Phase I trial of anti-GD2 monoclonal antibody hu3F8 plus GM-CSF: Impact of body weight, immunogenicity and anti-GD2 response on pharmacokinetics and survival

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ABSTRACT

Fifty-seven stage 4 patients with refractory/relapsed neuroblastoma were enrolled in a phase I trial (Clinicaltrials.gov NCT01757626) using humanized anti-GD2 monoclonal antibody hu3F8 in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2). Nevertheless, according to the FDA boxed warning, the incidence of cancer treatment modalities, for children with high risk neuroblastoma, 4 anti-GD2 monoclonal antibodies (mAbs) have been tested extensively in humans: 14G2a, ch14.18, hu14.18, and mouse 3F8 (m3F8). In 2015, ch14.18 (dinutuximab, UnituxinTM) became the first IgG drug to receive FDA approval. The current recommendation is to use dinutuximab in combination with cytokines granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-2 (IL-2). Nevertheless, according to the FDA boxed warning, it has significant neurologic and systemic toxicities at 17.5 mg/m² per day for 4 consecutive days of inpatient treatment. The European SIOPEN adopted a bio-similar antibody ch14.18/CHO plus IL-2 for treating patients with refractory/relapsed stage 4 neuroblastoma.

Previous immunotherapy trials have found the incidence of anti-drug antibody (ADA) in the form of human anti-mouse antibody (HAMA), or human anti-chimeric antibody (HACA), or human anti-human antibody (HAHA) to vary. In the most recent studies, ADA response was 70–80% for HAMA (m3F8), 19–21% for HACA (ch14.18), and 40% for HAHA (hu14.18K322A). The formation of HAMA has generally delayed, even sometimes prevented, repeat cycles of m3F8 treatment. However, it is noteworthy the overall survival among patients with high risk stage 4 neuroblastoma (i.e. diagnosed at ≥ 18 months of age or with MYCN amplification) upon treatment with m3F8 in combination with subcutaneous GM-CSF (Clinicaltrials.gov NCT00072358) was promising. According to their disease status at protocol entry, overall survival was 45% for primary refractory patients, 44% for 2nd remission and 67% for first remission patients, all with 10 years of followup. In contrast to other anti-GD2 antibodies, m3F8 was administered over 30–120 minutes in the outpatient setting. Thus, to remove immunogenicity of m3F8 while building on its favorable efficacy and tolerability, the humanized version of 3F8 (hu3F8) was first tested in a phase I trial at Memorial Sloan Kettering Cancer Center. Because of the favorable toxicity profile (30 minute outpatient infusion on Monday, Wednesday, and Friday), it was combined with fixed doses of GM-CSF in a second phase I trial (Clinicaltrials.gov NCT01757626) for patients with refractory or relapsed stage 4 neuroblastoma again in the outpatient setting.
In this report, besides determining the immunogenicity of this anti-GD2 antibody hu3F8, we uncovered the influence of body weight on its pharmacokinetics (PK). Antibodies are given intravenously, and dosing based on body surface area or body weight is generally accepted as the standard, especially among pediatric patients. However, dose adjustment may need to be further refined to lessen inter-subject PK variability. Study on the PK of ch14.18 in 14 neuroblastoma patients suggested that antibody clearance was fourfold higher in younger children, and appeared to be age dependent.8 Even in the same age group, weights could vary 2.5 to 3 folds in children.12 Various models have been proposed to account for the differences in drug clearance based on weight and age.13-15 Here, we described the impact of body weight on the PK of hu3F8, in particular, the serum concentration-time curves [area under the curve (AUC)]. Antibody-dependent cell-mediated cytotoxicity is the key anti-tumor mechanism for IgG1 antibody immunotherapy. In vitro, its efficiency is dependent on the antibody concentration in the culture medium, and by extrapolation, in vivo effectiveness is dependent on the antibody concentration in the extracellular fluid or in the blood over time. Thus, factors that influence AUC or drug exposure will impact anti-tumor efficacy.

In this study, serum anti-GD2 antibody levels were also monitored periodically starting at least 30 d after the last antibody dose of hu3F8 received. The ability of the patient to mount a de novo host anti-GD2 response after being treated with hu3F8 was unexpected. More importantly, the AUC of this anti-GD2 response over time was found to be highly prognostic of patient outcome.

Results

Influence of body weight on the pharmacokinetics of hu3F8

A total of 57 neuroblastoma patients with stage 4 refractory/relapsed disease were treated. There were 15 dosage levels in this phase I trial, ranging from 0.9 mg/kg up to 9.6 mg/kg of total dose given per cycle. The treatment and serum collection schedule are detailed in Table 1. These neuroblastoma patients

| Day | Treatment | Serum collection schedule |
|-----|-----------|---------------------------|
| –4  | sc GM-CSF |                          |
| –3  | sc GM-CSF |                          |
| –2  | sc GM-CSF |                          |
| –1  | sc GM-CSF |                          |
| 0   | sc GM-CSF |                          |
| 1   | iv hu3F8 + sc GM-CSF | pre-hu3F8, 5 min post-hu3F8, 3 h, 6 h |
| 2   | sc GM-CSF | 24 h                      |
| 3   | iv hu3F8 + sc GM-CSF | pre-hu3F8, 5 min post-hu3F8 (48 h) |
| 4   | sc GM-CSF | 72 h                      |
| 5   | iv hu3F8 + sc GM-CSF | pre-hu3F8, 5 min post-hu3F8 (96 h) |
| 6   |                       | 120 h                     |
| 8   |                       | 168 h                     |
| 10  |                       | 216 h                     |
| 12  |                       | 264 h                     |

Table 1. Treatment and serum collection schedule for cycle #1 pharmacokinetics of hu3F8.

(33 males and 24 females) ranged from 2.4 to 31.3 y of age (median 6.8) at the start of hu3F8 treatment, and 0.6–9.0 (median 3.1) years from diagnosis. As shown in Table 2, a large variation in cycle #1 AUC was observed at some hu3F8 dose levels. At individual dose level, AUC was consistently higher among patients with larger body weights (Fig. 1). Similar correlations were observed between AUC and body surface area, as one would expect, given the strong linear correlation between body weight and surface area (Fig. 2A), but not between AUC and age, since children of similar ages had quite variable body weights (Fig. 2B). This strong impact of body weight on the PK of antibody therapy was unexpected, since all hu3F8 dosing was already based on the patient’s size in kg. Because AUC is expected to correlate with drug effect, this AUC-body weight relationship may have therapeutic implications. Clearance at steady-state (Clss) also demonstrated this body weight effect, albeit in an inverse relationship (data not shown).

Estimation of total drug exposure during treatment

Analysis of the PK of hu3F8 given at treatment cycle #1 for each dose level was detailed in another report. Besides having a strong linear correlation between the dose of hu3F8 with the peak serum hu3F8 concentration (R² = 0.96), and dose with AUC (R² = 0.93), AUC was found to correlate with the peak serum hu3F8 concentration (R² = 0.87, Fig. 3). Using serum samples collected at 5 min post hu3F8 infusion for every subsequent treatment cycle for every patient, we estimated the total drug exposure of all subsequent cycles of individual patients based on the linear equation in Fig. 3. As expected, patients who did not progress received additional hu3F8 treatment cycles, resulting in a higher accumulative drug exposure and improved survival (data not shown).

Influence of human anti-hu3F8 antibody response (HAHA) on the PK of hu3F8

Patients (n = 57) in this trial received a median of 4 cycles (range from 1 to 15 cycles), with 5 patients receiving treatment spanning more than 12 months. Per protocol, they must have negative HAHA (defined in Patients and

Table 2. High coefficient of variation of cycle #1 AUC among patients at certain dose levels.

| Total dose (mg/kg) | AUC (ug/mL/day) | SD | CV  |
|-------------------|-----------------|----|-----|
| 0.9               | 23.79           | 4.50 | 0.19|
| 1.8               | 83.37           | 34.30 | 0.41|
| 2.4               | 69.38           | 23.40 | 0.34|
| 3.0               | 87.99           | 16.97 | 0.19|
| 3.6               | 113.95          | 16.86 | 0.15|
| 4.2               | 116.81          | 12.00 | 0.10|
| 4.8               | 176.37          | 29.42 | 0.17|
| 5.4               | 179.75          | 24.08 | 0.13|
| 6.0               | 176.83          | 45.97 | 0.26|
| 6.6               | 194.70          | 2.35  | 0.01|
| 7.2               | 193.36          | 9.53  | 0.05|
| 7.8               | 261.07          | 108.31 | 0.41|
| 8.4               | 268.31          | 51.92  | 0.19|
| 9.0               | 248.82          | 104.91 | 0.42|
| 9.6               | 323.85          | 67.54  | 0.21|

AUC: area under the curve; SD: standard deviation; CV: coefficient of variation.
Materials section) to be eligible for retreatment. A total of 14 patients (25% of the cohort) had positive HAHA response, with testing being performed within 10 days from the last hu3F8 dose received (median 7 days). 12/14 patients had HAHA response before their third treatment cycle. It is noteworthy that 75% of all patients never had positive HAHA despite being repeatedly challenged, as well as a history of previous exposure to other anti-GD2 antibodies, including m3F8 and/or ch14.18 among 82% of the cohort (47/57 patients).

Because negative HAHA was a prerequisite for additional treatment cycles of hu3F8, patients with positive HAHA received fewer cycles, and less total drug exposure. HAHA response was associated with patients receiving treatment cycles (the median) of hu3F8 (Fisher’s exact test, p < 0.004).

Moreover, when hu3F8 and HAHA were concomitantly measured on cycle #1 serum samples (n = 73), a marked difference in serum hu3F8 concentration was observed: 5.54 ± 4.55 ug/mL among HAHA negative samples versus 0.22 ± 0.24 ug/mL for HAHA positive samples (p < 0.0001, Fig. 4). This provided the rationale for delaying retreatment until HAHA turned negative.

**Anti-GD2 response**

A de novo anti-GD2 antibody titer developing in this patient cohort following hu3F8 treatment reflects an unexpected vaccination effect of passive immunotherapy. Forty patients had available serum samples collected periodically starting at least 30 days from their last infusion of hu3F8. Based on each patient’s specific t1/2 and C_last, residual serum hu3F8 level on the date of the serum sample was estimated, and samples with detectable residual serum hu3F8 were excluded from this analysis. Anti-GD2 titer (also measured in ng/mL) was integrated over time (i.e., AUC). Anti-GD2 response was expressed as AUC per unit time (AUC per month) and tested for its prognostic significance on survival outcome. PFS analysis was censored at the time of the next systemic therapy (or progression), OS analysis was censored at the time of the next systemic therapy (or last followup) or death, whichever came earlier.

As shown in Fig. 5A, using the median cut point (23 ng/mL/month), anti-GD2 response over time was highly prognostic for PFS (p = 0.0018), and trending for OS (p = 0.07). While there was no correlation between anti-GD2
response with dosage level, formation of HAHA before patient’s third treatment cycle was associated with lower anti-GD2 response (Fisher’s exact test, $p = 0.034$). Though not statistically significant, there was also a trend of lower anti-GD2 response if the patient received $\leq 4$ cycles (the median) of hu3F8 ($p = 0.089$), or if they had previously received anti-GD2 antibody (i.e., having progressed following prior anti-GD2 antibody therapy, $p = 0.085$).

To test if there was any in vitro functional role of such induced anti-GD2 antibody, sera from 3 patients with anti-GD2 response was compared with their corresponding pre-treatment sera in an ADCC assay. As shown in Fig. 6, augmented ADCC was found to be statistically significant at serum dilution of 1:50 and 1:100.

Discussion

This report analyzed parameters that had expected as well as unexpected influence on the pharmacokinetics of hu3F8. One striking observation was the effect of body weight on AUC. At each dosage level (there were a total of 15 dosage levels), a larger sized patient invariably had higher AUC and lower Clss.

Since dosing was based on body size, it has always been assumed that the PK of IgG among pediatric patients would be generally similar to adults. The correlation of body weight with AUC would have easily been overlooked, since there were only a few patients per dose level in this study, and in most other trials, only adults or only young children were studied using a single dose of antibody.

The explanation for the influence of body size on the PK of antibody is likely manifold. Children have a higher percentage of body weight derived from their total body water, which is mainly in the extracellular fluid space. In addition, they have a relatively larger organ weight (e.g., liver and spleen) per body size when compared with adults. There is growing evidence in the literature regarding differences in their PK profiles. Among pediatric renal transplant patients, clearance of basiliximab was statistically higher in children compared with adolescents. Daclizumab showed a lower AUC in younger patients when compared with older adolescents. Alemtuzumab (Campath-1H) drug exposure was lower in younger patients when compared with older adolescents. Natalizumab tended to be underdosed in adolescents with Crohn’s Disease when compared with adults.

PK analysis of cetuximab among adult patients with solid tumors found a significant correlation of antibody clearance with both BSA and body weight. A 4-fold increase in clearance was observed among younger children in a study of 14 patients receiving anti-GD2 antibody ch14.18, leading to the conclusion that PK was age-dependent with an even faster clearance for girls. Our results suggest that body weight, and not age, has the strongest influence on the PK of hu3F8.

It should be noted that not all studies observed such PK differences in children. For example, when bevacizumab and infliximab were administered to children, age had no significant influence on the PK of these antibodies, although weight was not tested as an independent variable, and a large inter-patient variability in drug exposure was observed. The use of gemtuzumab in the treatment of pediatric patients with refractory/relapsed AML also showed no correlation between clearance and body weight or age.

Serum samples post-hu3F8 collected within 10 days of the last dose showed a highly significant inverse correlation between positive HAHA and serum hu3F8 concentration, consistent with HAHA’s functional significance as a neutralizing antibody that can accelerate clearance. Before the third
cycle of hu3F8, 21% of the patients developed HAHA response. Two additional patients developed HAHA late (after 9 and 12 cycles, respectively). The remaining patients (75%) never developed HAHA even after repeated hu3F8 treatment cycles. This was a huge improvement from the incidence of HAMA when m3F8 was administered - 120/169 (71%) patients developed HAMA when treated with m3F8 in their first remission, 5 84/105 (80%) among primary refractory patients, 6 and 79/101 (78%) during second remission. 7 Of note, 47 of the entire cohort (82%) had prior sensitization to other anti-GD2 antibodies, be it m3F8 or ch14.18. Thus, this data suggest that hu3F8 was fairly non-immunogenic in light of the 40% HAHA response rate reported for another humanized anti-GD2 antibody hu14.18K322A, 9 while comparable to the HACA incidence for ch14.18.4,8

We also explored the relationship between the de novo anti-GD2 response elicited during the course of this study and its impact on patient outcome. The patient cohort in this phase I trial was heterogeneous, all with multiple relapses before receiving hu3F8, and many had subsequent progressions and additional therapies. For the outcome analyses, PFS was censored at the time of disease progression or time of the next systemic therapy, while OS was clocked from protocol entry to date of next systemic therapy or last followup or death. Interestingly, higher anti-GD2 response (above the median cut point) was prognostic for PFS and trending for OS, despite the small patient sample size. Even though this trial is a passive antibody therapy, the development of de novo anti-GD2 antibody in these patients suggests a vaccination effect that may be protective. While this vaccination effect of hu3F8 will require further investigation, the potential of an idiotype network has been previously observed with m3F8.5-27 Such an effect was also reported when anti-N-glycolyl-ganglioside antibody P3 was administered to immune competent mice. 28 In a rabbit and an apoE−/− mouse model, an affinity enhanced P3 antibody with the ability to inhibit LDL-chondroitin sulfate association, induced an active anti-chondroitin sulfate antibody response, preventing the formation of, and arresting the progression of atherosclerosis. 29-31 In our patients, the ability to mount a spontaneous anti-GD2 response was negatively influenced by the HAHA response but not by hu3F8 dosage level. Patients with positive HAHA (resulting in fewer treatment cycles received) had anti-GD2 response below the median. A negative correlation was also observed among patients who had prior disease progression following anti-GD2 mAb therapy. One could speculate that earlier failure on any anti-GD2 therapy was a result of anergy to GD2 vaccination. These results suggest that anti-GD2 titer could be a predictive response marker following anti-GD2 antibody immunotherapy, especially for patients treated with hu3F8 in remission at a time when there is no evidence of clinical disease.

In summary, we found that hu3F8 was weakly immunogenic even with multiple repeat treatments. Drug exposure as measured by AUC (which correlated strongly with peak serum hu3F8) was positively associated with body weight at every mg/kg dose given, while development of HAHA response significantly reduced the serum trough level of hu3F8. Lastly, spontaneous anti-GD2 response as a measure of the vaccination effect was strongly prognostic for PFS and deserves an in depth analysis when a larger homogeneous cohort undergoing uniform therapy becomes available.
Patients and methods

Fifty seven patients enrolled in a standard 3+3 dose escalation designed phase I trial (Clinicaltrials.gov NCT01757626) had written informed consent in accordance to institutional review board guidelines. They received escalating doses (ranging from 0.9 to 9.6 mg/kg per treatment cycle) of intravenous hu3F8 plus 500 ug/m2/day of subcutaneous cytokine GM-CSF at Memorial Sloan Kettering Cancer Center in the outpatient setting. Protocol began accrual in December 2012 and closed in May 2016. All patients had high risk refractory/relapsed stage 4 neuroblastoma (12 of them with MYCN amplified disease); disease status at protocol entry was ≥ 2nd remission (n = 26), primary/secondary refractory disease (n = 24), and progressive disease (n = 7). Details on study design, toxicity, and response will be the subject of another report.

Quantitation of serum Hu3F8 was performed by a validated ELISA. Anti-3F8 idiotypic antibody A1G432 was used to capture serum hu3F8 (hu-IgG1 antibody) on 96-well microtiter plates (Thermo, 14245142) followed by a reaction with peroxidase-conjugated mouse anti-human IgG1-Fc specific antibody (Southern Biotech, 9052–05). Color reaction using hydrogen peroxide (Fisher Chemical, H325–100) and o-phenylenediamine (Sigma, P8287–100TAB) was measured with an ELISA plate reader at 490 nm. Serum hu3F8 was quantified by referencing to a hu3F8-IgG1 standard curve. The limit of detection was 1.25 ng/mL.

Pharmacokinetics (PK) of hu3F8 was studied by quantifying serum hu3F8 concentration by ELISA. Analysis was performed by non-compartmental analysis of the serum concentration-time data using the Phoenix WinNonlin software program 7.0 (Certara, Princeton, NJ). Based on the dosing interval (t) of 48 hours, key parameters determined included area under the serum concentration-time curves (AUC 0–264 and AUC 0–1) using the log-linear trapezoidal calculation method, peak serum concentration (average of 5 min post-infusion at day 1, 3, and 5), trough serum concentration (average of pre-infusion at day 3 and day 5), terminal half-life (t1/2), clearance (Clss) and volume of distribution (Vss) in steady-state, and mean residence time.

Detection of HAHA (Human anti-hu3F8 antibody) response was determined by a validated ELISA assay. Sera were first reacted with hu3F8-IgG1-F(ab’2) coated on the 96-well microtiter plates, followed by peroxidase-conjugated goat anti-human IgG1-Fc specific antibody (Southern Biotech, 2047–05). Based on a human high-titer serum reference standard, 42 normal controls were measured to establish an upper limit of normal (mean ± 3SD) which served as a cut-point for HAHA positivity (≥ 1300 units/mL; 3.9 ng/mL).

Quantitation of anti-GD2 response was determined by coating disialoganglioside GD2 (EMD Millipore Corp., 345743) at 20 ng per well on 96-well microtiter plates. Sera were added to the plates followed by reaction with peroxidase-conjugated mouse anti-human IgG1-Fc specific antibody. Color reaction using hydrogen peroxide and o-phenylenediamine was measured with an ELISA plate reader at 490 nm. Anti-GD2 response was quantified in ng/mL by referencing to a hu3F8-IgG1 standard curve. By using GraphPad Prism 6, AUC of serial samples was calculated, and normalized to ng/mL per month. Anti-GD2 antibodies measured in 48 normal samples was 12.3 ± 25.9 ng/mL.

Antibody-dependent cell-mediated cytotoxicity (ADCC) by 51 chromium release Target cells LAN-1 were labeled at 100 μCi of 51Cr (Perkin Elmer, CR110514) per 106 cells, and incubated for 1 h at 37°C. Cells were then washed and resuspended in 10% bovine serum (Sigma, 12H045) in RPMI 1640 (Mediatech, 15050295) [F10]. Patient sera were serially diluted in F10 and added in triplicates to a 96 well U-bottom plate, followed by effector NK-92MI cells stably transfected with the human CD16 Fc receptor. Effector:target ratio was kept at 20:1. Labeled target cells were then added last and the plate

Figure 6. Antibody dependent cell mediated cytotoxicity was demonstrated in sera from patients with induced anti-GD2 antibodies.
incubated in a 37°C, 5% CO2 incubator for 4 h. Released 51Cr in the ADCC supernatant was collected for gamma counting, and % specific lysis determined.

**Statistical Analysis** included Fisher’s Exact Test for comparison between 2 categorical variables. The Kaplan-Meier method was used to estimate the probability of survival, and the log-rank test for univariate association between variables and progression free survival (PFS) and overall survival (OS).

**Acknowledgements**

We thank the neuroblastoma research nurses and nurse practitioners for their expertise in caring for our patients enrolled in this clinical trial, and the neuroblastoma data management team for data collection. We in particular thank Yi Feng and Hoa Tran of the neuroblastoma research laboratory for their technical support.

**Disclosure statement**

Hu3F8 was licensed by Memorial Sloan Kettering Cancer Center (MSK) to Y-mAbs Therapeutics, Inc.; MSK and NK Cheung have financial interest in Y-mAbs Therapeutics.

**Source of support**

Supported in part by the Band of Parents Foundation, Kids Walk for Kids with Cancer NYC, Isabella Santos Foundation, Katie Find a Cure Foundation. Supported in part by the Band of Parents Foundation, Kids Walk for Kids with Cancer NYC, Isabella Santos Foundation, Katie Find a Cure Foundation. Supported in part by the Band of Parents Foundation, Kids Walk for Kids with Cancer NYC, Isabella Santos Foundation, Katie Find a Cure Foundation.

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