Comparison of Pain Outcomes between Two Anti-GD2 Antibodies in Patients with Neuroblastoma

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Abstract

Background—Addition of anti-GD2 antibody ch14.18 to the treatment of neuroblastoma has improved outcomes. The most common side effect of ch14.18 is neuropathic pain, which may in part be complement-mediated. Hu14.18K322A is a humanized anti-GD2 antibody designed to diminish complement activation and induce less pain. We compare the pain outcomes in patients treated with ch14.18 and those treated with hu14.18K322A, and explore dose-dependent relationships between pain scores, opioid requirements and complement levels in patients treated with hu14.18K322A.

Patients and Methods—Opioid (morphine equivalent mg/kg) and anxiolytic requirements during course 1 (4 days) in patients treated with hu14.18K322A and ch14.18 were reviewed. Correlations between antibody dose and pain scores, opioid requirements, and complement levels were examined for patients receiving hu14.18K322A.

Results—Patients treated with hu14.18K322A (n=19) had lower opioid requirements than those who received ch14.18 (n=9). The differences in median opioid requirements (mg/kg) were statistically significant for the overall course (1.57 vs. 2.41, p=0.019) as well as for days 3 (0.34 vs. 0.65, p=0.005), and 4 (0.32 vs. 0.64, p=0.010). No difference in anxiolytic use was observed between the two groups. In the group treated with hu14.18K322A, we found a positive correlation between antibody dose administered and pain scores, but no correlation between antibody dose and opioid requirements or changes in complement levels.

Conclusions—In this retrospective analysis, hu14.18K322A induced less pain than ch14.18 based on opioid requirements.

Keywords

Anti-GD2 antibodies; pain; opioids; pediatric oncology; neuroblastoma

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CONFLICT OF INTEREST STATEMENT

The authors do not have any conflict of interest to declare.

INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor in childhood [1]. Nearly 40% of patients with neuroblastoma have advanced disease at the time of diagnosis [2]. For these patients, treatment with the human-mouse chimeric 14.18 (ch14.18) anti-GD2 monoclonal antibody (mAb) combined with cytokines significantly improves clinical outcomes [3]. The antigen-binding domain of the ch14.18 mAb recognizes the disialoganglioside GD2, while the Fc domain recruits effector white blood cells to promote tumor cell lysis via antibody-dependent, cell-mediated cytotoxicity (ADCC) [4]. In normal human tissue, GD2 expression is limited to the central nervous system, skin melanocytes, and peripheral nervous tissues. Neuroblastoma cells highly express this antigen on their cell surface [5]. Achieving a higher dose of circulating mAb may be beneficial, considering the dose-dependent relationship in which ch14.18 mAbs elicit natural killer cells to lyse neuroblastoma cells via ADCC *in vitro* [4]. In pharmacokinetic studies of anti-GD2 mAbs, higher peak serum levels of mAb are achieved with administration of higher doses of antibody [6-8]. However, the dose of ch14.18 that can be administered to patients is limited by toxicities, most notably neuropathic pain [9-11]. The painful response is also observed with the administration of other anti-GD2 agents, such as the murine 3F8 mAb [6], the hu14.18-IL2 mAb-cytokine fusion protein [12,13], and the murine 14G2a mAb [14,15], in both adults and children.

Hu14.18K322A mAb is a humanized version of the ch14.18 mAb engineered with a point mutation (lysine to alanine) at position 322 in the Fc domain of the antibody. Lysine at this position on the antibody is crucial for complement-dependent cytotoxicity [16], a process implicated in the pain toxicity associated with anti-GD2 mAb infusion [17]. The loss of complement-dependent cytotoxicity as mediated by anti-GD2 mAb does not have an appreciable effect on anti-tumor activity when administered at therapeutic doses in mouse studies [18]. This finding highlights the importance of ADCC-mediated anti-tumor activity. To further exploit the anti-tumor effects of ADCC, hu14.18K322A was produced in a cell line with decreased fucosylation activity to increase ADCC activity [19].

The pain associated with anti-GD2 therapy is similar to other neuropathic pain syndromes and is relatively opioid-resistant [20]; nevertheless, opioids are routinely utilized for pain control during anti-GD2 infusions. Systemic anti-GD2 therapy-induced pain is characterized by mechanical allodynia without thermal hyperalgesia in animal models [21]. In rat models, which closely approximate the human pain experience with anti-GD2 agents in terms of timing and quality, an anti-GD2–specific increase in background activity of Aδ and C pain fibers results in decreased mechanical stimulus thresholds of Aδ fibers and allodynia [22]. The intensity and magnitude of mechanical allodynia are results of ch14.18's ability to fix complement [17]. In contrast, hu14.18K322A produces diminished and faster-resolving allodynia [17]. In a phase I dose escalation study of hu14.18K322A in children with refractory/recurrent neuroblastoma, pain was noted to occur more intensely during the first course of mAb, administered as a 4-hour daily infusion for 4 consecutive days [8].

In this study, we sought to compare pain outcomes as reflected by the opioid and anxiolytic requirements between patients treated with ch14.18 and those treated with hu14.18K322A

antibody regimens in a single institution. In addition, we explored correlations between pain scores and hu14.18K322A mAb dose levels and correlations between pain scores and changes in serum complement levels in patients who received hu14.18K322A mAb.

METHODS

This study was approved by the institutional review board as a retrospective review of patients with neuroblastoma treated at St. Jude Children's Research Hospital with ch14.18 or hu14.18K322A mAb during course 1. Patients who received ch14.18 were enrolled on Children's Oncology Group (COG) protocol, ANBL0032 (NCT00026312), the results of which have previously been reported [3]. The COG study was for patients with high-risk neuroblastoma following myeloablative chemotherapy. The ch14.18 mAb regimen was administered at a dose of 25 mg/m^2/day over 10 hours daily for 4 consecutive days (days 3-6); patients also received granulocyte-macrophage colony stimulating factor (GM-CSF) (days 0-13) and isotretinoin (days 11-24) during the first course (24 days) of treatment.

Hu14.18K322A was administered to patients with refractory or recurrent neuroblastoma at dosages of 40, 50, 60, or 70 mg/m^2/day over 4 hours daily for 4 consecutive days as part of a single-agent phase I dose escalation study, as previously reported [8]. In that study, cohorts of patients were treated with a starting dose of 2 mg/m^2/day escalating to 70 mg/m^2/day. The maximum tolerated dose of hu14.18K322A was established as 60 mg/m^2/day. In the current report, our primary objective was to assess the pain outcomes compared with the currently used ch14.18 dose of 25 mg/m^2/day, thus we included only patients who received hu14.18K322A at higher doses (40 mg/m^2/day).

The ch14.18 mAb and hu14.18K322A protocols specified the use of opioids for premedication regimens for pain symptoms in the form of morphine, fentanyl, or hydromorphone. The ch14.18 mAb protocol specified a morphine loading dose of 50 mcg/kg immediately prior to ch14.18 administration, followed by a continuous infusion of 20-50 mcg/kg/hr to continue for two hours after completion of the ch14.18 infusion, with the option of additional doses and increased infusion rate as needed. In our institution, this concept was applied by the use of patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA), depending on the child's age and developmental level. The hu14.18K322A protocol specified the use of a morphine loading dose at the discretion of the ordering physician and allowed the use of hydromorphone or fentanyl as alternatives.

Patient characteristics, including age, sex, race/ethnicity, and baseline weight, as well as antibody dose received were collected for the first course of antibody infusion. In addition, pain intensity data and pain and anxiety treatment data were collected and analyzed.

Pain was assessed by the daily maximum and minimum pain scores; the scores and the pain assessment tools used were noted. Pain was assessed using age-appropriate tools, according to the institutional standard of care: Faces Legs Activity Consolability Cry [23] for children < 4 years old, Wong-Baker FACES [24] for patients 4-7, and the numerical pain scale [25] for patients > 7 years old. The COG protocol using ch14.18 did not mandate strict acquisition of pain scores; pain was assessed in qualitative terms in the form of detailed

nursing notes, and the institutional policy regarding pain score documentation was applied. The phase I study using hu14.18K322A mandated pain score collection 5 minutes prior to antibody infusion, every 30 minutes during the infusion, and continuing at least 2 hours after completion of the infusion.

Pain treatment data included opioid requirements (morphine equivalent, mg/kg/day) and duration of opioid therapy. Opioid medications were administered intravenously either as PCA/NCA or intermittent as-needed dosing. For analysis, all opioid doses were converted to intravenous morphine equivalent doses based on opioid equianalgesic potency. The following relationships were used: fentanyl:morphine, 100:1; hydromorphone:morphine, 5:1; and oral codeine:IV morphine, 12:1.

Anxiolytic medications included lorazepam and midazolam; midazolam (1 patient, 1 dose) was converted to lorazepam equivalent using a 1:1 ratio (per institutional pharmacy guidelines). All daily values were collected based on a 24-hour cycle starting at 6:00 AM.

Laboratory data included serum complement levels (C3, C4, and CH50 or total complement activity) at baseline and the day after the last dose of hu14.18K322A (day 5). These laboratory data were not available for patients treated with ch14.18.

Statistical Analysis

The Wilcoxon rank sum test was used to compare groups on continuous variables including age, weight, median opioid requirements, and anxiolytic requirements. Fisher's exact test was used to compare proportions (sex and race). Pearson's correlation coefficients were used to evaluate the association of pain scores from patients who received hu14.18K322A with antibody dose, opioid requirement, and change in complement components before and after antibody infusions and tested by Fisher's z transformation test. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 28 pediatric patients with neuroblastoma were evaluated in this study: 9 patients received ch14.18 at a dose of 25 mg/m^2/day, and 19 patients received hu14.18K322A at doses ranging from 40 to 70 mg/m^2/day. Three patients each received hu14.18K322A at 40 and 50 mg/m^2/day, 11 received 60 mg/m^2/day, and 2 received 70 mg/m^2/day. Patient characteristics are summarized in Table I. Patients ranged in age from 1.8 to 14.1 years (median, 5.3 years); the patients receiving ch14.18 were younger (median, 3.0 years) than the patients receiving hu14.18K322A (median, 7.2 years, p = 0.0010).

The opioid delivery methods and the analgesic (opioid) and anxiolytic (benzodiazepine) requirements over course 1 of therapy are also summarized in Table I. All patients treated with ch14.18 had opioid delivered via PCA/NCA; of 19 patients receiving hu14.18K322A, 17 received opioids via intermittent IV doses, and two started on an intermittent dosing regimen and were switched to a PCA delivery method due to a need for continuous pain control. Lower opioid and anxiolytic requirements were found for patients treated with hu14.18K322A; the differences in median opioid requirements reached statistical

significance for days 3 and 4 and for the total doses over course 1. Anxiolytic requirements were higher in the group treated with ch14.18, but the difference was not statistically significant.

Serum complement values C3, C4, and CH50 for patients who received hu14.18K322A were analyzed. For each of the measures, a significant increase was observed between values before and after infusion. The increase in serum complement levels (C3, C4, and CH50) was not dose-dependent (p = 0.1862, 0.3642, and 0.2040, respectively) and did not correlate with pain scores (p = 0.1418, 0.3546, and 0.2583, respectively) or opioid requirements (p = 0.5928, 0.9397, and 0.6823, respectively).

The analysis of the associations between maximum pain score reported by patients receiving hu14.18K322A and the antibody dose level was conducted by treating the mAb dose as a continuous variable. The results indicate that there was a positive correlation between the hu14.18K322A dose and the maximum pain score on days 1 and 2 of antibody infusion and the overall course 1, with a Pearson correlation coefficient (p value) of 0.7210 (0.0016), 0.5739 (0.0253), and 0.6940 (0.0029), respectively. No significant correlation was detected between opioid requirement and the hu14.18K322A dose [Pearson correlation coefficient (p value), 0.0663 (0.7874)].

DISCUSSION

This study compares pain outcomes between the anti-GD2 antibody ch14.18 regimen and the hu14.18K322A regimen, which was engineered to diminish complement activation and elicit less pain. Furthermore, we performed an analysis to evaluate the correlations between specific dose levels of hu14.18K322A and pain scores, opioid requirements, and serum complement levels.

Patients receiving hu14.18K322A required lower doses of opioids over the total course and on individual days of therapy than patients receiving ch14.18, despite higher antibody doses (40, 50, 60, and 70 vs. 25 mg/m^2/day) over the same time intervals. All differences were statistically significant, as daily values and as overall cumulative doses over course 1 of therapy, except on day 1 and 2.

Our method of using opioid requirement as a pain outcome measure was not used in any of the previous clinical trials of ch14.18 that evaluated pain as an outcome measure [3,26-28]. These studies reported pain by describing the grade of pain, a somewhat imprecise measure of pain outcome; some studies reported pain outcomes per number of antibody infusion courses, rather than by the number of patients. The variability in pain outcome measures makes comparisons between trials difficult. Ozkaynak et al [26], in a series of 22 patients with neuroblastoma treated with ch14.18, described neuropathic pain in 68% of the first courses of antibody therapy (13/19); 2 of the 13 episodes were classified as grade 4, described by Common Terminology Criteria for Adverse Events as severe pain despite the use of parenteral opioids. Gilman et al [27] described 25 patients receiving ch14.18 who experienced neuropathic pain of grade 3 (defined as requiring morphine) as "common." Grade 3 and grade 4 (not defined) pain was reported in 35% and 87.3% of courses,

respectively, at doses of 20 and 25 mg/m^2/day. In another trial involving ch14.18, Simon et al. [28] reported on 151 patients who received 695 cycles of ch14.18; pain despite analgesic therapy was present in 33.1% of patients and 15.7% of courses, and analgesic therapy was defined as the recommendation to use concomitant IV morphine starting at a dose of 1 mg/kg/day for pain control. Other analgesic drugs, tramadol, paracetamol, and dipyrone, were allowed. A more detailed account of opioid therapy, from Kushner et al. [29], pertained to 38 patients treated with a heat-modified 3F8, intended to reduce pain. The structured opioid regimen for pain management during antibody infusions comprised of premedication with morphine (0.05 to 0.1 mg/kg) or hydromorphone (0.0075 to 0.015 mg/kg); the dose-limiting toxicity of pain was defined as 7 doses of opioids within 2 hours, where a dose was defined as hydromorphone 0.015 mg/kg or an equianalgesic dose of morphine. This is the only other study to our knowledge to give the details of opioid doses as premedication and during the course of antibody infusions.

Most of the patients receiving hu14.18K322A in our study had significantly higher serum complement levels after infusion than before. In contrast, other anti-GD2 antibody regimens have been associated with complement fixation/activation in humans as measured by a decrease of serum complement components C3 and C4, as well as overall complement activity (CH50), in comparisons between samples acquired before and after course 1 [8,10,12,14,15,30,31]. Complement activation has been implicated in ch14.18-induced pain in animal models [17] and in the mechanism of hyperalgesia [19]. The ch14.18 mAb is a strong activator of complement, a role once thought to be an important mechanism of its anti-tumor effect [11] and a trait shared by the 3F8 and 14G2a mAbs. The design of hu14.18K322A incorporated a point mutation to ameliorate the ability of this antibody to activate complement as compared with ch14.18, a goal verified *in vitro* [17]. Further, *in vivo* rat experiments have shown that the allodynia and hyperalgesia induced by ch14.18 are alleviated when the antibody is injected into rats with an impaired complement pathway, suggesting a role for complement in anti-GD2 mAb infusion-induced pain [17].

In the patients who received hu14.18K322A reviewed in this study (40 mg/m^2/day or higher), we did not find a correlation between antibody dose and change in complement measures C3, C4, and CH50. *In vitro* studies have shown that hu14.18K322A does not activate complement in a dose-related manner [17]. Our inability in treated patients to find a dose-dependent change in these components appears to be a validation of this finding. We found no correlation between change in complement components and either opioid requirements or pain scores. Despite hu14.18K322A not activating human complement, the presence of pain side effects would argue that complement activation is not the only mechanism of pain side effects associated with anti-GD2 antibodies.

Statistical analysis showed a positive correlation between pain scores, but not opioid requirements, and antibody dose levels. No clear relationship between increased pain and dose escalation was found in an earlier study of ch14.18 [26]. We did not find a correlation between pain scores and daily opioid requirements, which is consistent with findings from a study of heat-modified 3F8 mAb [29], in which no positive correlation between opioid rescue doses and doses of monoclonal antibody was seen. The lack of correlation between pain scores and opioid requirements may be a reflection of individual variability in reporting

pain scores and of the limitation of pain scores as measures of pain compared with functional outcomes.

Our study has the limitation of a retrospective design, which explains the limited data available for analysis. In addition, while we compared ch14.18 and hu14.18K322A, we note that the ch14.18 antibody was given in conjunction with GM-CSF and not as a single agent. Furthermore, all patients who received ch14.18 received opioids via PCA/NCA before starting antibody therapy, while patients treated with hu14.18K322A received opioids as intermittent dosing as needed. The pain literature shows that patients receiving opioids via PCA generally require lower amounts of opioids than those on intermittent dosing [32]. The opioid delivery method discrepancy is a factor we could not control in this retrospective review, but the possibility of a larger opioid requirement disparity than we were able to show is worth noting. We compared the anxiolytic requirements to assess their potential to bias opioid requirements; no statistically significant difference between antibody treatment groups was found, despite lower requirements for anxiolytic therapy in the hu14.18K322A group.

Additional study limitations to consider include: 1) hu14.18 and ch14.18 may have different GD2 affinity characteristics, which could have affected the pain outcomes; 2) ch14.18 was given in an earlier era, and given the nature of a learning curve in dealing with pain side effects, clinicians might have learned to manage pain better in the case of hu14.18K322A; 3) analgesics were non-uniform between the two groups; nevertheless, the use of conversion factors (to iv morphine equivalent) for comparison is an acceptable method in the pain literature; 4) different doses and schedules of antibody were used: ch14.18 (25 mg/m^2/day over 10 hours) versus hu14.18K322A (40-70 mg/m^2/day over 4 hours) and a longer the infusion duration might have contributed to the increased use of opioids.

We initially sought to quantify pain intensity and duration by comparing pain scores collected before, during, and after antibody infusions. This comparison was complicated by significantly different methods of collection of pain scores between patients treated with hu14.18K322A and those treated with ch14.18. Because pain is a highly subjective factor, a standardized method of pain score solicitation must be implemented to produce interpretable, consistent data [33]. In our study, pain score data were biased at the point of collection. Patients who received hu14.18K322A and were prescribed opioids for administration as needed were asked for a pain score before and after intervention with opioid medications per institutional policy. Patients who received ch14.18 and an opioid delivered by PCA/NCA had quantitative pain scores solicited at standardized time intervals, according to the PCA/NCA standard of care, and had pain documented in a detailed qualitative manner in the nursing notes. Although pain was aggressively monitored and treated in both groups, this difference at the point of collection invalidated a comparison between maximum daily pain scores for the two antibody groups. Despite this limitation, we chose to use the pain scores for hu14.18K322A patients to answer other pain-related questions (i.e., pain experience per dose level and correlation with complement levels) for this antibody.

CONCLUSIONS

Anti-GD2 mAb therapy involving the antibody ch14.18 in combination with cytokines improves outcomes for patients with advanced neuroblastoma. The clinical success achieved with ch14.18 therapy has generated excitement and prompted the development of novel anti-GD2 therapeutic agents [8]. Efficacy in clinical practice will always be the primary outcome of interest. However, with the use of anti-GD2 agents, the toxicity of severe neuropathic pain cannot be ignored, given its ability to limit doses and the detrimental effects of pain on quality of life. We recommend that studies of anti-GD2 agents incorporate a systematic, prospective collection of pain outcome measures, including age-appropriate pain scores and opioid dosing, to facilitate comparison of this toxicity between studies. By applying this recommendation, hu14.18K322A mAb can be compared prospectively to other anti-GD2 agents, a comparison that would be of great clinical interest, especially with the addition of immunomodulatory agents and other biologics.

Acknowledgments

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Table I

Patient Characteristics and Analgesic and Anxiolytic Requirements (Course 1)

	Total	ch14.18	hu14.18K322A	p-value
No. of patients	**28 (100%)**	**9 (32%)**	**19 (53%)**	
Sex				
Male	13	4	9	1.00000 [*]
Female	15	5	10	
Weight (kg)				
Median (min, max)	18.1 (9.0, 82.9)	12,2 (9.0, 24.4)	21.6 (15.4, 82.9)	0.0137 [**]
Age at enrollment (years)				
Median (min, max)	5.3 (1.8, 14.1)	3.0 (1.8, 7.9)	7.2 (3.0, 14.1)	0.0127 [**]
Race				
White	18	8	10	0.0974 [*]
Black	3	1	2	
Other	7	0	7	
Opioid administration mechanism				
Patient/Nurse-controlled analgesia (PCA/NCA)		9		
Intermittent IV doses			17	
Intermittent and PCA/NCA			2	
Opioid used [***]				
Morphine		9	17	
Hydromorphone		1	4	
Fentanyl		0	1	
Oxycodone		0	1	
Median opioid requirements [1]				
Total course 1		2.41	1.57	0.0186 [**]
Day 1		0.61	0.51	0.5950 [**]
Day 2		0.67	0.41	0.0852 [**]
Day 3		0.65	0.34	0.0051 [**]
Day 4		0.64	0.32	0.0101 [**]
Anxiolytic requirements				
Number of patients requiring anxiolytic medications		3	9	
Anxiolytic (median and range, mg/kg/day)		0.10 (0.04, 0.14)	0.040 (0.012, 0.13)	0.2818 [**]

[*] Fisher's exact test;

[**] Wilcoxon rank sum test;

[1] Morphine equivalent, mg/kg/day;

[***] Opioid type for each patient may have changed during the course of treatment.