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Ocular Abnormalities in Patients Treated with a Novel Anti-GD2 Monoclonal Antibody, hu14.18K322A

Brian C. Tse, M.D.[1,2], **Fariba Navid, M.D.**[3,4], **Catherine A. Billups, M.S.**[5], **Thomas O'Donnell, M.D.**[1,2], and **Mary E. Hoehn, M.D.**[1,2,4]

[1]Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, Memphis, TN

[2]Department of Surgery, Division of Ophthalmology, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

[4]Department of Pediatrics, College of Medicine, University of Tennessee Health Science Center, Memphis, TN

[5]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

Abstract

Purpose—To determine the incidence and factors associated with the development of mydriasis and impaired accommodation in patients with refractory or recurrent neuroblastoma receiving the anti-GD2 antibody, hu14.18K322A.

Procedure—Eligible patients with refractory or recurrent neuroblastoma received escalating doses of hu14.18K322A ranging from 2 to 70 mg/m^2/dose for four consecutive days every 28 days. Retrospective chart review was performed, focusing on ocular abnormalities in these patients.

Results—38 patients (23 males; median age 7.0 years) underwent comprehensive eye exams prior to each course of therapy. Mydriasis was seen in 13 (34%) patients, while impaired accommodation was seen in nine (24%) patients. A dose-related effect was seen between hu14.18K322A and mydriasis (p=0.021) and impaired accommodation (p=0.029). Age and gender were not associated with ocular abnormalities. Ocular symptoms resolved in the majority of patients after the drug was discontinued.

Conclusions—Side effects of mydriasis and impaired accommodation have a dose-dependent relationship with hu14.18K322A. These side effects do not warrant discontinuation of treatment,

Corresponding author: Mary Ellen Hoehn, M.D., Hamilton Eye Institute, University of Tennessee Health Science Center, 930 Madison Ave, Room 473, Memphis, TN 38103, Phone: 901-448-5884, Fax: 901-448-1299, mhoehn@uthsc.edu.

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as they usually will resolve after completion of therapy. Management of ocular side effects should focus on treating symptoms with manifest refraction, bifocals, or tinted spectacles.

Keywords

pupil; accommodation; anti-GD2 antibody

Introduction

Neuroblastoma is the most common extra-cranial solid tumor of childhood. Nearly 40% of patients present with high-risk disease at the time of diagnosis. These patients have a worse outcome despite achieving a state of minimal residual disease after aggressive therapy, which includes autologous bone marrow transplantation and maintenance therapy with isotretinoin.[1] Recently, the addition of a human/mouse chimeric monoclonal antibody ch14.18, directed against the tumor-associated disialoganglioside GD2 (hereafter referred to as “GD2”), in concert with isotretinoin, granulocyte-macrophage colony-stimulating factor, and interleukin-2 during the maintenance phase of therapy was shown to improve survival rates compared to patients randomized to receive isotretinoin alone.[2] GD2 was recognized over three decades ago as an ideal therapeutic target for neuroblastoma because of its uniform expression on the surface of almost all neuroblastoma cells yet restricted expression on normal cells, primarily peripheral nerves, skin melanocytes, and neurons.[2] However, anti-GD2 antibodies, including ch14.18, cause significant neuropathic pain, which may, in part, be mediated by complement activation.[3–6] Thus, in an effort to minimize this side effect, research efforts have focused on developing an antibody that decreases complement activation while still maintaining anti-tumor activity.

Hu14.18K322A is a humanized monoclonal antibody directed against GD2. It is essentially the same as ch14.18 with the exception of minor changes that make it 98% derived from human genes while still retaining the same binding specificity as ch14.18. In addition, hu14.18K322A has a single point mutation (lysine to alanine) at position 322 in the CH2 domain that results in decreased complement activation.[7]

Interestingly, anti-GD2 antibodies have been associated with ocular symptoms of decreased accommodation and mydriasis.[3,6,8,9] The purpose of our study was to determine the incidence of, and any associated factors in, the development of mydriasis and/or impaired accommodation in patients with refractory or recurrent neuroblastoma enrolled in a phase I trial of hu14.18K322A.

Methods

A detailed description of the eligibility criteria and treatment plan of the institutional review board approved phase I trial of hu14.18K322A has been previously published.[10] Written informed consent was obtained from the parents or legal guardians of all participants. In brief, eligible patients with recurrent or refractory neuroblastoma received hu14.18K322A intravenously over four hours daily for four consecutive days every 28 days (1 course). As this was a dose finding trial, nine dose levels were evaluated starting at 2 mg/m^2/dose and escalating to 70 mg/m^2/dose. No intra-patient dose escalation was allowed. Patients could

receive subsequent courses of therapy if there was no disease progression or unacceptable toxicity. As part of the treatment protocol, an ophthalmologist performed a comprehensive eye exam at the time of study entry and prior to each course of antibody therapy. Eye exams were also performed if the patient developed ocular complaints at any point during therapy.

A retrospective chart review was performed. Eye clinic notes were reviewed for any documentation of mydriasis or decreased accommodation. A patient was deemed to have a pupillary abnormality or decreased accommodation only if there was documentation in the chart by the examining ophthalmologist. Patients who had pre-existing pupillary abnormalities prior to initiation of therapy were included in the study but only deemed to have treatment-induced mydriasis if their pupillary abnormalities worsened after initiation of therapy. Patients were defined as having decreased accommodation only if they required the use of reading glasses to read at near. Results were compared to patient demographic data and dose of hu14.18K322A received. Time to onset of symptoms from the start of initial dose of the antibody was measured. Time to resolution of ocular symptoms was also examined.

Associations among ocular abnormalities and gender were examined using Fisher's exact test. The exact Wilcoxon ranks sum test was used to examine the relationship between ocular abnormalities and age at study enrollment. The exact Kruskal-Wallis test was used to examine the relationship between the presence of ocular abnormalities and dose of hu14.18K322A.

Results

Thirty-nine patients with refractory or recurrent neuroblastoma were enrolled. One patient withdrew consent prior to receiving hu14.18K322A and was excluded from analysis. Patient characteristics are summarized in Table 1 and ocular abnormalities in Table 2. Thirteen of 38 patients (34%) had pupillary involvement, while nine patients (24%) had accommodation impairment that required reading glasses to correct. Eight of the nine patients with accommodation impairment also had mydriasis. None of the patients requiring reading glasses needed a change in the strength of their prescription during the course of their treatment.

Table 3 shows ocular abnormalities by dose level. A dose effect was seen with both mydriasis (p=0.021) and impaired accommodation (p=0.029). Of the 13 patients who received lower doses of hu14.18K322A (2, 4, and 6 mg/m^2/day), none had mydriasis or impaired accommodation. One of three patients each (33%) who received 10 and 20 mg/m^2/day had mydriasis. At higher dose levels, two of three patients (67%) who received 40 mg/m^2/day, one of three patients (33%) who received 50 mg/m^2/day, and eight of 11 patients (73%) who received 60 mg/m^2/day were observed to have mydriasis. Of note, neither of the two patients treated at the highest dose level of hu14.18K322A (70 mg/m^2/day) had documented mydriasis or impaired accommodation.

One patient who was deemed to have impaired accommodation had a pre-existing diagnosis of anisometropic amblyopia. While on therapy, however, she had decompensation of her vision and developed strabismus in her amblyopic eye. She required bifocals.

Six of 15 females (40%) had pupillary involvement, compared to seven of 23 males (30%). This difference was not statistically significant (p=0.73). There was also no evidence of a significant association between gender and accommodation impairment (p=1.0).

The median age of patients with pupillary abnormalities was 6.9 years, with a range of 3.0–14.1 years. The median age of patients with impaired accommodation was 6.9 years, with a range of 3.0–13.4 years. There was no evidence of significant associations between age and pupillary abnormalities (p=0.61) and impaired accommodation (p=0.95).

In patients with mydriasis only, median time to onset from their initial dose of antibody was 5.5 days (mean 19.2 days; range 5–75 days). In patients with accommodation defects, median time to onset was 12.5 days (mean 18 days; range 3–63 days). Of the five patients who developed mydriasis only, two had resolution at a median of 95 days after discontinuation of treatment. The three patients who did not have documented resolution were taken off study due to disease progression and returned to their referring institution. No follow up ophthalmology examinations were performed on these patients. Of the nine patients with accommodation deficits, eight had resolution at a median time of 186 days (range 49–531 days). The one patient who did not have documented resolution also did not have a follow up ophthalmology exam after meeting off study criteria.

Discussion

Hu14.18K322A is a promising new anti-GD2 antibody in the treatment of recurrent or refractory neuroblastoma. Ocular side effects of impaired accommodation and mydriasis have previously been reported in patients treated with the anti-GD2 antibody, ch14.18.[3,9] Our results show that there was a significant dose-dependent relationship between hu14.18K322A and ocular side effects. To our knowledge, this is the first report to demonstrate a dose-dependent relationship between an anti-GD2 antibody and ocular side effects, the higher the dose the more likely the patient was to have mydriasis or impaired accommodation. Interestingly, neither of the two patients treated with the highest dose of 70 mg/m^2/day had ocular side effects. Each of these patients only received one course, as the antibody was discontinued secondary to toxicity in each (serum sickness and hypertensive crisis). One of the patients had a normal eye exam after course 1, while the other did not return for her eye exam after completing her antibody course. There did not appear to be a cumulative dose effect on ocular side effects.

Onset of symptoms occurred early on after initiation of therapy, usually within the first two weeks. Consistent with previous studies, we saw reversal of ocular abnormalities in the majority of surviving patients after discontinuation of the study drug. Age and gender were not associated with pupillary abnormalities.

Previous reports on patients treated with anti-GD2 antibodies have shown an incidence of pupillary abnormalities ranging from 8–12%.[3,9] In our study in patients receiving

hu14.18K322A anti-GD2 antibody, we observed a higher incidence of both mydriasis (34%) and impaired accommodation (24%) than the previous studies. We postulate several reasons for the higher incidence of pupillary abnormalities. As part of the protocol, all patients in the study underwent comprehensive eye exams by an ophthalmologist prior to each course of antibody therapy and would, therefore, be more likely to have ocular abnormalities identified. Our study also had an older median patient population (7.0 years) compared to prior studies (4.0 and 4.8 years in Kremens and Ozkaynak, respectively).[3,9] The older patient population would more likely be able to verbalize changes in vision, which could account for the higher incidence of impaired accommodation. Lastly, relatively higher doses of hu14.18K322A were administered compared to ch14.18 in the previous studies, which may have contributed to the higher incidence of ocular abnormalities. The maximum tolerated dose of hu14.18K322A was 60 mg/m^2/day,[10] while the prior ch14.18 studies used 20 and 40 mg/m^2/day in Kremens and Ozkaynak, respectively.[3,9] As we have shown here, there is a dose-dependent relationship between hu14.18K322A dose and ocular side effects.

In the original manuscript detailing the phase I trial of hu14.18K322A, 20 patients were listed as having ocular or visual abnormalities.[10] Our data here indicates that only 14 patients had either mydriasis or impaired accommodation. The discrepancy between the data in these two papers can be explained by the difference in inclusion criteria. Ocular toxicity in the previous paper included patient-reported complaints of photophobia or difficulty seeing at near. In our current paper, ocular involvement was objectively determined based on pupillary exam by an ophthalmologist and need for bifocals.

It should be noted that more patients with impaired accommodation could have been missed, especially in the younger age group. Young children are less likely to complain of difficulties with near vision, although a surprising number were symptomatic in our cohort. Due to the widespread use of portable electronic devices, a common complaint was difficulty seeing the screen clearly. Dynamic retinoscopy would be a more reliable way to check accommodation in young children. It is also possible that a young child with significant hyperopia, might need spectacles for distance as well as near in order to prevent amblyopia. A dynamic as well as cycloplegic retinoscopy is recommended for all these patients.

Another possible limitation of this study is that it was retrospective. Even though patients were scheduled for eye examinations due to the risk of possible mydriasis and impaired accommodation, no prospective study was conceived. It was only after the relatively high number of ocular side effects was realized that this study was begun.

The proposed mechanism of mydriasis and impaired accommodation is a parasympathetic ocular deficit.[9] GD2 has previously been detected by immunohistochemistry in the ciliary muscle and iris. Expression of GD2 on peripheral motor and sensory nerve fibers is well known and is responsible for the immediate pain and allodynia following intravenous administration of anti-GD2 antibodies.[11]

As anti-GD2 therapy becomes more widespread in the management of neuroblastoma, patients on anti-GD2 therapy will begin to present in pediatric ophthalmology clinics.

Ocular abnormalities such as mydriasis and decreased accommodation should be recognized as common, early-onset side effects of anti-GD2 antibodies and do not warrant termination of treatment. Management should focus on diagnosing and treating symptoms with manifest refraction, retinoscopy (dynamic and cycloplegic), bifocals, and tinted spectacles, if necessary. Reassurance should be given to the patient and parents regarding the likely resolution of symptoms after cessation of treatment. Of course, in the setting of any suspicion of orbital involvement or Horner's syndrome, a proper workup should be initiated.

In summary, there was a dose-dependent relationship between pupillary abnormalities—mydriasis and decreased accommodation—and the anti-GD2 antibody, hu14.18K322A (the higher the dose, the more likely that ocular side effects will occur). The incidence of ocular side effects was seen at a higher rate than those associated with ch14.18. Side effects tend to appear shortly after initiation of therapy, do not warrant termination of therapy, and should be managed symptomatically. Reversal of ocular side effects upon discontinuation of the drug was seen in all surviving patients.

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Table 1

Patient characteristics (n=38)

Characteristic	N (%)
Sex	
Male	23 (60.5%)
Female	15 (39.5%)
Race	
White	25 (65.8%)
Black	4 (10.5%)
Other	9 (23.7%)
Age at Study Enrollment (years)	
Median	7.0
Range	2.6–16.2
Hu14.18K322A Dose (mg/m^2/dose)	
2	4 (10.5%)
4	3 (7.9%)
6	6 (15.8%)
10	3 (7.9%)
20	3 (7.9%)
40	3 (7.9%)
50	3 (7.9%)
60	11 (29.0%)
70	2 (5.3%)

Table 2

Summary of ocular abnormalities

Pupil Involved/Mydriasis	Accommodation Impaired		Total
	No	Yes	
No	24	1	25
Yes	5	8	13
Total	29	9	38

Table 3

Summary of Ocular Adverse Events by Dose Level

Dose Level ($mg/m^2/day$)	No. Patients	No. of Pts with Mydriasis	No. of Pts with Impaired Accommodation
2	4	0 (0%)	0 (0%)
4	3	0 (0%)	0 (0%)
6	6	0 (0%)	0 (0%)
10	3	1 (33%)	1 (33%)
20	3	1 (33%)	0 (0%)
40	3	2 (67%)	3 (100%)
50	3	1 (33%)	1 (33%)
60	11	8 (73%)	4 (36%)
70	2	0 (0%)	0 (0%)
Total	38	13	9