens sequester and remove normal blood cells from the circulation (hypersplenism). However, tumor cells continue growing in the marrow and this allows the disease to progress so that once treatment is indicated, the HCL is very far advanced. Interferon, now rarely used, was shown in a randomized trial to be inferior to the purine analog pentostatin and poorly effective after failure of pentostatin [29]. For the past 25–30 years, purine nucleoside analogs cladribine and pentostatin have been the first-line therapy in patients with HCL. Cladribine is used more often because it can be given in a single 5–7 day course, whereas pentostatin requires 3–6 months of every 2-week dosing. Second-line treatment of HCL has for decades been to be repeat purine analog as a single agent, particularly if the first response lasted at least 2–4 years. The guidelines from 2017 specify retreatment with initial or alternative purine analog $\pm$ rituximab if the CR was ≥2 years, alternative purine analog $\pm$ rituximab, clinical trial, or interferon if the CR was <2 years, and rituximab in either case if unable to receive another purine analog [12, 29]. In the last several years, because of the increased availability of additional options and clinical trials for first- or second-line treatment, retreatment with the same or even alternative purine analog alone is becoming less common.

The anti-CD20 monoclonal antibody (mAb) rituximab had marginal activity in once-relapsed or multiply relapsed HCL as a single agent, with the largest trial in relapsed HCL achieving 13% CRs and an overall response rate (ORR) of 25% in 24 patients [30]. Improved efficacy was achieved when rituximab was combined with purine analog [26, 31]. After the discovery of the BRAF V600E mutation in HCL, the small-molecule inhibitor vemurafenib, approved for BRAF V600E-positive (+) melanoma, was found to have efficacy in HCL [32, 33]. Vemurafenib demonstrated a high ORR in two phase II trials (one conducted in Italy, the other in the U.S.) in patients with relapsed or refractory HCL (ORR and CRR, 96% and 35%, respectively, in the Italian trial [n = 26]; 100% and 42%, respectively, in the U.S. trial [n = 24]). However, CRs remained MRD+, and median relapse-free survival of the Italian trial was only 19 months for CRs [33]. Results from a phase II trial of the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib were presented, reporting ORR 78% and CR 49%, and 30% of the CRs were without MRD [34]. When vemurafenib was combined with rituximab, 26 (96%) of 27 evaluable patients achieved CR, and 65% of the CRs were without MRD [35]. A phase II trial with the Bruton's tyrosine kinase inhibitor ibrutinib is ongoing, with initial results showing an ORR of 46% at a median follow-up of 22 months [36].

In HCLv, the response to first-line purine analog cladribine is poor, with 8% CR and a 44% ORR out of 39 cases reviewed from the literature [13, 20]. CRs in 86% of seven patients with HCLv were reported with rituximab given 1 month after cladribine [31, 37]. Rituximab begun the same day as cladribine achieved 90% CRs and 80% MRD-negative CRs in 10 patients with HCLv [13]. As synergy between rituximab and purine analogs works by rituximab sensitizing malignant cells to the purine analog [38], and because cladribine is excreted rapidly, immediate treatment with rituximab may be advantageous. Regardless, patients with HCLv should not be treated with cladribine alone, but rather should receive rituximab combined in some sequence with a purine analog. Patients with IGHV4-34+ HCL, which may be immunophenotypically identical to classic HCL, should also receive a purine analog

combined with anti-CD20 mAb rather than single-agent purine analog [22]. We have reported driver mutations in the *MAPK2* (MEK) gene in patients with this variant [39], and these mutations may be a target for MEK inhibition [24]. Ibrutinib with or without venetoclax has been reported anecdotally to achieve at least a temporary response in HCLv [40, 41]. However, as HCLv is BRAF wild type, patients are not candidates for BRAF inhibitor therapy, and new options are urgently needed. One type of treatment that has shown efficacy in multiply relapsed HCL and HCLv, and until now restricted to clinical testing, is the use of recombinant immunotoxins (RITs).

Moxetumomab Pasudotox

RITs are chimeric proteins containing the variable fragment (Fv) or antigen-binding fragment (Fab) region of a mAb attached by a peptide linker to a portion of a protein toxin [42]. The Fv binds to the cancer cell, and the toxin enters and kills the cell. *Pseudomonas* exotoxin A (PE), made by *Pseudomonas aeruginosa*, is used to make Moxe [43]. Native PE is a large protein that kills nonselectively, because it binds to lipoprotein receptor-related protein (LRP), a receptor that is found on many cell types [44]. To make Moxe, the region of PE (domain I) that binds to LRP is deleted and replaced with an Fv that binds with high affinity to CD22, which is highly expressed in HCL and other B-cell malignancies. This alteration converts the toxin to one highly selective for CD22-expressing cells.

The mechanism by which Moxe and other RITs kill target cells is complex and still not fully understood [45]. PE contains three major domains (I, II, and III). As described above, in Moxe, domain I is replaced with an Fv that can bind to CD22, enabling Moxe to bind to CD22 on the cell surface and internalize by receptor-mediated endocytosis. Within the endocytic compartment, Moxe is cleaved by furin within domain II [46], and the Fv is transferred to lysosomes where it is destroyed. The "killing' domain III undergoes retrograde trafficking by its carboxy terminus [47] to the endoplasmic reticulum from which it is translocated to the cytosol. In the cytosol, domain III catalyzes the ADP ribosylation and inactivation of elongation factor-2 leading to arrest of protein synthesis and apoptotic cell death [48].

BL22, which contains the Fv portion of mAb RFB4 fused to PE38 and is the predecessor to Moxe, was constructed by cloning the Fv region of the anti-CD22 mAb RFB4 isolated by Peter Amlot in England [49] and attaching the Fv to PE38 [50]. The Fv of BL22 was stabilized by engineering a disulfide bond connecting the light and heavy chains of the Fv [51]. BL22 was evaluated in clinical trials and found to be active in patients with drug-resistant HCL but, unfortunately, had very little activity in acute lymphoblastic leukemia, another disease target for anti-CD22 RITs [52]. To increase the activity of BL22, the CDR3 region of the heavy chain was mutated, and variants with a high affinity for CD22 were isolated. The most promising mutation contains V_H amino acids 100, 100a, and 100b converted from Ser-Ser-Tyr to Thr-His-Trp [53]. This mutant, originally called HA22, bound to CD22 with 14-fold higher binding owing to a lower off-rate. This molecule was renamed CAT-8015 and eventually Moxe. The mutations in CDR3 increased the cytotoxic activity of the RIT and did not increase its risk of hemolytic uremic syndrome (HUS), a syndrome involving transient thrombocytopenia, renal insufficiency and hemolytic anemia.

In phase I and II trials, BL22 achieved 47%–61% CRRs in multiply relapsed HCL [54–56]. In 6%–13% of patients with HCL, a reversible form of HUS was observed, which appeared to require the CD22 Fv, because HUS had not been seen with LMB-2 and other RITs containing PE38 [57–59].

Clinical Studies of Moxetumomab Pasudotox-tdfk

The safety and efficacy of Moxe for the treatment of patients with relapsed and refractory HCL after two or more prior therapies were assessed in a phase I dose escalation trial in 49 patients [60, 61] and in an international pivotal phase III trial in 80 patients [62]. The eligibility and design of the trials are summarized in Table 1, efficacy is in Tables 2 and 3, and safety is in Table 4.

Trial Design

The phase I trial (NCT00462189) was designed with dose escalation in three or four patients each at 5, 10, 20, 30, and 40, and 50 μg/kg every other day for three doses (QOD × 3), followed by a fixed-dose cohort. As shown in Table 2, 16 patients received 5–40 μg/kg QOD × 3, and 33 received 50 μg/kg QOD × 3. The phase III (pivotal) trial (NCT01829711) was designed as a single-arm non-placebo–controlled trial, with all patients receiving Moxe at 40 μg/kg QOD × 3. Owing to improved production of the phase III material, the specific activity of the phase III material was slightly higher than the phase I material, so 40 μg/kg during phase III was considered approximately equivalent to 50 μg/kg during phase I. As shown in Table 1, eligibility for the two trials was similar, with the main difference in phase III being the lack of antidrug antibody (ADA) testing to determine eligibility for enrollment or retreatment. This difference in eligibility for phase III was expected to lead to a ∼25% decrease in response rates because of lack of selection of an ADA-negative population. In the phase III trial, there was a six-cycle limit, based on the number of cycles needed during phase I for most patients to achieve an optimal response.

Clinical Efficacy

Responses in the phase I trial were first evaluated after 28 patients [60] and finally after a total of 49 patients [61]. Patients received a median of two prior courses of a purine analog (range, 1–7), including cladribine in all patients, and 61% had received prior rituximab. Moxe induced an overall response in 86% of patients. CR was achieved in 57% of patients. CR was not related to the number of prior courses of purine analog or duration of response to the last course of purine analog. However, of eight patients with prior splenectomy, none achieved CR; of 41 patients who had not had prior splenectomy, 28 (68%) achieved CR.

Long-term follow-up results from 33 patients on the expanded phase I cohort receiving 50 μg/kg QOD × 3 for 143 cycles showed a median CR duration of 42.4 months [61]. Among 32 patients assessable for MRD by BMA flow cytometry (the most stringent assessment), the median (range) CR duration was 13.5 (4.9–42.4) months in patients positive for MRD (n = 9), versus not reached in patients negative for MRD (n = 11; p < .001). Of the 11 MRD-negative CRs, 10 (91%) had

Table 1. Design of phase I and phase III (pivotal) trials (applies to both unless indicated)

Eligibility
Confirmed diagnosis of HCL/HCLv
At least one indication for treatment
Neutrophils <1/nL
Hemoglobin <10 g/dL
Platelets <100/nL
Symptomatic splenomegaly
Lymphocyte count >20/nL (phase I)
More than two prior therapies
More than two prior purine analogs, unless <2-y response or unacceptable toxicity to first course (phase I)
More than two prior purine analogs, or one prior purine analog plus more than one course of rituximab or BRAF inhibitor (phase III)
No prior immunotoxin
ECOG performance status 0–2
No central nervous system disease
Acceptably low or absent level of antidrug antibodies (phase I)
No prior mAb therapy for 1 mo, no other treatment for 3 wk (phase III)
No prior treatment within 4 wk (phase III)
Creatinine clearance >60 mL/min by Cockroft-Gault formula (phase I)
Creatinine clearance >60 mL/min by Cockroft-Gault formula or creatinine <1.5 mg/dL (phase III)
Treatment
Moxetumomab pasudotox administered as 30-minute infusion on days 1, 3, and 5
Cycles 28 days apart
Moxetumomab pasudotox dose 5–50 μg/kg (phase I)
Moxetumomab pasudotox dose 40 μg/kg (phase III)
Retreatment requires low or absent level of antidrug antibodies (phase I)
Retreatment requires no progressive disease or unacceptable toxicity
Two retreatment cycles after documentation of CR without MRD (phase I)
No retreatment after documentation of CR without MRD, or after cycle 6 (phase III)

Phase I trial, NCT00462189; phase III trial, NCT01829711.
Abbreviations: CR, complete remission; ECOG, Eastern Cooperative Oncology Group; HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant; mAb, monoclonal antibody; MRD, minimal residual disease.

ongoing CR for 16.3–72.1 (median 42.3) months, and nine patients were still without MRD at the end of the study.

In the phase III trial, at a median follow-up of 16.7 months, 75% of patients experienced an objective response, 80% experienced a hematological remission, 33 patients (41%) achieved CR, and 24 (30%) achieved durable CR [62]. Durable CR required resolution of cytopenias to persist for at least 6 months after first documentation of CR. Of the nine CRs not qualifying for durable CR, only two had cytopenias recur during the 6-month follow-up period. In five patients, CR was documented too late to report 6 months of resolved blood counts, and the remaining two patients could not comply with the 6-month follow-up period. Of the patients who achieved a CR, 82% (27/33) had an immunohistochemistry MRD-negative status, indicating that most CRs were without MRD.

Pharmacokinetic Properties

Pooled data from the phase I trial and phase III trials in patients with HCL were used to develop a population pharmacokinetics model [63]. Moxe pharmacokinetics were linear from 5 μg/kg to 50 μg/kg dosing and well described by a one-compartment model. Moxe clearance was shown to decrease between days 1 and 5 of cycle 1, consistent with B-cell depletion. Phase III patients with ADA titers above 1:10,240 had an approximately fourfold increase in clearance compared with those with lower titers. These data plus the lower response rates in patients with high titers indicate that ADA, if high enough, is neutralizing. Also, high titers do not cause significant toxicity, but they do block efficacy [63].

Pharmacokinetic parameters were assessed in the phase III trial using a noncompartmental approach [64]. Pharmacokinetic exposure increased from the first to the third dose of cycle 1, most likely because of post-treatment depletion of mostly malignant but also normal B cells expressing CD22. Moxe treatment caused a rapid and sustained depletion of circulating B cells positive for the mature B-cell marker CD19 (mean reduction from baseline on day 8: 89%). Higher pharmacokinetic exposure was significantly associated with low baseline CD19+ B-cell counts. The relationship with pharmacokinetic exposure was weakened after dosing and CD19+ B-cell depletion.

Patients with high (equal to or greater than the median) pharmacokinetic exposure had a better response than those with lower pharmacokinetic exposure [63]. In the phase I trial, the rate of complete response was 67%–71% in the high pharmacokinetic-exposure group, compared with 46%–50% in the low-pharmacokinetic-exposure group. In the phase III trial, patients with higher Moxe exposure had higher ORR, CR, and durable CR rates compared with patients with lower exposure. Patients with ADA >10,240 had fourfold higher clearance compared with patients with lower ADA levels, which were associated with lower CR and durable CR rates but similar ORR rates compared with patients with lower ADA.

Immunogenicity

Because Moxe contains a bacterial toxin fragment, immunogenicity is expected, with the potential to neutralize its activity. In the phase I trial of Moxe in patients with HCL, antidrug antibodies were detected in 65% (17/26) of evaluable patients after a median of two treatment cycles [60]. Possibly owing to blunted humoral immunity in patients with HCL treated with purine analogs and often prior rituximab, doses of Moxe in patients with ADA could still achieve CR, including CR without MRD. Cell-mediated immunity may also be lower in HCL, as demonstrated by patients with HCL recognizing fewer T-cell epitopes than mesothelioma patients [65]. Thus, the phase III trial did not exclude patients with immunogenicity from enrollment or retreatment. The incidence and prevalence of ADA in the phase III trial were 66% and 88%, respectively [64]. ADA was detected in 84% of patients, including 59% at baseline.

Table 2. Efficacy results of phase I trial of moxetumomab pasudotox-tdfk

Dose level	*n*	ORR, *n* (%)	PR, *n* (%)	CR, *n* (%)	MRD-neg CR, *n* (%)
5 μg/kg QOD × 3	3	3 (100)	3 (100)	0 (0)	0/3 (0)
10 μg/kg QOD × 3	3	3 (100)	1 (33)	2 (67)	0/2 (0)
20 μg/kg QOD × 3	3	2 (67)	0 (0)	2 (67)	0/2 (0)
30 μg/kg QOD × 3	3	2 (67)	1 (33)	1 (33)	0/3 (0)
40 μg/kg QOD × 3	4	3 (75)	1 (33)	2 (50)	1/3 (33)
50 μg/kg QOD × 3	33	29 (88)	8 (24)	21 (64)	11/32 (34)
Total	49	42 (86)	14 (29)	28 (57)	12/45 (27)

Response rates were determined based on the total number of patients treated, not the total evaluable for response.
Abbreviations: CR, complete remission; MRD, minimal residual disease; NE, nonevaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; QOD × 3, every other day for three doses.

Table 3. Efficacy results of phase III trial of moxetumomab pasudotox-tdfk (dose level 40 μg/kg every other day for three doses for all patients)

Total treated	Blinded independent central review (*n* = 80)	Investigator-assessed (*n* = 80), *n* (%)
CR	33 (41)	41 (51)
MRD-neg CR	27 (34)	26 (33)
Durable CR	24 (30)	38 (48)
PR	27 (34)	22 (28)
PD	2 (3)	3 (4)
NE	6 (8)	5 (6)
ORR	60 (75)	63 (79)

Response rates were determined based on the total number of patients treated, not the total evaluable for response.
Abbreviations: CR, complete remission; MRD, minimal residual disease; NE, nonevaluable; ORR, overall response rate; PD, progressive disease; PR, partial response.

ADA was higher in patients achieving stable disease and progressive disease than those with CR and partial response, suggesting that neutralizing antibodies did interfere with efficacy, at least at high levels. Thus, Moxe was effective despite significant immunogenicity.

Safety

The most common treatment-related adverse events in the phase I trial (Table 4) were hypoalbuminemia (observed in 69% of patients), elevated aminotransferase levels (alanine aminotransferase: 63%; aspartate aminotransferase: 61%), peripheral edema (43%), fever (43%), myalgias (41%), headache (37%), nausea (33%), fatigue (29%), other edema (25%), hypotension (25%), chills (22%), creatinine elevation (18%), proteinuria (18%), capillary leak syndrome (CLS; 16%), dizziness (14%), increased weight (14%), hematuria (14%), elevated gamma glutamyl transferase levels (12%), and arthralgia (10%) [61]. Two patients had reversible laboratory changes that were consistent with grade 2 (non-dose limiting) HUS. In these two patients, one on 30 and one on 50 μg/kg QOD × 3, the platelet count reached a nadir of 106 and 120/nL, and the creatinine reached a peak of 1.53 and 1.66 mg/dL, respectively [60]. These two grade-2 events were not considered dose limiting, and no other dose-limiting toxicities were observed. However, mild and moderate toxicities like hypoalbuminemia, proteinuria, edema, dizziness, hypotension, and weight gain were all considered manifestations of CLS. This toxicity has been attributed to damage to endothelial cells, but the

Table 4. Treatment-related adverse events during phase I and III testing

	Percentage of patients	
Adverse events	Phase I	Phase III
Most common grade 1–2		
Hypoalbuminemia	69	15
Alanine aminotransferase	63	19
Aspartate aminotransferase	61	18
Peripheral edema	43	26
Fever	43	20
Myalgias	41	13
Headache	37	21
Nausea	33	28
Fatigue	29	18
Other edema	25	13
Hypotension	25	<10
Chills	22	15
All grade 3–4		
Lymphopenia	4	7.5
Hemolytic uremic syndrome	0	5.0
Capillary leak syndrome	0	2.5
Nausea	0	2.5
Anemia	0	2.5
Leukopenia	4	2.5
Hypertension	0	2.5
Thrombocytopenia	0	2.5
Neutropenia	2	2.5
Acute kidney injury	0	2.5
Febrile neutropenia	2	0
Fever	1	0
Alanine aminotransferase	6	0
Gamma Glutamyltransferase	4	0
Low haptoglobin	4	0
Acute kidney injury	0	2.5

detailed mechanism is not clearly established. CLS is not specific to CD22 targeting and has been seen with other RITs [57, 59, 66, 67].

In the phase III trial, the most frequent treatment-related adverse events were nausea (28% of patients), peripheral edema (26%), headache (21%), and fever (20%) [68]. Ten patients experienced CLS and/or HUS; all cases were manageable and reversible: seven patients (9%) had CLS (grade 2: $n = 5$; grade 4: $n = 2$); seven patients (9%) had HUS (grade 2: $n = 2$; grade 3: $n = 3$; grade 4: $n = 2$); and four patients (5%) had both CLS and HUS. HUS and CLS were the most common adverse events leading to withdrawal of therapy. HUS began on or before day 8, similar to CLS. As in the phase I trial, patients with HUS did not require plasmapheresis for resolution of HUS, indicating that the mechanism of HUS is different from that observed with Shiga-like toxin.

During the phase III trial, we identified two strategies that may prevent or lessen the severity of CLS and HUS. They are based on the observation that capillary leak is gradual and constant and that hypovolemia may increase the risk of HUS because renal injury and increased concentration of Moxe in the glomerular capillaries. The first strategy is to avoid intravenous fluid other than the 1 liter required before and after each dose, and instead to encourage water (or other beverage) intake up to 250 mL (∼1 cup) per hour and not to go more than 2–3 hours at night without drinking. Second, symptoms worsening dehydration or preventing drinking, namely fever, nausea, or headache, were treated effectively and rapidly with dexamethasone 4 mg orally. Of the first nine patients treated on the phase III trial without these recommendations, three (33%) had grade 3 HUS events, but after instituting these precautions, only one (6%) of the next 17 patients had a grade 1 HUS. Patients should keep a log of fluid intake, which should be checked by the treatment team at least daily, at least by phone or e-mail and/or text. Patients should also be monitored for HUS on day 8 by checking hematology and chemistry labs, looking for decreases in platelets, haptoglobin, and hemoglobin and increases in creatinine, indirect bilirubin, lactate dehydrogenase, and urine hemoglobin. Schistocytes increase late, and less than 5 per high power field on day 8 does not rule out HUS. Evidence of CLS, including proteinuria, hypoalbuminemia, edema, and weight gain, is common, usually low grade, and should not be confused with HUS. If HUS does develop, patients generally do well with supportive care without plasmapheresis, and intravenous fluid may also be unnecessary and in fact may cause fluid overload. HUS begins to resolve around day 12–16, first with platelets and then with creatinine correcting. Abnormalities should reverse and the worst long-term consequence of HUS is usually inability to continue retreatment with Moxe to facilitate MRD-free CR.

Future Development

Moxe was active in a phase I study in pediatric patients with relapsed or refractory childhood acute lymphoblastic leukemia, with a safety profile supporting further clinical study [69]. A phase II trial designed to confirm these results was completed. In HCL and HCLv, improved efficacy may be possible by decreasing immunogenicity and enhancing tumor penetration by Moxe through improved reduction in HCL and HCLv tumor burden. To achieve both goals, Moxe is being combined with rituximab, thus reducing levels of normal B cells, humoral immunity [70], and HCL and HCLv burden. As reviewed above, rituximab alone had low response rates in HCL, although it did decrease tumor burden [30]. Use of Moxe immediately following rituximab may result in elimination of MRD not possible before cytoreduction with rituximab. Although rituximab could not block immunogenicity of a >200 kDa mAb conjugate in patients with solid tumors [71], it might block immunogenicity from the 63 kDa Moxe molecule in patients with HCL who have impaired immunity. A trial of Moxe combined with rituximab is underway at National Institutes of Health for relapsed or refractory HCL and HCLv. Rituximab is given on day 1 of cycles spaced 4 weeks apart, except cycle 1, where rituximab is started 3 days before the first of three doses of Moxe.

An early access program for Moxe in relapsed or refractory HCL is being initiated (NCT03501615).

Conclusion

Moxe is a new option for patients with relapsed or refractory HCL and HCLv in the U.S. following Food and Drug Administration approval in September 2018. It is unique in its achievement of MRD-negative CR in this chemo-resistant population, without chemotherapy-type toxicities. Elimination of MRD enhances the durability of CR, allowing many patients to be followed treatment free. Moxe is approved in third line, and achievement of MRD-free CR without chemotherapy makes its use appropriate prior to third-line chemotherapy or nonchemotherapy agents that are unable to clear MRD. Current goals include increasing MRD-negative CRs by combining Moxe with rituximab. Future development will include testing Moxe combined with other agents for CD22+ malignancies in addition to HCL and HCLv.

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Disclosures

Robert J Kreitman: Co-inventor on the NIH patent for Moxetumomab Pasudotox (IP); **Ira Pastan:** Co-inventor on immunotoxin patents assigned to the Government of the United States of America, as represented by the Secretary of the Department of Health and Human Services, on behalf of the NIH, and which are licensed by MedImmune (IP).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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