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A Phase I Study of Human/Mouse Chimeric Anti-ganglioside GD2 Antibody ch14.18 in Patients with Neuroblastoma

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9 patients with stage IV neuroblastoma were treated with 19 courses of human/mouse chimeric monoclonal anti-ganglioside GD2 antibody ch14.18 at dose levels of 30, 40 and 50 mg/m²/day for 5 days per course. The maximum tolerated dose (MTD) per injection was 50 mg/m²/day. 7 patients received more than one course of treatment, and none revealed any human anti-mouse antibody (HAMA) response. Clinical side-effects of patients treated with ch14.18 were abdominal and joint pains, pruritus and urticaria. One patient presented with a transient pupillatonia, while 2 others showed a unilateral atrophy of the optical nerve that was probably attributable to prior therapies. A complete remission was seen in 2 patients, partial remission in 2 patients, a minor response in 1 patient and stable disease in 1 patient. 3 patients showed tumour progression. Thus, our results indicate that treatment with chimeric MAb ch14.18 can elicit some complete and partial tumour responses in neuroblastoma patients.

Key words: neuroblastoma, therapy, chimeric MAb ch14.18
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INTRODUCTION

THE EFFECTIVE treatment of stage IV neuroblastoma patients still remains one of the biggest challenges in paediatric oncology, since their overall survival rate has not significantly improved during the last 20 years. This lack of success has occurred despite the introduction of therapeutic modalities such as high-dose radiotherapy with ^{131}meta-iodobenzylguanidine (mIBG) [1] and/or high-dose chemotherapy followed by allogeneic or autologous bone marrow or peripheral stem cell transplantation [2].

The generation of monoclonal antibodies (MAb) directed against antigens preferentially expressed on tumour cells has led to a number of applications of such reagents in cancer therapy [3]. One of the tumour antigens that served as a target for MAb-mediated therapy is disialoganglioside GD2, which is extensively expressed (up to 1.5×10^7 sites per cell) on melanoma [4] and neuroblastoma cells [5, 6]. In this regard, treatment with murine anti-GD2 MAb 3F8 resulted in one partial remission among 9 adult patients with melanoma and two partial remissions among

6 paediatric neuroblastoma patients [7, 8]. Furthermore, murine anti-GD2 MAb 14.G2a produced one partial remission in a phase I trial of 12 melanoma patients [9] and two partial remissions in another clinical trial of 5 paediatric neuroblastoma patients [10].

Our rationale for performing a phase I clinical trial with paediatric neuroblastoma patients with the human/mouse chimeric variant of MAb 14.G2a, i.e. MAb ch14.18 was based on our encouraging initial clinical results with MAb 14.G2a, and on relevant preclinical data obtained with MAb ch14.18. Firstly, treatment of paediatric neuroblastoma patients with MAb 14.G2a resulted in two complete and two partial remissions among 6 patients available for objective evaluation [11]. Because all patients treated with murine MAb 14.G2a developed strong and prolonged human anti-mouse antibody (HAMA) responses that precluded repeated use of this antibody, we reasoned that the human/mouse chimeric MAb ch14.18, which was designed to minimise HAMA responses, could provide more optimal conditions for therapy. Secondly, although preclinical data indicated both MAbs to be equally effective in mediating complement-dependent cytotoxicity (CDC), ch14.18, containing a human Fc-region, proved far more effective than 14.G2a in neuroblastoma cell killing, mediated by antibody-dependent cellular cytotoxicity (ADCC) [12]. Although, at this time, it is not well understood what constitutes the *in vivo* correlate of *in vitro* effector functions of anti-tumour MAbs, there is evidence in the literature suggesting that they may play a key role in growth suppression and destruction of some human tumours [13]. Thus, we postulated that the increased ADCC, mediated by MAb ch14.18, may further optimise conditions for effective therapy of neuroblastoma.

Based on all these considerations, we initiated a phase I clinical trial of stage IV paediatric neuroblastoma patients with anti-GD2 MAb ch14.18. We report here on the results of this study whose objectives were to determine toxicity and maximum tolerated dose (MTD) of ch14.18, as well as to assess HAMA responses and anti-tumour activities after repeated treatment cycles.

PATIENTS AND METHODS

Patients

All patients selected for this study presented with stage IV neuroblastoma according to the classification of Evans and colleagues [14]. The diagnosis of neuroblastoma stage IV and the presence of measurable disease were the major criteria for inclusion of paediatric patients in this study, since GD2 is ubiquitously expressed on most of these tumour cells. The parents of all patients treated in this study signed a written consent form after they had been informed of its possible risks and benefits. The study was approved by the ethics committee of the University of Tübingen. All patients were kept off any other therapy for at least 4 weeks prior to the initial injection of MAb ch14.18.

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Study design

Doses of ch14.18 were escalated at 10 mg/m^2/day in cohorts of five courses with 30 mg/m^2/day for the first five courses, 40 mg/m^2/day for the next five courses and 50 mg/m^2/day for the last five courses. After reaching the MTD of 50 mg/m^2/day after 15 courses, four additional courses with 40 mg/m^2/day were applied.

MAb ch14.18

The construction of the human/mouse chimeric anti-GD2 MAb ch14.18 has been described previously [15], and was produced for clinical trials by Repligen, Inc. (Needham Heights, U.S.A.). The final product was tested for nucleic acids, murine viruses, bacteria, fungi, mycoplasma and pyrogens, and met the standards set for good manufacturing practice (GMP). Appropriate amounts of the antibody were dissolved in 100 ml normal saline, and various doses of ch14.18 (30 mg/m^2/day to 50 mg/m^2/day) were infused intravenously into patients daily for 5 days at 12.5 ml/h over a period of 8 h each. These doses were selected on the basis of our previous results obtained with murine anti-GD2 MAb 14.G2a [11]. The time between individual treatment cycles ranged from 8 to 12 weeks. Prior to each infusion of ch14.18, steroids were given prophylactically as an intravenous bolus as 1–2 mg/kg body weight in order to prevent allergic or anaphylactic side-effects. An intravenous infusion of morphine (1–2 mg/kg/day) was started prior to the antibody treatment and continued throughout treatment with ch14.18.

Determination of serum concentrations of MAb ch14.18

A double antibody technique was used for quantitation of ch14.18 serum levels. Briefly, 100 μl of patients' sera at appropriate dilutions were incubated in duplicate with 100 μl of diluted (1:10000) rabbit anti-murine 14.18 F(ab')$_2$ (kindly donated by Dr A. LoBuglio, University of Alabama, Birmingham, Alabama, U.S.A.) and 100 μl of ^{125}I-labelled ch14.18 (20000 cpm). After incubation for 16–18 h at 4°C, bound ^{125}I-labelled ch14.18 was separated from free radiolabelled antibody by precipitation with goat anti-(rabbit IgG) antibody (Dianova, Hamburg, F.R.G.) in 4% polyethylene glycol. After centrifugation of this mixture, the radioactivity of the precipitate was determined with a gamma-scintillation counter. A standard curve of ch14.18 ranging from 1 to 500 ng/ml diluted in normal human serum was used to calculate the amount of ch14.18 in patients' sera.

Determination of human anti-mouse antibody (HAMA)

The amount of human anti-(mouse IgG) antibodies in patients' sera was measured with an ELISA test kit (ImmunoSTRIP HAMA) (Medac Diagnostica, Hamburg, F.R.G.), as previously described [11]. The lower detection limit of HAMA in this test was 40 ng/ml.

Lytic activity of serum

The lytic activity of patients' sera during treatment with ch14.18 was measured in a ^{51}Cr release assay. Briefly, cultured neuroblastoma cells SK-N-LO originally described by Biedler and colleagues [16] were labelled with ^{51}chromium, as described previously [17]. Radiolabelled target cells (5×10^3) in RPMI 1640 culture medium (100 μl) were seeded in individual wells of 96-well microtitre plates. Sera obtained from patients before, during and after therapy with ch14.18 were each added to these wells at a final dilution of 1:6 and the plates were incubated for 4 h at 37°C. Supernatants were then harvested and the release of

^{51}chromium was measured. The percentage of specific lysis was calculated as:

$$\frac{(\text{experimental } ^{51}\text{Cr release}) - (\text{spontaneous } ^{51}\text{Cr release})}{(\text{maximal } ^{51}\text{Cr release}) - (\text{spontaneous } ^{51}\text{Cr release})} \times 100.$$

Evaluation of tumour response

Tumour responses were determined by diagnostic mIBG-scintigraphy [18, 19] and, if applicable, by computed tomography (CT) and/or nuclear magnetic resonance (NMR) scans, as well as by evaluations of tumour markers. Thus, catecholamines in plasma and urine specimens of patients were kindly determined by Prof. D.A. Hunneman, as described previously [20]. Neuron-specific enolases were measured in the sera of patients with a fluoroimmunoassay (Delfia NSE kit) purchased from Pharmacia (Freiburg, F.R.G.). The mIBG-uptake was assessed on a semi-quantitative basis in terms of decrease, stability or increase of tumour size.

RESULTS

Clinical profiles of patients

All 9 paediatric patients with neuroblastoma stage IV treated with ch14.18 had received prior therapy with several cycles of chemotherapy and/or high-dose [^{131}I]mIBG, autologous bone marrow or peripheral stem cell transplantation or other experimental therapeutic approaches. It is evident from the information summarised in Table 1 that despite these intensive therapies, 6 of the 9 patients did not achieve a complete remission and 3 relapsed after such therapy. These patients were kept off therapy for at least 4 weeks prior to antibody treatment, and received steroids (1–2 mg/kg) that alleviated allergic side-effects to some extent during treatment with MAb ch14.18.

Serum levels of MAb ch14.18

After the administration of three dose levels of ch14.18 at 30 mg/m^2/day (five courses), 40 mg/m^2/day (nine courses) and 50 mg/m^2/day (five courses), serum concentrations of ch14.18, determined twice daily before (base levels) and after (peak levels) every infusion of the antibody, ranged from a minimum base level of 3.6 μg/ml to a maximum peak level of 73.7 μg/ml. The data, summarised in Table 2, indicate that ch14.18 did not form complexes with circulating ganglioside GD2, which is bound by lipoproteins [5].

Induction of human anti-(mouse IgG) antibody

Analyses of each patient's serum for the presence of human anti-(mouse IgG) antibodies (HAMA) before, during and after therapy with ch14.18 indicated the absence of any HAMA (data not shown). This is in contrast to results obtained in our initial phase I clinical trial with murine anti-GD2 MAb 14.G2a, where all paediatric neuroblastoma patients had HAMA responses either during or shortly after therapy [11].

Lytic activity of patients' sera

In order to assess whether the infusion of MAb ch14.18 generates a lytic activity in patients' sera against GD2-positive human neuroblastoma cells, serum was collected during the 10 treatment cycles and tested for lytic activity in a 4-h chromium release assay. Prior to antibody infusion, only a minimal amount of lytic activity against neuroblastoma target cells was observed. However, as shown in Figure 1, a considerable amount of lytic activity was generated during antibody treatment, measuring as much as 100% in some serum samples. These data indicate *in vivo* activation of complement during antibody treatment and GD2 which is shed into neuroblastoma patients' sera [5] does not form complexes with anti-GD2 MAb ch14.18 circulating in the serum.

Table 1. Clinical profiles of patients

Patient no.	Age (years) /sex	Prior therapy	Disease sites	Status
1	6/F	Chemo, ABMT, APBST, MAb 14.G2a	Adrenal	Partial remission
2	10/F	Chemo, ABMT, radiotherapy	Abdominal, bone	Relapse
3	5/M	Chemo, APBST	Abdominal, skull, LN	Partial remission
4	7/M	Chemo, APBST, radiotherapy	Bone	Partial remission
5	9/F	Chemo, radiotherapy ABMT	Adrenal, bone	Relapse
6	2/F	Chemo, APBST	Skull	Partial remission
7	9/F	Chemo, MAb3F8	Paravertebral	Partial remission
8	6/M	Chemo, APBST	Bone	Partial remission
9	7/F	Chemo, ABMT	BM, bone	Relapse

Chemo, chemotherapy; ABMT, autologous bone marrow transplantation; LN, lymph node; APBST, autologous peripheral blood stem cell transplantation.

Table 2. Amount of ch14.18 and range of serum levels

Patient no.	Course	Dose/day* (mg/m²)	Dose/ course (mg/m²)	Total dose (mg/m²)	Serum level† (μg/ml)
1	1	30	150	150	8.8–22.1
2	1	40	200		23.7–64.0
	2	40	200	400	17.5–63.0
3	1	30	150		15.8–36.4
	2	40	200	350	7.3–30.4
4	1	50	250		18.2–63.1
	2	50	250	500	18.5–59.8
5	1	30	150		14.1–42.5
	2	40	200		3.6–45.5
	3	50	250		8.6–62.6
	4	40	200	800	9.8–40.9
6	1	40	200		14.1–44.1
	2	50	250	450	15.8–63.5
7	1	30	150		11.3–36.7
	2	30	150		10.6–46.6
	3	50	250	550	14.2–73.7
8	1	40	200		11.5–42.2
	2	40	200	400	13.4–44.8
9	1	40	200	200	18.8–70.3

*Each treatment cycle was 5 days and the time between cycles ranged from 8 to 12 weeks.
†Lowest base and highest serum peak level of MAb ch14.18.

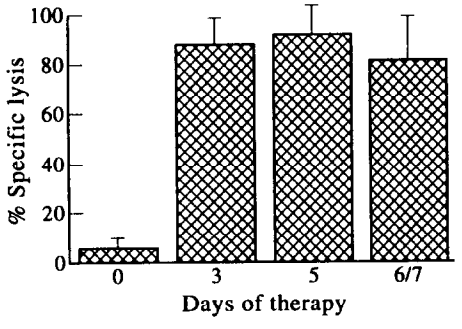

Figure 1. Specific lytic activity of patients' sera against neuroblastoma target cells during and after 10 cycles of treatment with ch14.18. The final dilution of the sera in the chromium release assay was 1:6. Error bars indicate standard deviation (S.D.) of these data.

Clinical side-effects

The most salient side-effect observed during treatment with ch14.18 was pain, predominantly in the abdomen and joints of the lower and upper extremities, as was noted previously with MAb 14.G2a [11]. However, pain was adequately controlled by the continuous intravenous infusion of morphine started prior to antibody treatment and continued throughout the therapy. At dose levels of 50 mg/m²/day, pain was most pronounced and patients required amounts of morphine that cause undesirable side-effects, thus 50 mg/m²/day is the maximal tolerable dose (MTD) for ch14.18.

Whenever very severe pain occurred during ch14.18 infusion, it was interrupted until pain was relieved, which usually occurred within 1 h. Other side-effects observed were allergic reactions like pruritus, exanthema and urticaria. These symptoms were seen during nine courses, beginning on the first day of antibody treatment [11]; however, such side-effects could easily be treated by the application of anti-histamines. In cases where this treatment proved inadequate to relieve the allergic side-effects, additional steroids were administered. Another transient side-effect which was seen in 1 patient was a pupillotonia, possibly due to binding of ch14.18 to GD2, which is present in the eye. 2 patients showed a unilateral optical atrophy; however, 1 of these patients, no. 4, presented with this symptom prior to treatment with ch14.18. Table 3 summarises the clinical side-effects observed during the treatment cycle with ch14.18.

Tumour response

All patients could be evaluated objectively for tumour response by means of scintigraphy with [^{123}I]mIBG, CT and/or NMR scans before and from 8 to 12 weeks after the end of treatment. In most cases, mIBG uptake by tumours proved to be the only useful diagnostic tool, except that one complete remission, lasting only 2 months, could be documented with NMR scanning, with the complete disappearance of a single lesion in patient no. 7. Additionally, patients' sera were monitored for such tumour markers as neuron-specific enolase and catecholamines prior to and after treatment; however, these did not prove to be useful for diagnostic purposes.

A complete remission was induced in 2 patients; however, in 1 of these patients, no. 7, this remission lasted only 2 months and then the patient presented with local relapse. Despite two additional cycles of treatment, further tumour progression was observed in this patient. Another complete remission was achieved in patient no. 4, who is still under continued observation (>14 months). Two patients, nos 5 and 8, showed a partial remission that could only be induced after several cycles of antibody treatment. Figure 2 provides an example of mIBG scintigraphy in patient no. 5, prior to treatment with ch14.18 (Figure 2a) and after the fourth cycle of this therapy (Figure 2b). This finding clearly illustrates the advantage of ch14.18, which did not induce HAMA unlike its parental murine MAb 14.G2a, and could be administered in repeated treatment cycles. This resulted in much larger cumulative dose levels which, in some cases, did achieve tumour responses otherwise not possible with lower dose levels of antibody. In addition, patient no. 6 presented with stable disease, patient no. 1 showed a minor response and 3 patients had progressive disease. Patient no. 6 who, after treatment with ch14.18, presented with stable disease for >9 months, was then treated with retinoic acid. Patient no. 7, who after one treatment cycle was in complete remission for 2 months, relapsed and was then treated by surgery and interleukin-2. All tumour responses observed after treatment with MAb ch14.18 are summarised in Table 4.

DISCUSSION

A phase I clinical trial was performed with the chimeric anti-GD2 antibody ch14.18 in 9 paediatric patients with stage IV

Table 3. Clinical side-effects associated with the infusion of ch14.18

Dose levels (mg/m²)	No. of courses	Side-effects				
		Pain	Fever	Urticaria	Pupillatonia	Opticus atrophy
30	5	5/5	4/5	1/5	0/5	0/5
40	9	7/9	4/9	5/9	0/9	0/9
50	5	4/5	2/5	3/5	1/5	2/5

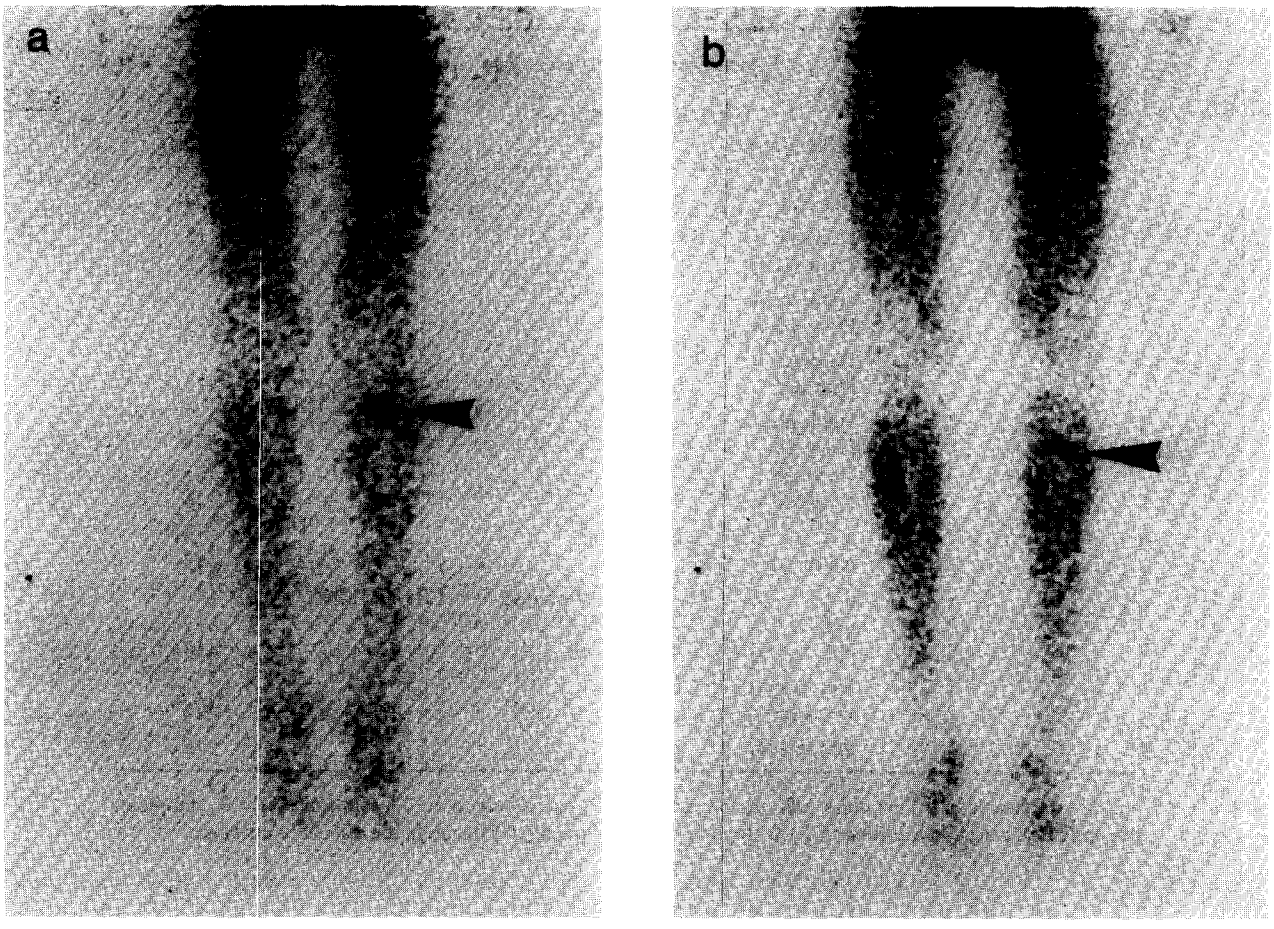

Figure 2. mIBG scintigraphy profile of patient no. 5 prior to antibody treatment (a) and after the fourth cycle of treatment with MAb ch14.18 (b). The tumour site in the tibia is marked with an arrow.

neuroblastoma. Although all of these patients were heavily pretreated prior to antibody treatment, including high-dose chemotherapy, with subsequent autologous peripheral stem cell or bone marrow transplantations, 6 patients did not achieve complete remission and 3 relapsed after such therapy. The rationale for performing this clinical trial with MAb ch14.18 was based on previously encouraging results achieved in a phase I trial with its murine parental MAb 14.G2a [11]. The objectives of the phase I trial with MAb ch14.18 were to measure toxicities and establish a MTD, to determine any HAMA responses and particularly to assess whether lack of HAMA facilitates the use of multiple treatment cycles achieving higher cumulative dose levels than were possible with the murine MAb 14.G2a [11].

The most salient clinical side-effect of ch14.18 was the pain experienced by the patients, especially during infusion of the antibody, similar to that observed previously during the injection of murine MAb 14.G2a [11]. Although the reason for this pain is not entirely clear, immunohistochemical analyses indicated staining of nerve fibres with anti-GD2 MAb, suggesting the expression of GD2 on these nerve fibers (G. Kaiserling, personal communication). However, the pain could be controlled by initiating a continuous intravenous infusion of morphine. Nevertheless, a dosage of ch14.18 of 50 mg/m^2/day required very high amounts of morphine for pain control that produced undesirable side-effects. Therefore, we stopped escalation of ch14.18 at this dose level, and considered it to be the MTD for this antibody. Pain, primarily located in the abdomen and pelvis, was also the major side-effect reported in a phase I clinical trial of adult melanoma patients treated with ch14.18 [21]. Besides nausea, other side-effects were not seen in this study. In addition, some of the toxicities observed in our study were also not seen, possibly because the total dose levels ranged only from 10 to 100 mg ch14.18 and were thus considerably lower than those used by us.

Other side-effects observed, such as urticaria, pruritus and exanthema, were already seen in our previous phase I clinical trial with murine MAb 14.G2a [11]. However, all patients treated with MAb 14.G2a exhibited a strong HAMA response, whereas patients treated with ch14.18 did not. Thus, it is obvious that HAMA responses are not responsible for this spectrum of clinical side-effects. A clear-cut difference was observed between murine MAb 14.G2a and its chimeric variant ch14.18, as far as the occurrence of hypertension is concerned. Thus, while some neuroblastoma patients treated with MAb 14.G2a [11], as well as with another murine anti-GD2 MAb, 3F8 [7], experienced hypertensive episodes, this side-effect was not observed during the treatment cycles with ch14.18. However, at this time, we have no explanation for this observation.

Evidence to support the contention of *in vivo* activation of complement components is provided by the lytic activity of the patients' serum observed during antibody treatment. In this regard, although the titre of patients' serum in the chromium release assay was low (1:6), a high specific lysis was observed. This lytic activity found in patients' serum is a further indication

Table 4. Tumour response after treatment with ch14.18

Patient no.	Course	Tumour response after each cycle: mIBG uptake	CT/NMR/ ultrasound	Overall tumour response	Survival (months)
1	1	Decrease	No change	MR	>24
2	1	Decrease	n.d.		5
	2	Progression		PD	
3	1	Stable disease	n.d.		
	2	Progression		PD	3
4	1	Decrease	n.a.		
	2	Decrease	n.a.	CR	>14
5	1	Stable disease	n.a.		
	2	Decrease			
	3	Decrease			
	4	Decrease		PR	>16
6	1	n.d.	No change		
	2	No change		SD	>17
7	1	n.d.	Complete response	CR (2 months)	
	2	n.d.	Relapse		
	3	n.d.	Progression		>18
8	1	Decrease	n.d.		
	2	Decrease		PR	>12
9	1	Progression	n.d.	PD	6

n.a., not applicable; n.d., not done; MR, minor response; PR, partial response; SD, stable disease; CR, complete response; PD, progressive disease; CT, X-ray computed tomography; NMR, magnetic resonance imaging.

that GD2, shed into sera of neuroblastoma patients [5], does not inactivate the anti-GD2 antibody in the serum. Essentially, all gangliosides shed into the circulation are bound to lipoproteins [22] and, due to their amphipatic nature, form micelles [23] that are unable to react with anti-ganglioside antibodies, unless the serum is first extracted with chloroform/methanol to dissolve these complexes [5]. However, we have found, thus far, no correlation between lytic activity of the patients' serum and their tumour response. Further studies with more patients may have to be performed in order to assess whether such a correlation exists.

The transient pupillatonia in 1 patient was another side-effect, which was also seen in a patient treated with MAb 14.G2a [11]. In this regard, a recent immunohistochemical study indicated the presence of GD2 in the ciliary muscle and iris of the eye (R. Bachmann, personal communication). Therefore, the paralysis of accommodation could be due to a direct cytopathic effect of the antibody on eye structures. The reason for the unilateral opticus atrophy is not clear at this time, especially since patient no. 4 presented with this condition prior to treatment with ch14.18. Consequently, this particular side-effect may be related to previous therapies, including irradiation of the skull and/or high-dose myeloablative chemotherapy with subsequent stem cell transplantation. Patient no. 6 developed a unilateral opticus atrophy between two cycles of treatment with ch14.18; however, since metastases in this patient's skull were locally irradiated between these treatment cycles, the opticus atrophy could indeed be related to this therapeutic modality. Incidentally, the local irradiation did not produce any anti-tumour response. More than 4 weeks thereafter, patient no. 6 received another treatment cycle with ch14.18 and remains with stable disease and mIBG-positive metastasis. This patient was considered to be evaluable, since she received no other therapy at least 4 weeks prior and 4 weeks after antibody treatment.

A clear tumour response in response to treatment with MAb ch14.18 could be seen in 4 neuroblastoma patients. In most patients, analysis of tumour markers in the serum (catecholamine, neuron-specific enolase) proved uninformative, whereas positive mIBG uptake of tumour sites was the only useful diagnostic criteria. Because quantitative measurements of mIBG uptake are quite difficult, we evaluated it semi-quantitatively as either decreased, stable or increased uptake. CT, ultrasound or NMR scanning failed to be of diagnostic value in most of our cases. However, a complete remission was documented in patient no. 7 by the complete disappearance of a single lesion in a NMR scan; however, this complete remission lasted for only 2 months. Another complete response was achieved in patient no. 4, as documented by a negative mIBG scintigraphy after the second cycle with ch14.18. This patient is still in complete remission after >14 months. The possibility that treatment with ch14.18 affects the capacity to accumulate mIBG instead of killing the tumour cells is unlikely since patients with clinical progressive disease after treatment with ch14.18 showed increased uptake of mIBG. Partial remissions were induced in patient nos 5 and 8 after several treatment cycles of ch14.18. In these 2 patients, a tumour response was observed after every treatment cycle, indicating that resistance of neuroblastoma cells against treatment with ch14.18 did not develop. Thus, patient no. 5, who received four treatment cycles, did not show any tumour response after the first cycle, but presented with stable disease; however, after each of the following three cycles, a partial remission was induced in this patient (Table 4),

indicating that tumours not responding to the first treatment cycle could still respond to additional treatment cycles with ch14.18. Findings such as these clearly indicate the advantage of chimeric MAb ch14.18, which, in contrast to its parental MAb 14.G2a, does not elicit a HAMA response, and can thus be used in repeated treatment cycles, resulting in a cumulative dose of up to 800 mg/m^2 (Table 2). Although we could not detect any HAMA response to ch14.18 with the ELISA test kit, we cannot rule out the development of a human antichimera antibody (HACA) response, as reported for melanoma patients treated with ch14.18 [24]. It should be pointed out, however, that in this case, this type of antibody response was found to be three orders of magnitude less than the HAMA response produced by murine MAb 14.G2a in melanoma patients [24].

The following conclusions can be drawn from the results of this phase I trial: chimeric MAb ch14.18 can be applied repeatedly without causing severe allergic or anaphylactic side-effects and without the induction of HAMA. In some patients, a prolonged anti-tumour response could be induced. Several cycles of treatment with MAb ch14.18 may be required to induce partial or even complete responses, and it is evident that ch14.18 is most suitable for this purpose. Tumour size decreased in some cases after each treatment cycle, indicating that resistance against ch14.18 did not develop in these patients. The results of this phase I clinical trial warrant consideration for further use of ch14.18 in patients with paediatric neuroblastoma, particularly as a means for targeting radionuclides other than iodine to this highly radiosensitive tumour, or for using this antibody in combination with cytokines, such as interleukin-2 or granulocyte–macrophage colony stimulating factor, to activate immune effector cells and thus to increase the effectiveness of ch14.18 for cancer therapy.

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