BRIEF REPORT
Ofatumumab for a Rituximab-Allergic Child With Chronic-Relapsing Paraneoplastic Opsoclonus–Myoclonus

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Ofatumumab is a fully human anti-CD20 monoclonal antibody in phase II–III trials for various autoimmune and lymphoreticular diseases. We used it to treat a rituximab-allergic child with severe, chronic-relapsing, opsoclonus–myoclonus syndrome (OMS), characterized by persistent cerebrospinal fluid (CSF) B-cell expansion and T-cell dysregulation. He had relapsed despite chemotherapy, plasma exchange with immunoadsorption, and resection of ganglioneuroblastoma, detected 3 years after OMS onset. The four ofatumumab infusions (1,195 mg/m^2 total dose) were well tolerated, and CSF B-cell expansion was eliminated. No further relapses have occurred in 3 years, but he remains on low-dose ACTH with neuropsychiatric residuals of OMS. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: anti-B-cell therapy; ganglioneuroblastoma; paraneoplastic disorder; plasma exchange/immunoadsorption

INTRODUCTION

Rituximab, the prototypic anti-CD20 monoclonal antibody, has been used to treat a variety of pediatric autoimmune disorders, including opsoclonus–myoclonus syndrome (OMS) [1,2]. Cerebrospinal fluid (CSF) B-cell expansion in OMS is a biomarker of disease activity [3], and rituximab is extremely effective in normalizing CSF B-cell frequency with clinical benefit [1].

Anaphylactic reaction to the mouse component (25% of the molecule) of the chimeric antibody is said to be rare, but has been reported in children [4]. In contrast to infusion reactions, which can be handled by adjusting the rate of infusion or pre-administering antihistamine or steroid, an individual who is truly allergic to the mouse component will not tolerate reintroduction of rituximab [5]. For that reason, fully humanized anti-CD20 biologicals are an attractive alternative [6,7]. Ofatumumab, a second-generation anti-CD20 antibody, is one such agent recently FDA approved for chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab [8–10].

We present a child who epitomizes severe, refractory, chronic-relapsing OMS with its persistent CSF B-cell expansion resistant to multiple chemotherapies. Ganglioneuroblastoma was not found until later. His inability to tolerate rituximab led us to try ofatumumab as a compassionate use agent and determine its effect on immunological biomarkers of disease activity.

CASE STUDY

The patient was a 22-month-old African-American male, who presented with irritability, trembling, ataxia, and opsoclonus, and loss of ambulation. A week into the neurological problems, he developed an RSV infection. CT scan of chest, abdomen, and pelvis was negative for tumor. Lumbar puncture disclosed leukocytosis (CSF WBC = 17 mm^{-3}, 75% neutrophils, 17% monocytes, 8% lymphocytes). He was first treated with high-dose solumedrol for 5 days then oral prednisolone 5 mg/kg for 2 days each week. There was significant improvement (50–75%), and he began to walk with a walker. However, he relapsed within 2 months of initial presentation, following an episode of otitis media, and did not improve when steroids were reintroduced. He was then treated with monthly IVIg for three courses, and later with azathioprine (first at 2 mg/kg, subsequent doses at 4 mg/kg) without improvement.

At the age of 30 months, he was evaluated at the National Pediatric Myoclonus Center. Exhibiting florid opsoclonus and myoclonic jerks, he was unable to stand or walk independently. He had trouble sleeping, extreme irritability, rage attacks, drooling, dysarthria, and hypotonia. A serum paraneoplastic antibody panel (Athena Diagnostics, Worcester, MA) was negative for eight antibodies, including anti-Hu. The serum neuron-specific enolase was slightly elevated at 16.1 mcg/L (normal < 12.5). He was placed on high-dose ACTH (H.P. Acthar Gel, 80 IU/ml) [1] and improved considerably. However, ACTH had to be discontinued due to severe hypertensive encephalopathy, and his neurologic disorder reverted to baseline severity. He received six cycles of low-dose cyclophosphamide (1,000 mg/m^2) without improvement.

He remained non-ambulatory and unable to feed himself at the age of 4 years and 4 months (2 years after OMS onset). Hence, ACTH was cautiously reintroduced at 24 IU/m^2 on alternate days (QOD), with monitoring by the renal clinic and treatment with amlodipine 2.5 mg QD for mild blood pressure elevation, trazodone 75 mg at bedtime (QHS) for sleep, and risperidone 0.5 mg BID for rage. There was some improvement in OMS on ACTH. CSF evaluation revealed lowered B-cell numbers but marked CSF T-cell dysregulation (Fig. 1). Methotrexate 5 mg/m^2 was started orally once a week and was titrated to 12.5 mg. Neurological
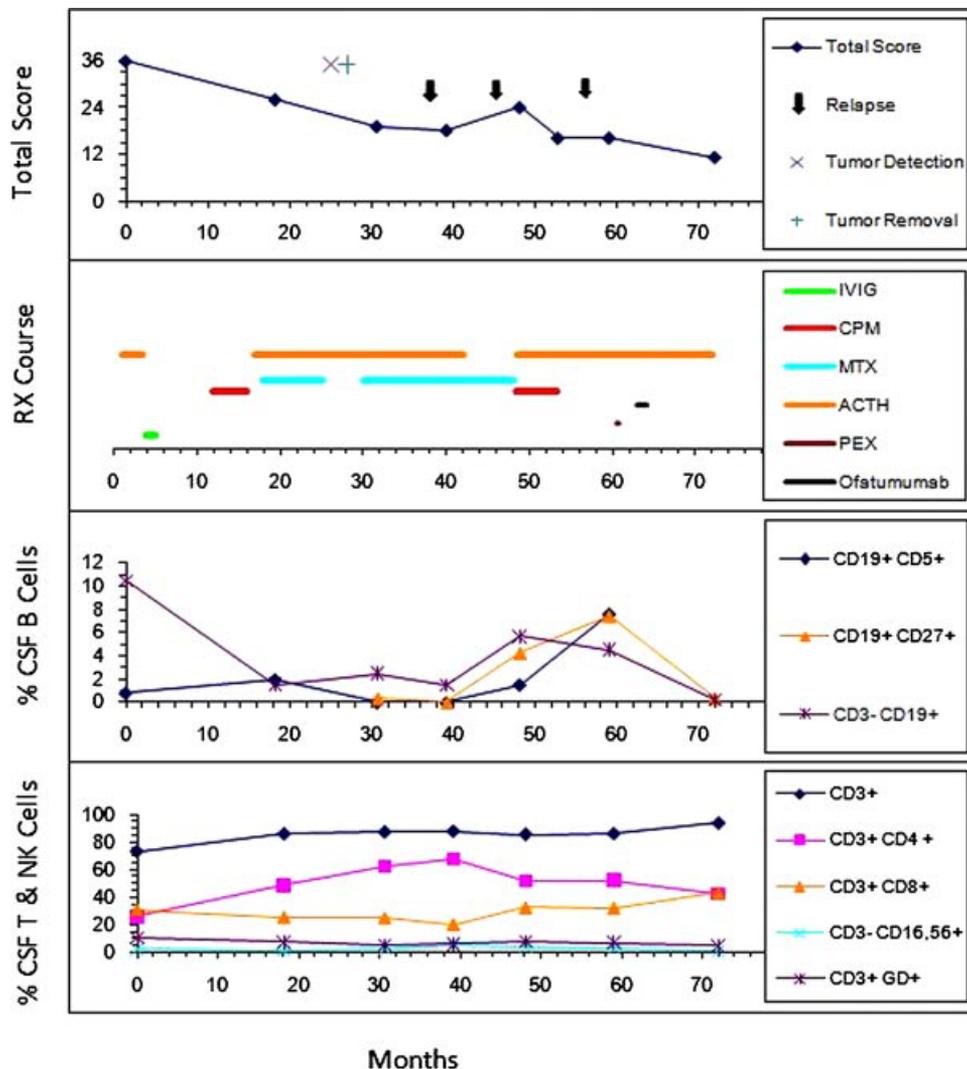
Fig. 1. Longitudinal clinical and immunological data from the first evaluation at our center. **A**: Total score. At each clinical evaluation, the patient was videotaped using a standardized protocol [1]. Videotapes were scored by a blinded, trained rater from 0 to 3 in severity for each of 12 items. The maximum motor severity is 36 points. **B**: Types and duration of immunotherapy. ACTH was given at 75 IU/m^2 twice daily (BID) for 1 week, daily (QD) for 2 weeks, then on alternate days (QOD) with dose tapering. **C**: Frequency of CSF total B-cells and B-cell subsets. The marked initial CSF B-cell expansion decreased on therapy with cyclophosphamide and tandem methotrexate. Though not precisely timed, the second and third relapse while followed at our center was associated with an increase in CSF total B-cells, in memory B-cells, and the CD5+ B-cell subset. After the treatment with ofatumumab, CSF B-cell frequency dropped below 1% into the normal range for the first time in the patient's course. In peripheral blood (not shown), CD19+ B-cell frequency fell to <1% at 1 month, and the absolute size of the circulating B-cell pool reflected the same changes. **D**: Frequency of other CSF lymphocyte subsets. Relapse was associated with reduction of the CSF T_h/T_s ratio, which also was profoundly low on the initial sampling but improved substantially before the flurry of relapses. Other lymphocyte subsets showed no major changes in frequency.

improvement was noted 4 months later. He stood with a wide base, and ran without falling, but still had myoclonus, dysarthria, and hyperactivity. Due to the difficult course and elevated serum neuron-specific enolase of 21.5 mcg/L, repeat body cavity CT and MIBG scans were recommended.

A mass was identified on CT scan in the right paraspinal region adjacent to the right renal hilum when he was almost 5 years old (3 years after OMS onset). It was resected and found to be an intermixed Schwannian stroma-rich ganglioneuroblastoma. Methotrexate was discontinued but restarted at 12.5 mg

weekly (3 months after tumor removal) for persistent neurologic and CSF abnormalities. Neurologic deterioration was noted when ACTH was tapered from 3 to 2 IU/m^2 QOD, without apparent signs of infection, and he stopped walking. ACTH was resumed and he returned to school in 4–5 days. At 6 years of age, on ACTH 4 IU/m^2 QOD and methotrexate 12.5 mg once weekly, he had significant residual symptoms. An attempt to treat ADHD with atomoxetine was unsuccessful.

Another relapse occurred when he was 6 years and 10 months old, 3 months after ACTH discontinuation and 1 month after a

sinus infection that was treated with antibiotics. He drooled and could not feed himself or walk. ACTH was restarted at 16 IU/m^2 QD for 2 weeks, then QOD. Attempted reintroduction of rituximab failed due to allergic reaction (severe uncontrollable cough despite a reduced infusion rate). He was given six more cycles of cyclophosphamide (1,000 mg/m^2) and continued on ACTH 16 IU/m^2 QOD. He improved, but had moderately severe residual neurological deficits. A switch from risperidone to aripiprazole 5 mg QD diminished his aggressive behavior.

At 7 years and 9 months, the patient relapsed again, exhibiting uncontrolled shakiness and terrible behavior, such as rages and inattention. He was more ataxic but ambulatory. The CSF immunophenotype showed active autoimmune disease, but CT scans showed no tumor recurrence. He received two plasma exchanges with protein A column immunoadsorption (ProSorba®, Fresenius, Bad Homburg, Germany) a month apart until he pulled out the catheter.

A request for compassionate use of ofatumumab was approved by the US Food and Drug Administration (IND # 100629), and our Institutional Review Board, and the mother's written consent was obtained. Ofatumumab (HuMax-CD20®) was supplied by Genmab A/S (Copenhagen, Denmark) and licensee GlaxoSmithKline Plc (Middlesex, UK). The total dose was scaled for pediatric use from the 2,200 mg administered in adults, based on an average weight of 70 kg or 1.83 m^2. The patient's body surface area was 1.05 m^2. Per the supplier's request, the IV infusion dose was 55 mg/m^2 initially, then 380 mg/m^2 on the subsequent 3 weeks (1,195 mg/m^2). Fifteen minutes prior to ofatumumab infusion, the patient was pre-medicated with acetaminophen 15 mg/kg, dexamethasone 1 mg, and cetirizine HCl 0.16 mg/kg. The infusions were well tolerated. Immunological data were collected (Table I). No toxicities were noted with ofatumumab.

The patient was seen three times after ofatumumab until the age of 9 years. He remained dependent on ACTH 13 IU/m^2 QOD. Opsoclonus was absent, and he could run, though awkwardly. Medications for rage were changed from aripiprazole to olanzepine, then ziprasidon. Now, at 11 years of age, ACTH has been tapered to 9 IU/m^2 QOD. He is still shaky, dysarthric, and ataxic, but has had no seizures on topiramate. He takes trazodone 150 mg QHS for sleep, quetiapine 50 mg for rage, and attends special education classes.

DISCUSSION

Neuroblastoma is the most common extracranial tumor of childhood arising from neuroendocrine tissue. Ganglioneuroblastoma-intermixed, such as described in this patient, is the most common type of ganglioneuroblastoma of favorable histology identified in a Children's Oncology Group (COG) review and tends to remain localized with low metastasizing potential [11]. Resection is adequate as definitive therapy and for tumor control. Tumor related deaths are extremely rare. In contrast, unfavorable histology ganglioneuromas have higher metastasizing potential and poorer survival. Thus, this patient's chances of surviving tumor free are excellent.

We report the novel use of ofatumumab, a fully human anti-CD20 monoclonal antibody, for pediatric OMS. Although the child was severely allergic to the chimeric anti-CD20, presumably due to the mouse component, he tolerated the fully human anti-CD20 without incident. Ofatumumab successfully depleted CSF and blood B-cells, and circulating B-cell repletion was similar to that of rituximab. Because ofatumumab works like other anti-CD20 agents, one also would anticipate the same efficacy in non-refractory OMS as demonstrated for rituximab [1,2,12],

TABLE I. Immunological Responses to Ofatumumab at 1 Year

	CSF		Blood	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
WBC count	2	0	—	—
B-cells				
CD19+ (total)	4.5% (↑)	0.2%	46%/559 (↑)	3.7%/28 (↓)
CD20+ (mature)	7.4% (↑)	0.6%	43%/531 (↑)	2.5%/18 (↓)
CD27+ (memory)	7.4% (↑)	0.4%	7.1%/88	0.4%/3 (↓)
CD27-IgD+ (naïve)	0.9%	0%	36%/447	2.2%/16 (↓)
T-cells				
CD3+ (total)	86%	93%	44%/534 (↓)	56%/426 (↓)
CD4+ (T$_h$)	52% (↓)	42% (↓)	23%/282 (↓)	24%/187 (↓)
CD8+ (T$_s$)	32% (↑)	44% (↑)	16%/199	23%/176
TCR γδ+	6.9%	4.7%	11%/61	20%/82
CD4 + CD25+	1.5%	3.5%	9%/43	3.1%/24
NK cells	2.8%	0.9%	7.7%/93	37%/275 (↑)
Ig (mg/dl)				
IgG	1.3	1.2	774	713 (↓)
IgM	0.05	0	164	72
IgA	0.06	0.08	87	81

CSF erythrocyte counts were zero. Arrows signify high or low values compared to reference ranges for either % or cell counts in blood. Cell percentages are of total lymphocytes. CSF and blood lymphocytes were measured by four-color dual-laser flow cytometry, using a panel of directly conjugated monoclonal antibodies to CD3, CD4, CD8, CD19, CD45, CD14, CD27, CD5, CD16/56, TCRγδ, IgD, and IgG1 isotypes, as described previously [3]. Post-treatment CSF oligoclonal bands were positive at 3, but IgG synthesis rate, IgG index, and Ig concentrations were normal. The pre-ofatumumab total B-cell % was greatly elevated in CSF (4.5-fold) and blood (2.6-fold). Cell counts are given as cells/µl. Serum IgG reference range was 751–1,560 mg/dl.

with a lower rate of infusion-related events, improved complement-dependent cytoxicity, and lower off-rates [9].

This report also provides insight into the complex clinical and immunological problems in children with chronic-relapsing OMS [13,14]: (1) the patient never went into full neurological remission; (2) dysregulation of CSF B- and T-cells was persistent; (3) there were more than three relapses, and after each, he did not fully return to baseline; (4) improvement on immunotherapy gave the impression that he was salvageable, but he developed cognitive impairment, ADHD, and chronic rage. In our experience, treatment-refractory, chronic-relapsing OMS is less common today in children treated early with triple immunotherapy protocols. It is not clear whether it is the consequence of suboptimal immunotherapy at disease onset or inherently more aggressive autoimmune disease, perhaps involving diverse and different immunological mechanisms.

Commentary on what role the late tumor appearance/detection may have played in this case and its causation would be speculative. The important point is that ganglioneuroblastoma was found 3 years after OMS onset, despite previous scans and 12 cycles of low-dose cyclophosphamide. Late-appearing neural crest tumors are uncommon in pediatric OMS [15], but should be looked for in the chronic-relapsing population.

ACKNOWLEDGMENT

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