

Correlation of Early Metastatic Response by ¹²³I-Metaiodobenzylguanidine Scintigraphy With Overall Response and Event-Free Survival in Stage IV Neuroblastoma

By Katherine K. Matthay, Veronique Edeline, Jean Lumbroso, Marie Laure Tanguy, Bernard Asselain, Jean Michel Zucker, Dominique Valteau-Couanet, Olivier Hartmann, and Jean Michon

Purpose: Metaiodobenzylguanidine (MIBG), specifically taken up in cells of sympathetic origin, provides a highly sensitive and specific indicator for the detection of metastases in neuroblastoma. The aim of this study was to correlate early response to therapy by MIBG scan, using a semiquantitative scoring method, with the end induction response and event-free survival (EFS) rate in stage IV neuroblastoma.

Patients and Methods: Seventy-five children older than 1 year and with stage IV neuroblastoma had ¹²³I-MIBG scans at diagnosis, after two and four cycles of induction therapy, and before autologous stem-cell transplantation. The scans were read by two independent observers (concordance > 95%) using a semiquantitative method. Absolute and relative (score divided by initial score) MIBG scores were then correlated with overall pretransplantation response, bone marrow response, and EFS.

Results: The pretransplantation response rate was 81%, and the 3-year EFS rate was 32%, similar to a concomitant group of 375 stage IV patients. The median relative MIBG scores after two, four, and six cycles were 0.5, 0.24, and 0.12, respectively. The probability of having a complete response or very good partial response before transplantation was significantly higher if the relative score after two cycles was ≤ 0.5 , or, if after four cycles, the relative score was ≤ 0.24 . Patients with a relative score of ≤ 0.5 after two cycles or a score of ≤ 0.24 after four cycles had an improved EFS rate ($P = .053$ and $.045$, respectively).

Conclusion: Semiquantitative MIBG score early in therapy provides valuable prognostic information for overall response and EFS, which may be useful in tailoring treatment.

J Clin Oncol 21:2486-2491. © 2003 by American Society of Clinical Oncology.

NEUROBLASTOMA IS the most common extracranial childhood tumor, and it arises from the sympathetic nervous system. It is metastatic in more than 50% of patients at the time of diagnosis, with a 5-year survival rate of only 30% to 40%.^{1,2} Approximately 10% to 15% of patients have tumors resistant to induction therapy, and 40% of children who attain complete remission (CR) or partial remission will relapse even after myeloablative therapy and treatment of minimal residual disease with 13-*cis*-retinoic acid.² At this time, many of the patients who eventually progress despite intensive therapy cannot be clearly identified early, even with the myriad clinical or biologic prognostic markers that have been described.³⁻⁵ If it were possible to identify these resistant patients soon after diagnosis, new treatments could be tested that might produce better survival rates.

One approach is to look for a sensitive measure of early response to therapy that will predict later response and survival. The Children's Cancer Group tested early bone marrow response after one cycle of chemotherapy using a sensitive immunocytologic method and found no prognostic significance, although quantitative tumor content of both bone marrow and blood at diagnosis and after three to four cycles of therapy was prognostic.⁶ Because scintigraphy with radiolabeled metaiodobenzylguanidine (MIBG) has been shown to be a highly sensitive and specific method of detection of local and metastatic disease in neuroblastoma, MIBG might be another surrogate marker for later overall response. Approximately 90% of children with neuroblastoma have tumors that concentrate MIBG, and with this sensitive method, nearly 90% of children with stage IV disease can be shown to have osteomedullary metastases at diagnosis.⁷⁻¹¹

Previous studies have indicated that a positive MIBG scan obtained just before myeloablative therapy may be a prognostic marker for a high likelihood of relapse.^{12,13} Attempts to test the reliability and prognostic value of semiquantitative assessment of MIBG-scan response have shown that this scoring system has good interobserver reliability, but there is varying correlation of the scan result at diagnosis or after two cycles of therapy with the disease response after four cycles.¹⁴⁻¹⁶ Thus far, no attempt has been made to correlate the early scan results with the response before transplantation or with overall event-free survival (EFS). The aims of the study reported in this article were to examine the correlations of early scintigraphic response by MIBG with overall response and bone marrow response at the end of

From the Department of Pediatrics, University of California San Francisco, San Francisco, CA; Departments of Pediatrics, Nuclear Medicine, and Statistics, Institute Curie, and Departments of Pediatrics and Nuclear Medicine, Institute Gustave Roussy, Paris, France.

Submitted September 25, 2002; accepted April 17, 2003.

Supported by the Bourse Henri Rothschild grant from the Institute Curie, Paris, France, as well as by donations from the Campini Foundation, the Conner Research Fund, the V Foundation, and the Kasle and Tkalcevik Neuroblastoma Research Fund, all in San Francisco, CA.

Address reprint requests to Katherine K. Matthay, MD, Department of Pediatrics, Box 0106, University of California School of Medicine, San Francisco, CA 94143-0106; email: matthayk@peds.ucsf.edu.

© 2003 by American Society of Clinical Oncology.

0732-183X/03/2113-2486/\$20.00

induction (before transplantation) and with EFS in children older than 1 year with stage IV neuroblastoma.

PATIENTS AND METHODS

Patients

Those eligible for this retrospective study comprised all children with newly diagnosed stage IV neuroblastoma who were older than 1 year of age and who were diagnosed and treated at the Institut Curie and the Institut Gustave Roussy (Paris, France) between June 1989 and June 2000. Parents or guardians gave informed consent for their children's treatment according to approved protocols that were either institutional or sponsored by the French Society of Pediatric Oncology, in accordance with French law. Each patient was required to have a positive MIBG scan with detectable osteomedullary metastases at diagnosis (MIBG1), have an MIBG scan available after two (MIBG2) and four (MIBG3) cycles of chemotherapy, and have a scan at the end of standard chemotherapy (MIBG4; before transplantation) or time of progression. Data extracted from the medical record included the dates of diagnosis, transplantation, progression, and death; overall response before transplantation; bone marrow response after four cycles of therapy and before transplantation; *MYCN* gene copy number; lactate dehydrogenase level; and chromosome 1p status. Disease evaluation at diagnosis, mid-induction, and end induction included four to eight bone marrow aspirates, two to four bone marrow biopsies, bone marrow immunocytology, a ¹²³I-MIBG scan, a computed tomography scan (or a magnetic resonance imaging scan), and urine catecholamines.

Therapy

Patients received chemotherapy, according to the French Society of Pediatric Oncology protocols, with cyclophosphamide, doxorubicin, vincristine, cisplatin, carboplatin, and etoposide on protocol NB87 (N = 52),¹⁷ NB92 (N = 15) (which made a slight variation on the sequence of NB87), or NB97 (N = 8) (which was similar to the Memorial Sloan-Kettering Cancer Center N6 regimen).¹⁸ Responding patients then were treated with either myeloablative doses of vincristine, melphalan, and total-body irradiation (n = 20) or with busulfan and melphalan (n = 42).^{3,19} All patients were treated with intent-to-deliver myeloablative therapy. The first cohort of patients on NB87 (n = 29) received only four cycles of induction if they attained CR, whereas those who attained partial remission received an additional two cycles of carboplatin and etoposide before myeloablative therapy. The remaining patients received the two additional cycles of chemotherapy before myeloablative treatment. All therapy given before myeloablation is labeled induction therapy in this report.

Semiquantitative Scoring of ¹²³I-MIBG Scans

The group of MIBG scans from each patient were read in a blinded fashion by one of two experienced nuclear medicine physicians (V.E. or J.L.), including the scan at diagnosis, the scan after two cycles of induction chemotherapy, the scan after four cycles of therapy (if different from pretransplantation scan), and the scan at the end of induction (or before transplantation). The scoring of the scans was performed as previously described, with a minor modification to include soft-tissue metastases.¹⁵ In brief, the body was divided into nine anatomic sectors for osteomedullary lesions (skull, upper arms, lower arms, chest, upper spine, lower spine, pelvis, upper legs, and lower legs), with a tenth general sector allocated for any extrasosseous metastases. In each region, the lesions were scored as follows for extension of metastases: The segmental score was graded as 0, no site per segment; 1, one site per segment; 2, more than one site per segment; and 3, massive involvement (> 50% of the segment). The absolute score was obtained by adding the scores of all the segments. The relative score was calculated by dividing the absolute score at each time by the corresponding pretreatment overall score. The primary tumor was not included in the score but was recorded. A concordance study was performed between the two readers (V.E. and J.L.), who were blinded to patient response and EFS, on the

Table 1. Patient Characteristics

Characteristic	No. of Patients (n = 75)	%
Age, years		
Median		2.9
Range		1.15-12.8
Follow-up, months		
Median		61
Range		7-121
<i>MYCN</i> gene amplification, n = 69	25	36
1p deletion, n = 49	19	38.8
LDH > 1,500 U/L, n = 69	26	37.7
Bone marrow positive at diagnosis, n = 75	66	88
3-year EFS	—	32.5
3-year survival	—	47.6
Response pretransplantation*		
CR/VGPR	19/10	38.6
PR	32	42.7
SD	10	13.3
PD	4	5.3
Patients undergoing BMT	62	—

Abbreviations: LDH, lactate dehydrogenase; EFS, event-free survival; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; BMT, bone marrow transplantation.

*International Neuroblastoma Response Criteria.

first 15 patients and showed a concordance of 97% to 99% for absolute score for all four time points (60 scans).

Statistical Analysis

For statistical comparisons, continuous relative and absolute scores were transformed into categorical variables according to their median values. Correlation of scores with disease response and bone marrow response were tested with the χ^2 test using the median score at a given time point. Survival and EFS curves were estimated by the Kaplan-Meier method and compared by the log-rank test.²⁰ Correlations of MIBG response with *MYCN* gene amplification, chromosome 1p deletion, and serum lactate dehydrogenase were based on the χ^2 test.

RESULTS

A total of 375 patients with stage IV neuroblastoma who were older than 1 year, including 329 patients with bone metastases, were diagnosed in this time period; 75 met scan eligibility for this study. The 3-year EFS rate of the study group was 32.5%, compared with 33% for all 375 stage IV patients over 1 year of age treated at the two institutions during this time period. The patient characteristics are listed in Table 1,²¹ which demonstrates that this group of study patients has the usual clinical and biologic characteristics typical of stage IV high-risk neuroblastoma patients. Sixty-two of the 75 patients underwent myeloablative therapy and autologous hematopoietic stem-cell transplantation; the 13 patients who did not were patients with no response to induction chemotherapy or with early progression and death. To determine whether changes in outcome over the 13-year study period might confound the analyses of EFS, we compared the outcome for the group of 36 patients in our study who were treated from 1987 to 1994 with the 39 patients who were treated from 1995 to 2000. The earlier group had a 3-year

Table 2. MIBG Scan Scores for All 75 Patients

Global MIBG Score	Median	Range
Absolute score		
MIBG1, at diagnosis	18	1-28
MIBG2, after two cycles	8	0-27
MIBG3, after four cycles	3	0-27
MIBG4, pretransplantation	2	0-27
Relative score		
MIBG2	0.5	0-1.73
MIBG3	0.24	0-1.82
MIBG4	0.12	0-1.2

Abbreviation: MIBG, metaiodobenzylguanidine.

EFS rate of 30.6% (95% confidence interval, 15.5% to 45.6%) compared with 36.4% (95% confidence interval, 20.2% to 52.5%) for the later group, with no significant difference in outcome ($P > .94$).

The median time from the initial MIBG scan (MIBG1) to the second MIBG scan (MIBG2) was 45 days, with 92% of patients between 1 and 2 months. Sixty-one of the patients had MIBG2 after two cycles of induction chemotherapy, and 14 patients had MIBG2 after three cycles of therapy. Time from diagnosis to the third MIBG scan (MIBG3), performed after the fourth cycle of induction chemotherapy, was 94 days, with 88% performed between 3 and 4 months. Sixty-one patients had their MIBG3 after four cycles of induction therapy, 10 had MIBG3 after five cycles of therapy, one had MIBG3 after six to seven cycles of therapy, and three patients did not have the third scan (one patient because of progression and two patients because of missing scans). The median time to the pretransplantation or to the end-of-induction-therapy MIBG scan (MIBG4) was 170 days (range, 83 to 301 days). Five patients who were in CR at the time of MIBG3 proceeded to myeloablative therapy after only four cycles of induction, and therefore, the pretransplantation scan (MIBG4) was identical to MIBG3. There was no significant difference in the median time to the end-induction scan (MIBG4) for patients with extension scores of 0 to 2 (median, 175 days) compared with patients with scores of ≥ 3 (median, 165 days).

Table 2 lists the median and range for the MIBG scores. As expected, there was a successive decrease in the median absolute and relative scores after two and four cycles of chemotherapy and at the end of induction. The relation of relative and absolute score to response is shown in Table 3. The frequency of achieving CR or very good partial response (VGPR) at the end of induction is significantly higher if the absolute MIBG2 score is ≤ 8 or the relative MIBG2 score is less than 0.5 ($P < .0001$); whereas the likelihood of achieving CR/VGPR at the end of induction significantly correlates with an absolute score at MIBG3 of ≤ 3 or a relative score of ≤ 0.24 ($P < .0001$). However, the absolute score at diagnosis did not correlate with the likelihood of response. Of patients with a relative score after two cycles of ≤ 0.5 , 66.7% achieved CR/VGPR, compared with 12.8% of patients if the relative score was more than 0.5 ($P < .001$); of patients with a relative score of ≤ 0.24 at MIBG3, 72% achieved CR/VGPR, compared with 5.6% of patients with relative score of more than 0.24 ($P < .0001$).

Table 3. MIBG Score and Overall Disease Response Before Transplantation

MIBG Score	Overall Disease Response Before Transplantation (no.)				
	CR	VGPR	PR	SD	PD
Absolute score					
MIBG1*					
≤ 18	12	6	14	5	2
> 18	7	4	18	5	2
MIBG2†					
≤ 8	17	8	10	1	2
> 8	2	2	22	9	2
MIBG3‡					
≤ 3	17	8	12	1	1
> 3	1	2	19	9	2
Relative score					
MIBG2†					
≤ 0.5	18	6	12	0	0
> 0.5	1	4	20	10	4
MIBG3‡					
≤ 0.24	18	8	10	0	0
> 0.24	0	2	21	10	3

NOTE. Disease response according to the International Neuroblastoma Response Criteria.

Abbreviations: MIBG, metaiodobenzylguanidine; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

*Not significant ($P > .35$).

†Frequency of CR/VGPR is significantly higher if the MIBG2 relative score is ≤ 0.5 or the absolute score is ≤ 8 ($P < .0001$).

‡Frequency of CR/VGPR is significantly higher if the relative MIBG3 score is ≤ 0.24 or the absolute score is ≤ 3 ($P < .0001$). Three patients do not have data for MIBG3 because of progressive disease ($n = 1$) and missing scans ($n = 2$).

MIBG score was also predictive of bone marrow response at the end of induction therapy (before transplantation). Table 4 shows the close correlation of both the relative MIBG score after two and four cycles of chemotherapy with bone marrow status before transplantation. Only one of 24 patients with an MIBG2 relative score of ≤ 0.5 had persistent tumor in the bone marrow at the end of induction, whereas 13 of 33 patients with a score greater than 0.5 had a positive bone marrow at the end of

Table 4. Relative MIBG Score and Bone Marrow Status Before Transplantation

Relative Score	Bone Marrow	
	Negative (no.)	Positive (no.)
MIBG2*		
≤ 0.5	23	1
> 0.5	20	13
MIBG3†		
≤ 0.24	23	2
> 0.24	19	11

Abbreviation: MIBG, metaiodobenzylguanidine.

*Likelihood of positive bone marrow is significantly higher if the relative MIBG2 score is > 0.5 ($P < .0025$).

†Likelihood of positive bone marrow before transplantation is significantly higher if the relative MIBG3 score is > 0.24 ($P < .015$).

Table 5. MIBG Scan Score and EFS

	Extension Score		5-Year EFS (%)			P
	A	v	A	v	B	
Absolute score						
MIBG1	≤ 18	> 18	33	14	.89	
MIBG2	≤ 8	> 8	33	17	.17	
MIBG3	≤ 3	> 3	39	11	.02	
MIBG4	≤ 2	> 2	36	16	.07	
Relative score						
MIBG2	≤ 0.5	> 0.5	37	15	.053	
MIBG3	≤ 0.24	> 0.24	36	16	.045	
MIBG4	≤ 0.12	> 0.12	32	22	.3	

Abbreviations: MIBG, metaiodobenzylguanidine; EFS, event-free survival.

induction ($P < .0025$). After four cycles of chemotherapy, only two of 35 patients with an MIBG3 relative score of ≤ 0.24 had a positive bone marrow before transplantation, whereas 11 of 30 patients whose relative score was greater than 0.24 had positive bone marrow ($P < .015$).

The relationship of both absolute and relative MIBG scan score and EFS is summarized in Table 5. The absolute score at diagnosis (MIBG1) and after two cycles of therapy (MIBG2) did not significantly correlate with EFS. However, patients with an absolute MIBG3 score of ≤ 3 had a 5-year EFS rate of 39% compared with 10.9% for patients with a score greater than 3 after four cycles of therapy ($P < .02$), and there was a trend for correlation of absolute score before transplantation (MIBG4) with EFS ($P = .07$, Fig 1). The early relative scores were more significantly related to EFS, with an improvement in EFS when the relative score was ≤ 0.5 after two cycles of chemotherapy ($P = .053$) or ≤ 0.24 after four cycles ($P = .045$, Fig 2A and 2B). However, the relative score before transplantation (≤ 0.12) was not significant, indicating that the rate of response is a more important prognostic factor early in therapy than later.

Next, various biologic factors were examined with regard to MIBG score. The percentage of patients with *MYCN*-amplified tumors was not significantly different, regardless of the relative

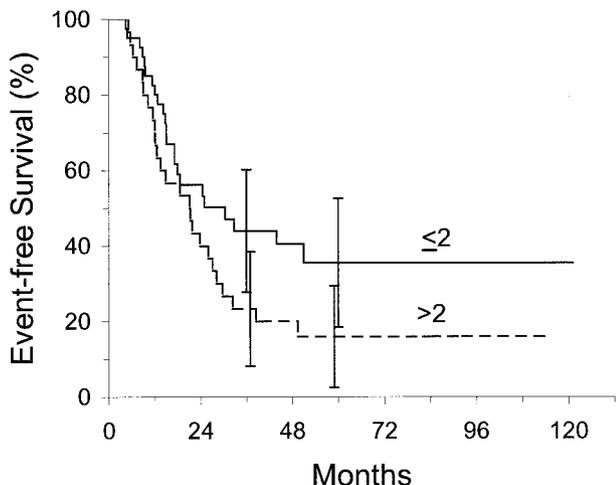


Fig 1. Event-free survival (EFS) according to absolute metaiodobenzylguanidine score before transplantation (≤ 2 v > 2 , $P = .07$).

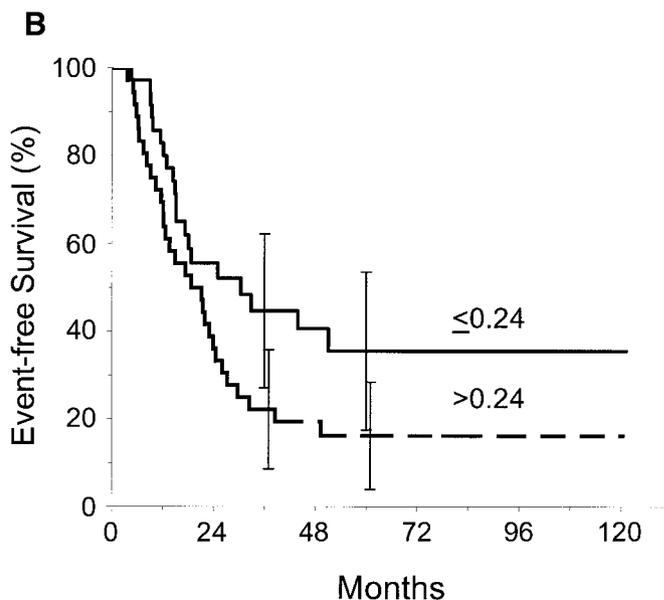
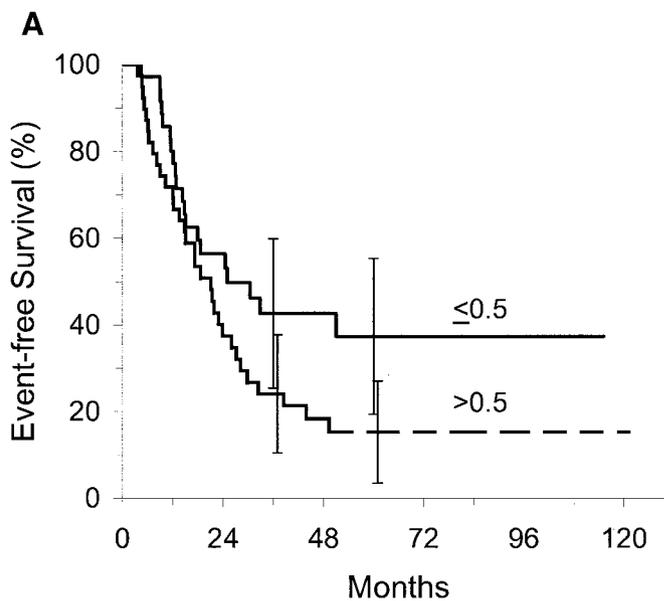


Fig 2. (A) Event-free survival (EFS) according to relative metaiodobenzylguanidine score after 2 cycles of induction chemotherapy (≤ 0.5 v > 0.5 , $P = .053$). (B) EFS according to relative score after 4 cycles of induction chemotherapy (≤ 0.24 v > 0.24 , $P = .045$).

MIBG score after two or four cycles of chemotherapy. However, in both cases, the percentage of patients with amplified tumors was greater in the more rapidly responding patients by MIBG. The percentage of patients with *MYCN* amplification was 44.1% in the group with relative scores after two cycles of ≤ 0.5 , compared with 28.6% for patients with relative scores greater than 0.5 ($P > .17$). Similarly, for the MIBG score after four cycles, the percentage of *MYCN*-amplified tumors was 44.1% in the group with scores ≤ 0.24 and 25% in the group with scores greater than 0.24 ($P > .1$). The percentage of patients with 1P deletion was significantly higher in the group with low relative scores (≤ 0.5) after two cycles of induction chemotherapy,

compared with the group with higher relative scores (62.5% v 16%, respectively; $P = .0008$). However, this result must be interpreted with caution because of missing IP data in 35% of patients. There was no correlation of lactate dehydrogenase with relative MIBG score after either two or four cycles of induction therapy.

DISCUSSION

The results of this study confirm that the semiquantitative MIBG scoring method is a reproducible result among trained nuclear medicine physicians and that early response according to the relative reduction in MIBG-positive metastatic lesions using this method is predictive of both overall response and bone marrow response at the end of induction chemotherapy, as well as of EFS. The use of such a scoring method will select the patients who might be moved to other novel therapeutic approaches because of an anticipated poor response to conventional induction therapy and a subsequent low expectation of EFS. In addition, this method may be used as a more quantitative evaluation of response in patients who are being entered into experimental therapeutic regimens but have no measurable disease by traditional Response Evaluation Criteria In Solid Tumors (RECIST) criteria,²² a common occurrence in high-risk neuroblastoma, which has a high probability of relapse in bone and bone marrow.²³

The scoring method used in this study was originally developed at the Institute Curie. As in the initial study by Ady et al,¹⁵ the interobserver concordance ratio was extremely good in the current study, although two different nuclear medicine physicians from two institutions read these scans independently, with a concordance ratio of greater than 0.97 for all time points for the global score. This study also validates and extends the close correlation between early response by MIBG score and overall response to induction therapy. Although Ady et al previously reported the correlation of response by MIBG at two cycles with overall response after four cycles, we have extended the study to show the correlation with both overall response and bone marrow response after all pretransplantation therapy, before final myeloablative conditioning, as well as with ultimate EFS.

Variations of this scoring method have been tested by other groups with varying prognostic significance.^{14,16} The scoring system tested by Suc et al¹⁴ differed from the scoring system in this article because it did not differentiate between a single focus of uptake, multiple foci, or diffuse uptake but, instead, simply scored the segments of the body as positive or negative. Their study of 86 patients at diagnosis with metastases by MIBG showed a significantly higher percentage of patients in CR at the end of induction if their initial MIBG score was less than 4 compared with the group with a score of ≥ 4 . A subsequent multi-institutional study by Frappaz et al¹⁶ examined 47 children with uniform induction and consecutive scans, using a further variation on the methods of Ady and Suc that examined intensity and extent (diffuse or focal) of uptake separately. This study

showed a good concordance (> 0.8) among six independent observers for the global intensity score, although correlation by each site was lower for the spine and ribs areas. However, these investigators did not find a significant correlation of relative score with overall response after four cycles of induction therapy, and they found that a high initial score correlated with poor response to chemotherapy but was not a sensitive predictive measure.

The early response by MIBG scan seems to be a more reliable and earlier prognostic factor than absolute or relative MIBG score before transplantation. The relative score after two cycles of therapy apparently has slightly greater reliability than the absolute score for prediction of EFS, although both measures significantly predict response at the end of induction. It is possible that the philosophy of this induction, in which the number of cycles of intensification was varied according to response, accounted for the lesser correlation of the absolute score before transplantation with EFS. Because some of the more resistant patients received more therapy to try to control metastatic disease, the absolute scores before transplantation do not reflect these biologic differences as closely as the early response data. However, there was no significant difference in the time to transplantation in the groups with higher or lower absolute scores. In a retrospective study, there is always the possibility that variations in therapy may have affected the response and EFS analyses. However, the variations were minor because all patients received the same chemotherapy agents for induction therapy and melphalan-based myeloablative regimens. Furthermore, the lack of difference in EFS of the two cohorts treated before and after 1994 indicates that changes in therapy over time did not affect the results of this study.

The identification early in induction of patients with poor metastatic response may allow novel therapy for this group. It has been previously shown that therapy for minimal residual disease for patients completing myeloablative therapy is much more effective if there is no measurable residual disease. Thus, treatment with 13-*cis*-retinoic acid has been shown to improve EFS after myeloablative therapy and to be most effective for patients in CR at the time of treatment.² One obvious possibility is to target the MIBG-positive lesions using therapeutic doses of ¹³¹I-MIBG before the myeloablative chemotherapy.^{24,25} Other approaches might include the earlier use of agents with a novel mechanism of action to target the cells resistant to the induction chemotherapy, such as immunotherapeutic or differentiating agents.

In conclusion, evaluation of early response by MIBG correlates with later response to induction therapy, bone marrow response, and EFS. The use of relative score after two or four cycles of induction therapy seems to be a more reliable predictor of EFS than the absolute score before transplantation. Identification of poor responders after two cycles of induction therapy will allow the routing of these patients into novel approaches.

REFERENCES

1. Philip T, Ladenstein R, Lasset C, et al: 1070 myeloablative megatherapy procedures followed by stem cell rescue for neuroblastoma: 17 years of European experience and conclusions. European Group for Blood and Marrow Transplant Registry Solid Tumour Working Party. *Eur J Cancer* 33:2130-2135, 1997

2. Matthay KK, Villablanca JG, Seeger RC, et al: Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *N Engl J Med* 341:1165-1173, 1999
3. Hartmann O, Valteau-Couanet D, Vassal G, et al: Prognostic factors in metastatic neuroblastoma in patients over 1 year of age treated with high-dose chemotherapy and stem cell transplantation: A multivariate analysis in 218 patients treated in a single institution. *Bone Marrow Transplant* 23:789-795, 1999
4. Maris JM, Matthay KK: Molecular biology of neuroblastoma. *J Clin Oncol* 17:2264-2279, 1999
5. Bown N, Cotterill S, Lastowska M, et al: Gain of chromosome arm 17q and adverse outcome in patients with neuroblastoma. *N Engl J Med* 340:1954-1961, 1999
6. Seeger RC, Reynolds CP, Gallego R, et al: Quantitative tumor cell content of bone marrow and blood as a predictor of outcome in stage IV neuroblastoma: A Children's Cancer Group Study. *J Clin Oncol* 18:4067-4076, 2000
7. Lumbroso JD, Guermazi F, Hartmann O, et al: Meta-iodobenzylguanidine (mIBG) scans in neuroblastoma: sensitivity and specificity, a review of 115 scans. *Prog Clin Biol Res* 271:689-705, 1988
8. Claudiani F, Stimamiglio P, Bertolazzi L, et al: Radioiodinated meta-iodobenzylguanidine in the diagnosis of childhood neuroblastoma. *Q J Nucl Med* 39:21-24, 1995
9. Hadley GP, Rabe E: Scanning with iodine-131 MIBG in children with solid tumors: An initial appraisal. *J Nucl Med* 27:620-626, 1986
10. Lastoria S, Maurea S, Caraco C, et al: Iodine-131 metaiodobenzylguanidine scintigraphy for localization of lesions in children with neuroblastoma: Comparison with computed tomography and ultrasonography. *Eur J Nucl Med* 20:1161-1167, 1993
11. Gordon I, Peters AM, Gutman A, et al: Skeletal assessment in neuroblastoma: The pitfalls of iodine-123-MIBG scans. *J Nucl Med* 31:129-134, 1990
12. Ladenstein R, Philip T, Lasset C, et al: Multivariate analysis of risk factors in stage 4 neuroblastoma patients over the age of one year treated with megatherapy and stem-cell transplantation: A report from the European Bone Marrow Transplantation Solid Tumor Registry. *J Clin Oncol* 16:953-965, 1998
13. Perel Y, Conway J, Kletzel M, et al: Clinical impact and prognostic value of metaiodobenzylguanidine imaging in children with metastatic neuroblastoma. *J Pediatr Hematol Oncol* 21:13-18, 1999
14. Suc A, Lumbroso J, Rubie H, et al: Metastatic neuroblastoma in children older than one year: Prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. *Cancer* 77:805-811, 1996
15. Ady N, Zucker JM, Asselain B, et al: A new 123I-MIBG whole body scan scoring method-application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. *Eur J Cancer* 31A:256-261, 1995
16. Frappaz D, Bonneu A, Chauvot P, et al: Metaiodobenzylguanidine assessment of metastatic neuroblastoma: Observer dependency and chemosensitivity evaluation. The SFOP Group. *Med Pediatr Oncol* 34:237-241, 2000
17. Coze C, Hartmann O, Michon J, et al: NB87 induction protocol for stage 4 neuroblastoma in children over 1 year of age: A report from the French Society of Pediatric Oncology. *J Clin Oncol* 15:3433-3440, 1997
18. Kushner BH, LaQuaglia MP, Bonilla MA, et al: Highly effective induction therapy for stage 4 neuroblastoma in children over 1 year of age. *J Clin Oncol* 12:2607-2613, 1994
19. Frappaz D, Michon J, Coze C, et al: LMCE3 treatment strategy: Results in 99 consecutively diagnosed stage 4 neuroblastomas in children older than 1 year at diagnosis. *J Clin Oncol* 18:468-476, 2000
20. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
21. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 11:1466-1477, 1993
22. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 92:205-216, 2000
23. DuBois SG, Kalika Y, Lukens JN, et al: Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. *J Pediatr Hematol Oncol* 21:181-189, 1999
24. Yanik GA, Levine JE, Matthay KK, et al: Pilot study of iodine-131-metaiodobenzylguanidine in combination with myeloablative chemotherapy and autologous stem-cell support for the treatment of neuroblastoma. *J Clin Oncol* 20:2142-2149, 2002
25. Klingebiel T, Bader P, Bares R, et al: Treatment of neuroblastoma stage 4 with 131I-meta-iodo-benzylguanidine, high-dose chemotherapy and immunotherapy: A pilot study. *Eur J Cancer* 34:1398-1402, 1998