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A New ^{123}I-MIBG Whole Body Scan Scoring Method—Application to the Prediction of the Response of Metastases to Induction Chemotherapy in Stage IV Neuroblastoma

N. Ady, J.-M. Zucker, B. Asselain, V. Edeline, F. Bonnin, J. Michon, R. Gongora and L. Manil

A new semi-quantitative scoring system is proposed, especially designed for the comparative interpretation of sequential whole-body meta-iodo-benzyl-guanidine (MIBG) scans in stage IV neuroblastoma children. This method was applied to assess whether MIBG scan at mid-course of induction chemotherapy could predict the final response. 27 newly diagnosed children were investigated by three sequential ^{123}I-MIBG scans performed at the beginning, at mid-course (6 weeks) and at the end of neoadjuvant chemotherapy (12 weeks). Whole body scans were divided into nine regions in which the extension of bone metastases was separately quoted (score range: 0–3). The overall absolute scores were obtained by adding the scores of the nine regions. Relative scores were calculated by dividing the absolute score at each time by the corresponding pretreatment score. The score at mid-induction correctly predicted the overall response of metastases at the end of induction ($P < 0.0001$) in most cases. This method is easy to use, reproducible, subject to little inter-investigator variation, and thus well adapted to multicentric trials.

Key words: MIBG, scintigraphy, neuroblastoma stage IV, induction chemotherapy, scoring method
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INTRODUCTION

NEUROBLASTOMA is one of the most frequent solid tumours in childhood. Most cases are diagnosed before the age of 5 years, with 50% occurring before the second birthday. Approximately 90 new cases are observed in France every year. The tumour is heterogeneous regarding its clinical features and evolution. Although the prognosis is favourable in localised neuroblastoma, the situation is quite different in metastatic tumours to bone (60% at the time of diagnosis). In spite of significant progress in paediatric oncology, metastatic neuroblastoma in children over 1 year of age remains a serious challenge. The prognosis has not been markedly improved over the last decade in patients with bone or bone marrow involvement. Treatment includes pre-operative induction chemotherapy, surgery, postoperative high dose chemotherapy (with or without total body irradiation), and autologous bone marrow transplantation.

^{123}I-MIBG is now considered as a first line method for the staging and follow-up of neuroblastoma [1–7]. However, a major problem is the lack of any reliable and precise scoring system to evaluate the bone response to therapy on MIBG scans. Some attempts based on the intensity of uptake have been proposed during the last decade in healthy adults [8] and in children with neuroblastoma [2], but do not seem to be used in multicentric

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trials. Therefore, we propose a new semi-quantitative method, based on calculation of distribution scores of the hot spots in the skeleton, allowing an easy and reproducible comparison of the sequential images.

No data are available concerning the value of MIBG scan at mid-course of induction chemotherapy in metastatic cases. Selection of poor responders at this stage could be important, since alternative treatments could be used earlier. To set up and test our scoring method, we performed three sequential MIBG scans during induction chemotherapy in order to evaluate, as precisely as possible, the metastasis response to therapy.

PATIENTS AND METHODS

Selection of patients

Between June 1989 and December 1992, 37 children with newly diagnosed stage IV neuroblastoma were referred to the paediatric department of the Institut Curie. Among them, 27 were included in this study (mean age 37 months, range 10–97 months; sex ratio M/F: 19/8). 9 children had to be excluded because of unavailable data at mid-course and 1 other for lack of MIBG uptake (negative scan). The site of the primary tumour was the abdomen in 25 cases, and one each in the mediastinum and the pelvis. Bone marrow involvement was demonstrated by cytology, histology and/or immunocytology in 25 cases, and urinary catecholamines were elevated in all patients at diagnosis.

All patients were previously untreated and were included in three successive induction protocols made up of four courses of multidrug chemotherapy, including cyclophosphamide, doxorubicin, vincristine, VP 16 and cis-platinum. Median follow-up was 18 months (range 10–52 months) after diagnosis.

MIBG

Iodine-123-labelled meta-iodo-benzyl-guanidine (MIBG) was obtained from Cis-Biointernational, Gif-sur-Yvette, France. Intravenous injection (3.7 MBq/kg, with a maximum of 110 MBq) was performed 22–26 hr prior to imaging.

Scintigraphy acquisitions

Three series of images were acquired, before or at the beginning of neoadjuvant chemotherapy (exam 1), after two courses (6 weeks later, exam 2) and after four courses, prior to surgery (12 weeks, exam 3).

Anterior and posterior whole body scans (256 × 1024 digital images, scanning 12 min/m) and lateral views of the head (256 × 256 digital images, 4 min/frame) were acquired using a General Electric large field of view rectangular STARCAM camera, fitted with a low energy, high definition collimator.

Image processing

Images were processed with a General Electric STAR 3000 computer. After completion of the three studies (12th week), whole body images and head lateral views were edited without indication of patient identity, but with a patient code number and the running number of the images (1, 2 or 3). The three corresponding images (anterior or posterior views, or head profiles) at the three times were edited on the same film, taking care to adjust the background activity to approximately the same level, in order to appreciate easily the tumour/background contrast. The skeleton was divided into nine areas, excluding the primary tumour, the neighbouring lymph nodes and the extra-skeletal metastases. These areas correspond to the head and the face (area 1), the neck and back vertebral column (area 2), the ribs and the sternum (area 3), the lumbar and sacral column (area 4), the pelvis (area 5), the arms (area 6), the forearms and the hands (area 7), the thighs (area 8), the legs and the feet (area 9) (Figure 1). In each region, the number of lesions was quoted as follows: 0, no site per segment; 1, one site per segment; 2, more than one site per segment; 3, massive involvement (>50% of the segment area). The overall *absolute* scores were obtained by adding the scores corresponding to each region (max. 27). *Relative* scores were calculated by dividing the absolute score at each time by the corresponding pretreatment overall score. The relative score of each patient at 6 weeks was calculated, and patients were distributed to four groups with scores arbitrarily chosen as ≤0.20 (lesions almost disappeared), >0.20–≤0.50 (lesions strongly reduced), >0.50–≤0.90 (lesions weakly but significantly reduced) and >0.90 (lesions not significantly reduced, unmodified or altered).

At 12 weeks, scintigraphic response to chemotherapy was defined as follows: complete response (CR): absence of visible lesion (absolute score = 0); very good partial response (VGPR): presence of one or two doubtful or borderline foci (absolute score ≤2 and only presence of spots of very low intensity); in the presence of a single spot with moderate (or high) intensity, patients were classified in the next group; partial response (PR): relative scores ≤0.50, excluding the VGPR and CR patients; and non-response (NR): relative scores >0.50.

These imaging criteria are comparable to those commonly considered in the evaluation of the therapeutic response (complete or partial remission, non-response).

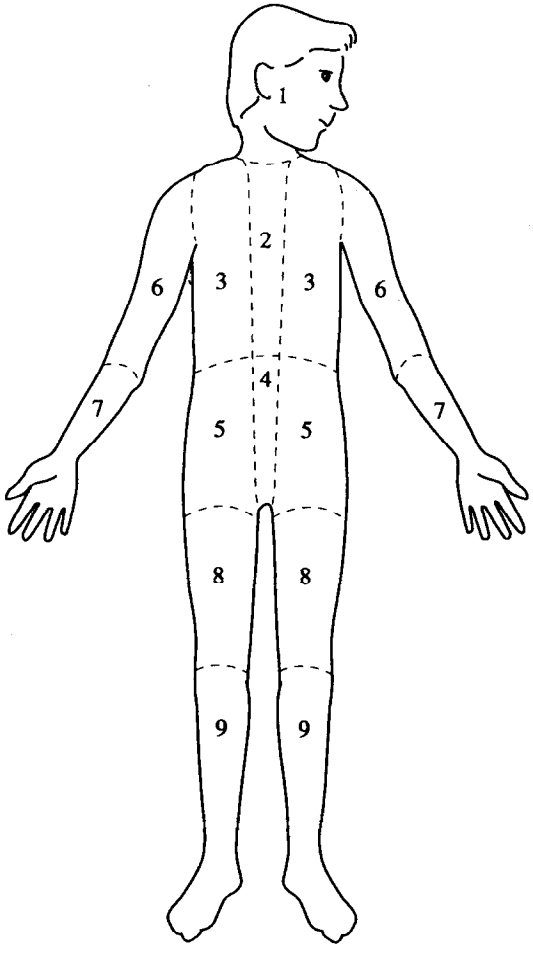

Figure 1. Scoring methodology: the nine regions of the skeleton.

All the images were scored by two independent specialists and the mean values of the scores were utilised. In order to assess the reproducibility of the method, images of 16/27 patients were interpreted independently by four investigators (including the previous two specialists).

Scintigraphy results were also compared to overall metastatic response and to bone marrow status alone. The criteria used to assess the overall response of metastases were clinical examination, bone marrow status and all imaging data (at least CT scan and MIBG scan, and in certain cases bone scan, X-rays and MRI, to explore metastases to bone and bone marrow, liver, distant lymph nodes, skin, lungs and central nervous system). Bone marrow status was assessed by bone marrow cytology, bone histology (at least four samples) and immunocytology. Urinary catecholamines (potentially related to the primary tumour, prior to surgery) were not taken into account. In case of discrepant results from different methods, the most abnormal data were considered as definitive.

Statistical methods

Correlation coefficients and regression slopes were calculated to assess the inter-investigator reproducibility of overall scores. χ^2 test and correlation coefficients were performed to quantify the relationship between the responses at different times during chemotherapy.

RESULTS

Scoring method and reproducibility

This scoring method appears to be very easy to use and reproducible. Correlation between four investigators (available in 16 patients) is presented in Table 1. Correlation coefficients were always ≥ 0.88 and usually > 0.96. The slope of the inter-investigator regression straight line was between 0.96 and 1.25 (Table 1).

Clinical results

Typical images of a complete responder and of a non-responder are presented in Figures 2 and 3, respectively.

Scinitigraphy response was determined at the end of induction chemotherapy (exam 3), in order to determine which patients had CR, VGPR, PR and NR. As shown in Table 2, MIBG score at mid-course (6 weeks) predicted correctly the final MIBG response in most patients ($P < 0.0001$). In particular, 4/5 children with a relative score (RS) ≤ 0.20 at mid-course ended with a CR and the fifth, a VGPR; of the children in the second group ($0.20 < RS \leq 0.50$), 1 had a PR, 4 had VGPRs and 2 had CRs, 5/6 patients with a RS between 0.51 and 0.90 had a PR, and 8/9 cases with $RS > 0.90$ did not respond. The quantitative correlation between the relative scores at 6 and 12 weeks,

Table 1. Determination of the score: correlation between four investigators (16 patients)

	Correlation coefficient			Regression slope		
	Inv. 1–2	Inv. 1–3	Inv. 1–4	Inv. 1–2	Inv. 1–3	Inv. 1–4
1st exam.	0.96	0.93	0.88	0.96	0.99	1.09
2nd exam.	0.96	1.00	0.97	1.01	1.13	1.20
3rd exam.	0.97	0.99	0.97	1.03	1.04	1.25

Inv., investigator.

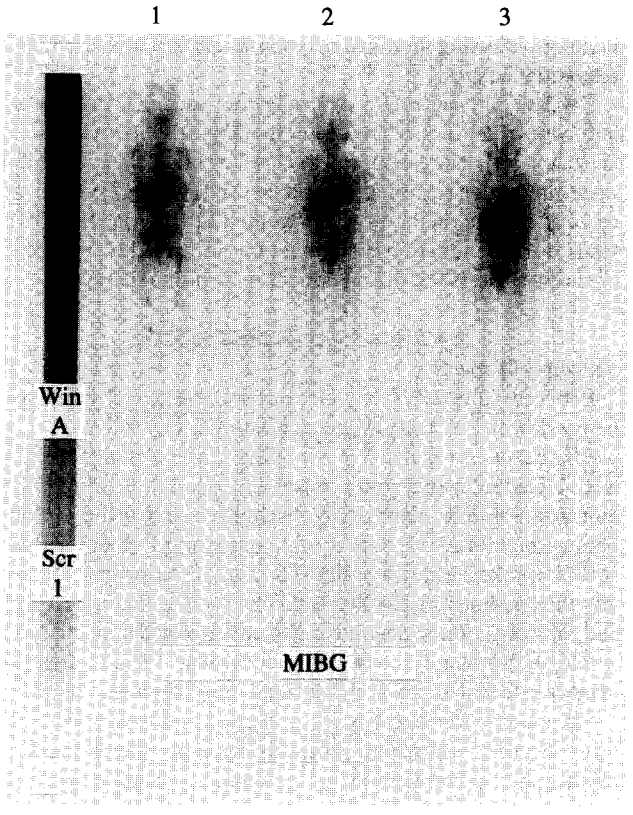

Figure 2. Typical example of a complete responder (CR): anterior whole body scans before (1), at mid-course (6 weeks) (2) and at the end (12 weeks) (3) of induction chemotherapy. Bone metastases are considerably attenuated at 6 weeks and completely disappeared at 12 weeks, prior to surgery. At this time, the right suprarenal primary tumour is still visible.

presented in Figure 4, indicates that NR, PR and "good responders" (VGPR + CR) could be predicted at mid-induction in most cases, but that VGPR were more difficult to separate from CR. As shown in Figure 5, the kinetic profiles of the absolute scores during induction chemotherapy confirmed that good responders were also early responders (at mid-course) in all but one case. Alternatively, the absolute pretreatment score alone did not give any information on the final response to therapy.

MIBG scores at mid-induction (and also at the end of induction, results not shown) correlated very well with the overall metastatic response ($P < 0.0001$, Table 3). There was also a significant relationship between bone marrow response and MIBG score at 6 weeks ($P < 0.05$) (Table 4). The short follow-up prevents any correlation between the MIBG score and the disease-free interval or survival duration.

DISCUSSION

This scoring method is easy to use, reproducible and only necessitates a short training of 1–2 hr. It facilitates the comparison between results obtained by different investigators and in different centres, and is readily adapted to multicentric trials. In this respect, it is noteworthy that, if one of the four investigators obtained mean higher absolute scores than the others, the evolution, expressed by the relative scores, was almost identical. The relative expression of the scores appeared to be more investigator-independent than the absolute scores and gave a more indicative image of the actual disease evolution.

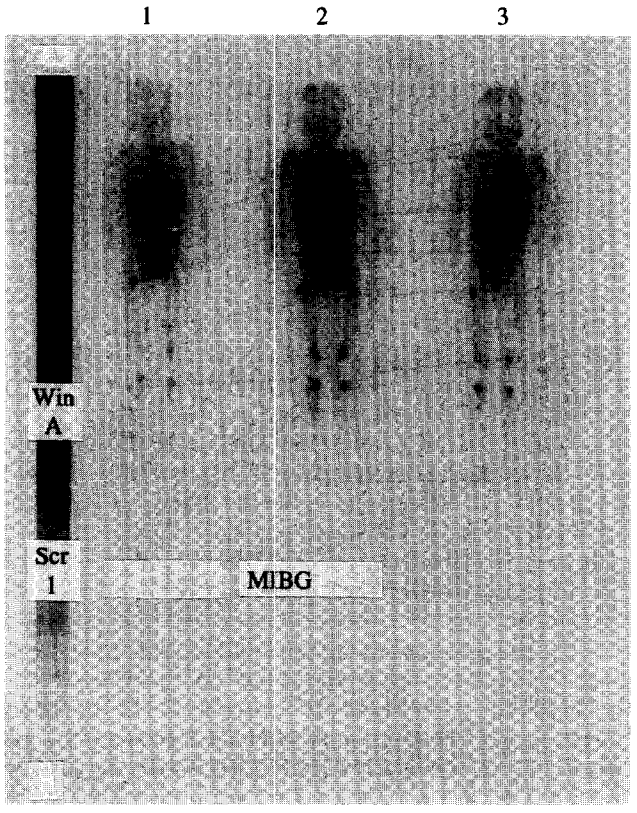

Figure 3. Typical example of a non-responder (NR): anterior whole body scans before (1), at mid-course (6 weeks) (2) and at the end (12 weeks) (3) of induction chemotherapy. Bone metastases remain unmodified throughout induction chemotherapy.

Table 2. MIBG relative score at 6 weeks as compared to MIBG response at 12 weeks

Relative score at 6 weeks	MIBG response at 12 weeks CR	VGPR	PR	NR	*n*
≤0.20	4	1	0	0	5
>0.20–≤0.50	2	4	1	0	7
>0.50–≤0.90	1	0	5	0	6
>0.90	0	0	1	8	9
n	7	5	7	8	27

$P < 0.0001$.

Definition of MIBG response: CR = absolute score = 0; VGPR = absolute score ≤2 and only low intensity spots; PR = relative score ≤0.50; NR = relative score >0.50.

Attempts for semi-quantification of MIBG uptake have been published previously. Nakajo and associates [8] proposed a semi-quantitative scoring system for the *normal* distribution of ^{131}I-MIBG in various organs using the following scale: grade 0 (no visible uptake), grade 1 (uptake just visible), grade 2 (uptake clearly visible), grade 3 (prominent uptake) and grade 4 (uptake yielding maximal film density). In neuroblastoma, Baulieu and associates [2] proposed a method using scores between 0 and 3 (0: absence of visible lesion; 1: visualisation of lesions only on digitally processed images; 2: hot spots visible on whole body scans and analogic images; 3: prominent hot spots). The scoring system proposed by Philip and colleagues [9] not only considered

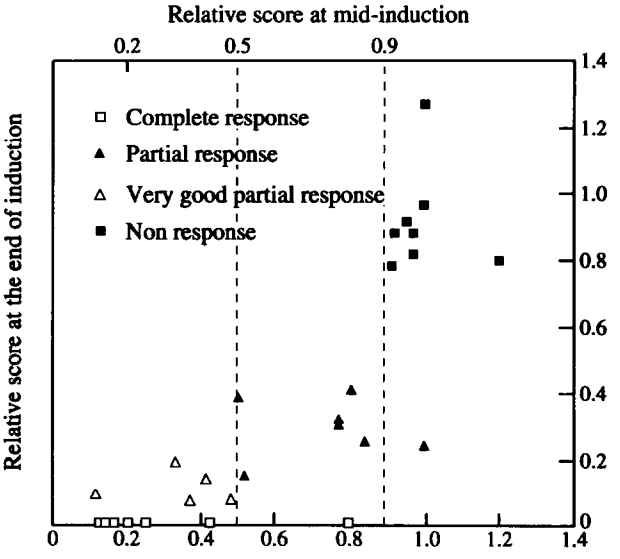

Figure 4.

MIBG scans but several modalities of disease exploration: patients were divided into complete responders (hot spots no longer visible), partial responders (regression ≥50%), non-responders (regression <50%) and in progressive disease (new lesions, extension of existing lesions). However, without quantification, the partial responders are often barely separable from the non-responders, and the decision is more subjective. As far as we know, none of these systems are currently used in multicentric clinical trials.

Our method is more precise and more sensitive (range of absolute scores 0–27), allows appreciation of subtle evolution and is less subjective than methods based on image intensity. For different reasons (limited number of patients, inter-investigator variation, need for significance of statistical analysis), we did not directly compare individual scores, but rather four categories of scores. To quantify the final response (12 weeks), relative scores were used when relevant, because they best describe the evolution. As commonly admitted in oncology, PR presents a tumour reduction ≥50% and NR a tumour reduction <50%, an absence of modification or a progressive disease. However, CR is an *absolute* criterion defined by the absence of lesion. It could also be described by the relative score 0, but only if the initial score is ≠ 0. These definitions of CR, PR and NR were acknowledged before the beginning of the study. VGPR represents a new class added during the study, to take into account the patients with almost but not completely normalised scores, since we observed that they were not strict CRs. Separation of this group from PRs was not obvious: we decided to restrict the VGPR class to patients with 1 or 2 doubtful (low intensity) images, rather than to patients with a given relative score, this latter expression being poorly sensitive when the initial score was low and when the response was almost complete. At 6 weeks, treatment was in progress, and instead of referring to CR (score 0 was never observed at this time), VGPR, PR or NR, we considered four groups with different relative score ranges. Obviously, the limits of the classes could not be predefined, but resulted from the comparison of the mid-course scores with the final response to obtain the optimal criteria.

The second conclusion is clinical. According to the quantitative analysis between the relative scores at 6 and 12 weeks, results

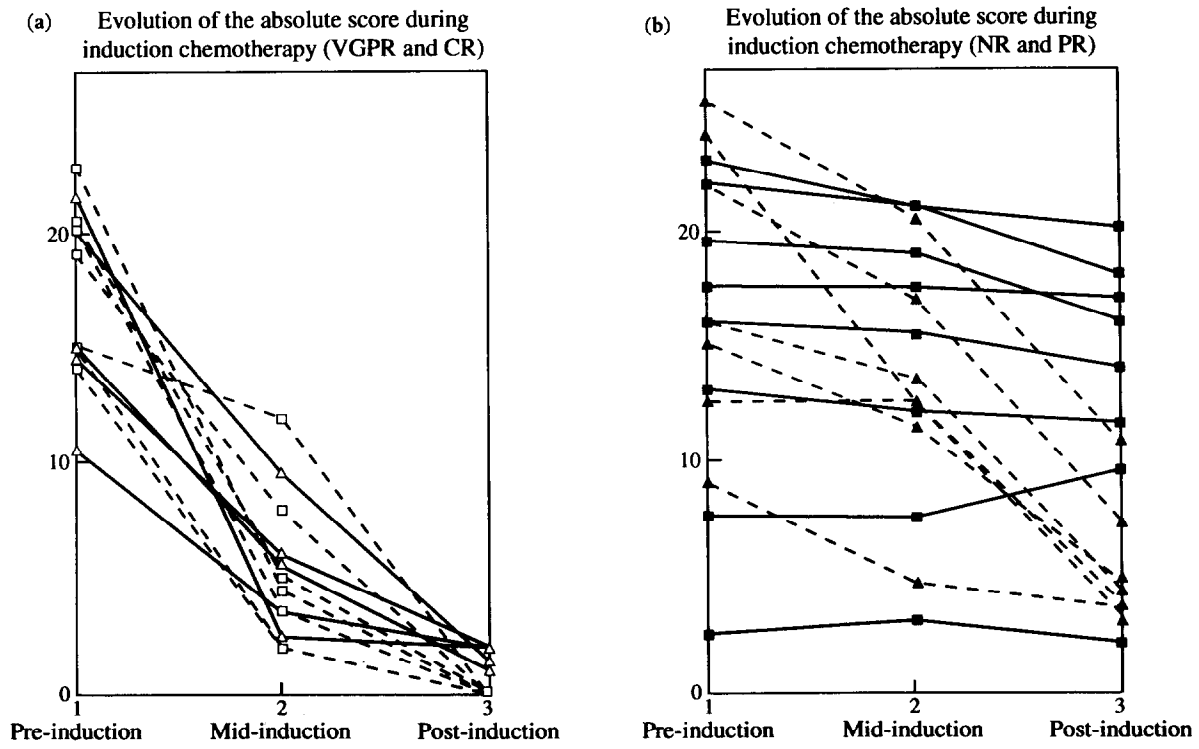

Figure 5. Evolution of the absolute score during induction chemotherapy. Same symbols as in Figure 4. CR and VGPR: (a); PR and NR: (b). CR and PR: broken lines; VGPR and NR: solid lines. In almost all cases, a good response (CR or VGPR) corresponded to an early response.

Table 3. Correlation between MIBG relative score at 6 weeks and the overall metastases response at 12 weeks

Relative score at 6 weeks	Overall response of metastases CR	PR	NR	*n*
≤0.20	4	1	0	5
>0.20–≤0.50	2	5	0	7
>0.50–≤0.90	0	6	0	6
>0.90	0	1	8	9
n	6	13	8	27

$P < 0.0001$.

CR, complete disappearance of all symptoms or signs of disease, no tumour detected; PR, regression of metastatic tumour mass larger than 50%; NR, no change or regression of the tumour mass lower than 50%.

Table 4. Correlation between MIBG relative score and bone marrow (BM) status at 6 weeks

Relative score at 6 weeks	BM+	BM−
≤0.20	0	5
>0.20–≤0.50	2	5
>0.50–≤0.90	2	4
>0.90	8	1
n	12	15

$P < 0.05$

Bone marrow involvement was considered as positive if at least one method (cytology, classical histology or immunocytology) was positive.

at mid-course seem to have real predictive value for the final response to induction chemotherapy: 11/12 patients with a score reduction ≥0.50 at 6 weeks ultimately had CRs or VGPRs. Conversely, 14/15 patients with lower score reduction at mid-course did not reach CR nor VGPR status. This test could be of use in selecting patients who benefit from a change in the chemotherapy schedule as early as mid-induction.

We also found a strong correlation between the MIBG scores at 6 weeks and the overall metastatic response. According to a study of the LMCE (multicentric French) group of 62 patients [10], the patient class in which all metastases had disappeared after induction had a better prognosis. A negative MIBG bone scan after induction (31 patients) strongly predicted survival (30% at 5 years versus 12% in the 31 bone positive patients) [10]. This finding stresses the fact that the patient subgroup with a negative MIBG scan (excluding the primary tumour) after induction chemotherapy has a better long-term progression-free survival. This conclusion is, however, controversial and not admitted by all investigators. Unfortunately, the relatively short follow-up did not allow us to correlate the MIBG scores with patients' survival. The relationship between bone marrow status and MIBG score at mid-induction was statistically significant. However, bone marrow status was a crude indicator, and only indicated that positive patients at mid-induction were probably not future complete responders. All 5 patients with a relative score ≤0.20 at mid-course had negative bone marrow at this time.

In conclusion, the scoring system we propose appears to be reliable and reproducible. However, it has to be tested in a larger series of neuroblastoma patients, particularly in multicentric trials. Early detection of non-responders to first line chemotherapy is important, and could lead to the early adoption of alternative strategies for these poor prognosis cases.

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

R. Handgretinger, K. Anderson, P. Lang, R. Dopfer, T. Klingebiel, M. Schrappe, P. Reuland, S. D. Gillies, R. A. Reisfeld and D. Niethammer

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