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Moxetumomab pasudotox as re-treatment for heavily-pretreated relapsed hairy cell leukemia

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Moxetumomab pasudotox (Moxe) is a bacterial toxin--based drug consisting of an anti-CD22 immunoglobulin variable domain genetically joined to *Pseudomonas* exotoxin (PE38) [1]. The drug was approved in September 2018 by the FDA to treat patients with hairy cell leukemia (HCL) who have undergone at least two lines of standard treatments. Its approval was based on its safety demonstrated in a phase 1 trial [2,3] and efficacy in a phase 3 trial that evaluated the drug in relapsed/refractory HCL and demonstrated a durable complete response (CR) of 30 percent, an objective response rate (ORR) of 75 percent, and 85 percent of complete responders achieving minimal residual disease (MRD) negativity [4]. The median duration of hematologic remission from CR, median duration of complete response, and median progression-free survival (PFS) were not reached. Here, we report on three patients with refractory HCL initially treated with Moxe achieving at least partial response (PR), who subsequently developed disease progression and were re-treated with Moxe.

We reviewed data from three patients with classic HCL treated at the National Institutes of Health (NIH), Stanford University, and Hospices Civils de Lyon in France. The first patient had HCL with a BRAF p.V600E mutation and was started on cladribine before initiating the first course of Moxe in 2007 on clinical trial. The patient achieved a PR after three cycles of 5 micrograms/kilogram (ug/kg) every other day for 3 doses (QOD x3), with positive neutralizing antibodies detected two months after initiating therapy [2]. (In the phase 1 clinical trial, patients received dosages of 5 to 50 ug/kg. The current approved dosage is 40 ug/kg.) The patient subsequently relapsed after two months and was treated with rituximab alone, bendamustine and rituximab, dabrafenib and trametinib, and finally

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S.C., H.G., and R.J.K. provided patient care. I.P. and R.J.K. performed ancillary tests, I.R.Y., S.C., H.G., and R.J.K. collected and analyzed results, wrote and reviewed the paper.

Disclosure statement

RJK and IP are coinventors on the NIH patent for Moxetumomab Pasudotox. IY, SC, and HG declare no competing financial interests.

pentostatin and rituximab. In January 2019, the patient developed worsening cytopenias with WBC 2.5 K/uL, ANC 1.575 K/uL, ALC 0.7 K/uL, hemoglobin 15 g/dL, and platelets 85 K/uL. Soluble CD22 was elevated at 3343 pg/ml and soluble CD25 was 43578 pg/ml. HCL cells were detectable in the peripheral blood by flow cytometry. A bone marrow aspirate showed 70 percent B cells consistent with HCL, and a bone marrow biopsy showed 50 to 60 percent HCL cells. The patient was then re-treated with six cycles of Moxe.

The second patient was originally treated with three courses of cladribine and a single course of rituximab, followed by the first course of Moxe on clinical trial in 2007 for four cycles of 20 ug/kg QOD x3. The patient underwent a bone marrow biopsy, which showed a complete response, with negative MRD by peripheral flow cytometry. By April 2019, the patient's CBC showed worsening cytopenias with a WBC 2.6 K/uL, ANC 1.092 K/uL, ALC 1.427 K/uL, hemoglobin 14.5 g/dL, and platelets 56 K/uL. The patient had low levels of neutralizing antibodies to PE38 [2], and the soluble CD22 was 6218 pg/ml with soluble CD25 6829 pg/ml. No circulating HCL cells were detected. The patient was re-treated with six cycles of Moxe for relapsed disease.

The third patient was diagnosed with HCL in 1992 and received interferon (1992 to 1994), pentostatin (1995), cladribine (2002, 2010, 2015), rituximab (2010 – 2012), and Rituximab and Fludarabine (2013). The patient relapsed in November 2015 with cytopenias (platelets 40 K/uL, neutrophils 0.3 K/uL, hemoglobin 10.7 g/dL). Six cycles of Moxe (40 micrograms QOD x3) were given from January to June 2016 on clinical trial, and the patient achieved a CR by CBC and bone marrow biopsy. In April 2019, new cytopenias developed (hemoglobin 14 g/dL, platelets 107 K/uL, and neutrophils 0.88 K/uL) with bone marrow aspirate confirming relapse of HCL. In July 2019, the patient was re-treated with six cycles of Moxe (40 micrograms QOD x3).

Responses (both initial and at re-treatment) were assessed as per the Hairy Cell Leukemia Foundation consensus guidelines [5], with a CR defined as near normalization of blood counts (hemoglobin >11 g/dL, platelets >100,000/microL, absolute neutrophil count >1500/microL), regression of splenomegaly on physical exam, and absence of morphologic evidence of HCL on both the peripheral blood smear and the bone marrow examination. Partial response was defined by near normalization of the peripheral blood counts with a minimum of 50 percent improvement in both organomegaly and bone marrow biopsy infiltration with HCL.

Patients' prior treatments and clinical outcomes are described in Table 1. Time from initial treatment with Moxe on clinical trial to re-treatment with Moxe after its FDA approval ranged from three to twelve years. All three patients were retreated with Moxe at 40 ug/kg QOD x3. After re-treatment, two of three patients demonstrated complete resolution of cytopenias and no peripheral HCL, with one patient's CR confirmed on bone marrow biopsy (but with positive MRD). The two patients who achieved complete resolution of cytopenias demonstrated an increase in neutralizing antibodies after they had become negative prior to re-treatment. Both remained elevated after completing treatment, with the longest duration seen at eight months after the completion of six cycles. Both patients also remain free of

cytopenias at the most recent follow-up (21 months and 18 months since completion of re-treatment, respectively).

The third patient was re-retreated with Moxe but without improvement in cytopenias. A bone marrow biopsy after re-treatment confirmed refractory disease with 80 percent infiltration of HCL. Neutralizing antibodies prior to re-treatment were not checked in this patient. The patient was treated with rituximab and ibrutinib, the latter of which was stopped due to allergic reaction and continued on rituximab with slight improvement in blood counts.

We acknowledge the ethical dilemma of prescribing a therapy that was not studied in re-treatment in clinical trials; the decision to re-treat was ultimately guided by perceived benefits (inducing a second remission) greater than possible harms of compounded or unknown adverse events. The risk of harm was also reduced by the duration of time that had elapsed since initial treatment.

While prognosis in HCL is generally favorable after treatment with purine nucleoside analogs pentostatin or cladribine [6–8], relapses occur in about half of patients initially treated with a purine analog after sixteen years of follow-up, with patients likely to experience serial relapses [9]. We report that in a heavily pretreated patient cohort, patients previously treated with Moxe may be safely re-challenged with Moxe and may benefit with a disease response. None of the three patients experienced serious adverse reactions including capillary leak syndrome or hemolytic uremic syndrome, and two of three patients had excellent disease response. We note the extended time that elapsed between initial treatment and subsequent re-treatment in this patient population; further study is required to elucidate whether similar safety and efficacy may be seen with earlier re-treatment. We also note that patients received higher, standard doses of Moxe during re-treatment, and we recommend further study to determine whether this correlates with depth of response.

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Table 1.

Prior treatments and clinical outcomes.

	Patient 1	Patient 2	Patient 3
Age	40	66	52
Response to initial Moxe	PR	CR	CR
Tolerability to initial Moxe	No significant toxicity	No significant toxicity	No significant toxicity
Neutralizing antibodies after initial treatment	Low positive	Low positive	Not assessed
Neutralizing antibodies before retreatment	Negative	Negative	Not assessed
Lines of treatment prior to initial Moxe	Cladribine	Cladribine, Rituximab	Interferon, Pentostatin, Cladribine, Rituximab, Fludarabine
Lines of treatment prior to re-treatment with Moxe	Rituximab, Bendamustine/Rituximab, Dabrafenib/Trametinib, Pentostatin/Rituximab		
Response to retreatment with Moxe	CR	Complete resolution of cytopenias	Refractory
MRD	Peripheral flow negative 0.1% by marrow flow	Peripheral flow negative; marrow not assessed	Not assessed
Neutralizing antibodies after retreatment	Positive	Positive	Not assessed
Tolerability of Moxe Re-treatment	No significant toxicity	No significant toxicity	Headaches, no other significant toxicity
Time between treatment and re-treatment with Moxe	12 years	12 years	3 years