

- In vitro* establishment and characterization of a human megakaryoblastic cell line. *Blood* 1990, 75, 1252–1261.
10. Wieland DM, Wu J, Brown LE, Magner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 1980, 21, 349–353.
 11. Mertens JJR, Vanryckeghem W, Carlsen L. Cu(I) supported isotopic exchange of acetylbound iodide, new future for fast high yield labeling. In Cox P, ed. *Progress in Radiopharmacy, Proceedings of the Second European Symposium on Radiopharmacy and Radiopharmaceuticals*. The Hague, Martinus Nijhoff, 1986, 101.
 12. Rudnick G, Humphreys CJ. Platelet serotonin transporter. *Meth Enzym* 1992, 215, 213–224.
 13. Glowinski JV, Kilty JE, Amara SG, *et al.* Evaluation of metaiodobenzylguanidine uptake by the norepinephrine, dopamine and serotonin transporters. *J Nucl Med* 1993, 34, 1140–1146.
 14. Vannucchi AM, Grossi A, Paoletti F, Rafanelli D, Bacci P, Ferrini PR. Constitutive expression of a megakaryocytic functional property by murine erythroleukemia (Friend) cells: the incorporation of serotonin. *Exp Hemat* 1992, 20, 1296–1301.
 15. Smets I, Loesberg C, Janssen M, Van Rooy H. Intracellular inhibition of mono(ADP-ribosylation) by meta-iodobenzylguanidine: specificity, intracellular concentration and effects on glucocorticoid mediated cell lysis. *Biochim Phys Acta* 1990, 1054, 49.
 16. Ramamoorthy S, Bauman AL, Moore KR, *et al.* Antidepressant- and cocaine-sensitive human transporter: molecular cloning, expression, and chromosomal localization. *Proc Natl Acad Sci USA* 1993, 90, 2542–2546.

Acknowledgements—We thank Paul Jonkergouw (Department of Safety, Health and Welfare, Netherlands Cancer Institute) for preparing the [^{125}I]MIBG. We would like to thank Dr R. Wanders, Dr P. Bakker and Professor L. Smets for critically reading the manuscript, and J. Cornelissen and Dr B. Kipp for the stimulating discussions. This study was supported by grant No. 93-01 from the “Stichting Kindergeeneeskundig Kankeronderzoek” (Foundation for Paediatric Cancer Research) and by grant NKI-94-808 of the Dutch Cancer Society to M. Rutgers.



Pergamon

European Journal of Cancer Vol. 31A, No. 4, pp. 606–611, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0959-8049/95 \$9.50+0.00

0959-8049(95)00048-8

A New Approach in the Treatment of Stage IV Neuroblastoma Using a Combination of [^{131}I]Meta-iodobenzylguanidine (MIBG) and cisplatin

R. Mastrangelo, A. Tornesello, R. Riccardi, A. Lasorella, S. Mastrangelo, A. Mancini, V. Rufini and L. Troncone

The outlook for disseminated neuroblastoma (NB) continues to be dismal. NB is a radiosensitive tumour. Owing to its high concentration in NB lesions, [^{131}I]meta-iodobenzylguanidine [^{131}I]MIBG has the potential for specifically delivering very large radiation doses to the malignant cells. Encouraging results have been reported with [^{131}I]MIBG used alone in patients resistant to conventional therapy and at diagnosis. We report the first attempt to explore the integration of this new treatment modality with chemotherapy. Among the drugs effective in NB, cisplatin was chosen because of its high degree of activity against NB, its mild haematological toxicity and the known synergism between cisplatin and radiation. 4 patients, 3 with relapsed, heavily pre-treated, progressive stage IV NB, and 1 with stage IV NB at diagnosis, all with a good [^{131}I]MIBG uptake, were investigated with combined therapy (CO-TH). Two complete remissions and one partial remission were observed in these patients 4–6 weeks following only a single course of both cisplatin and [^{131}I]MIBG at “standard” dosage. The only toxicity was haematological, which was significant and relatively long-lasting, but was not associated with any serious infections or bleeding tendency. The general condition of these patients during the entire study period was excellent. The fourth patient, investigated at diagnosis with a modified less intensive treatment, obtained a partial remission with mild haematological toxicity. During the subsequent courses of intensive multidrug chemotherapy, this patient showed haematological toxicity comparable with that experienced by patients treated with an identical drug combination, but without previous treatment with CO-TH. The provisional conclusion of this ongoing study is that this new form of CO-TH appears most effective in obtaining a rapid and excellent response in heavily pretreated relapsed patients with progressive disease, and should be further investigated in earlier stages of the disease.

Key words: neuroblastoma, cisplatin, [^{131}I]meta-iodobenzylguanidine, synergism
Eur J Cancer, Vol. 31A, No. 4, pp. 606–611, 1995

INTRODUCTION

DESPITE INTENSIVE chemotherapy regimens, prognosis continues to be very poor in disseminated neuroblastoma (NB) [1]. Owing to NB sensitivity [2], progress might be made with high-dose radiation. However, delivery of a high radiation dose is limited by host tolerance. Attention has recently focused on the use of [^{131}I]meta-iodobenzylguanidine ([^{131}I]MIBG), a radioactive drug extremely useful for diagnosis and follow-up of NB, and capable of selectively delivering a high dosage of radiation to the NB cells. Encouraging results have been reported in patients resistant to conventional therapy [3, 4], and good results have also been observed with the use of [^{131}I]MIBG at diagnosis, although in a small number of patients [5–8]. In both these circumstances, the radiopharmaceutical was administered alone, and the only significant toxicity was myelosuppression, which was more serious in intensively pretreated patients. In an attempt to improve the long-term results in stage IV NB, integration of this new treatment modality with conventional chemotherapy would not only appear justified, but also highly desirable.

We report the first attempt to explore this new therapeutic approach in which [^{131}I]MIBG treatment has been combined with cisplatin. Among the drugs effective in NB, cisplatin was chosen because of its high degree of activity against NB associated with a mild haematological toxicity; above all, pre-clinical trials in cultured cells and animal tumours have established a synergism between cisplatin and radiation [9, 10] when the agents are given closely following one another. The mechanism of this synergism remains uncertain, but one component of cisplatin's radiopotential appears to be the inhibition of repair of potentially lethal radiation damage [11]. So far, most of the experimental studies have been carried out by using single doses of both cisplatin and radiation. Whereas conventional radiotherapy is delivered over a period of several weeks in multiple treatment fractions, the mode of administration of [^{131}I]MIBG, injected in a single dose, closely resembles the animal models. Therefore, one of the aims of the combined therapy (CO-TH) would be to potentiate NB cell kill without increasing toxicity, thereby improving the therapeutic ratio.

PATIENTS AND METHODS

4 stage IV NB patients were treated with CO-TH. Three patients had relapsed progressive disease after multi-agent chemotherapy which included cisplatin, and their characteristics and observed responses are shown in Table 1. A fourth patient, also with progressive disease, was investigated at diagnosis. All patients showed a good [^{131}I]MIBG uptake. Tumour extent was evaluated by computerised tomography (CT) scan, [^{131}I]MIBG scan, bone marrow (BM) aspirations from four different sites and biopsy from two sites; evaluation of bone disease was performed with both technetium-99 scans and with [^{131}I]MIBG scans. 24 h urine collections for catecholamines and catecholamine metabolites were also performed. The following treatment schedule was planned for the relapsed patients: day 1, cisplatin 50–60 mg/m² i.v. over 6 h; day 2, [^{131}I]MIBG 100–120 mCi at high specific activity (> 1.1 GBq/mg) i.v. over 6 h followed, a week later, by the same treatment combination. The patient

treated at diagnosis had a somewhat different schedule (see case 4). In all cases, [^{131}I]MIBG was given after preventing thyroid uptake by the administration of Lugol's solution. Because of the known dosimetric inaccuracies by [^{131}I]MIBG scintigraphy measurements, no attempt was made to estimate the absorbed radiation dose by the tumour lesions. Informed consent was obtained from parents. Re-evaluation of all measurable lesions and assays of the urinary catecholamine metabolites were performed 4–6 weeks after CO-TH. Toxicity evaluation included complete and differential blood counts, serum electrolytes, liver enzymes, audiogram and renal function tests.

Case 1

A 5-year-old boy was treated in fourth relapse with massive bone marrow (BM) infiltration. At diagnosis, in the neonatal period, the patient showed several enlarged right laterocervical lymph nodes. Partial resection of the mass was performed, but 2 years later a systemic relapse was observed, including bony lesions and enlarged abdominal lymph nodes. He was treated with a total of 6 courses of carboplatin (500 mg/m² × 2 days) and etoposide (100 mg/m² × 3 days) over an 8-month period, with partial remission. 1 year later, because of progressive disease, 4 D-CECaT regimen courses (desferal, cyclophosphamide, carboplatin, 500 mg/m² × 2 days, etoposide and thiothepa) were administered with a mild response. 6 months before admission, a full blown relapse was observed, which included massive BM involvement. Following an initial minimal response to 4 courses of melphalan, progressive disease was again observed and the child was referred to our Centre. On admission, he presented with generalised pain. Physical examination, CT scan and [^{131}I]MIBG scan demonstrated large abdominal and inguinal lymph nodes. A mediastinal mass was also present (Table 1). A [^{131}I]MIBG scan displayed diffuse and intense uptake of the cortical bones and BM. Massive BM involvement was present. Catecholamines, vanillylmandelic (VMA) and homovanillic acid (HVA) were within normal limits. The white blood cell count (WBC) and the absolute neutrophil count were within normal limits, whereas thrombocytopenia was present, with the platelets level at 68,000/mm³. 5 weeks after CO-TH, physical examination and CT scan showed disappearance of all soft tissue masses; 2 BM aspirations and a BM biopsy showed no evidence of BM infiltration. [^{131}I]MIBG scan showed no evidence of disease. Haematological toxicity was characterised by WHO grade 3 neutropenia lasting 2 weeks, thrombocytopenia WHO grade 3–4 for 3 weeks. 2 months later, 3 months from the beginning of CO-TH, a generalised relapse was observed.

Case 2

A 4-year-old boy with stage IV NB with a large right adrenal tumour and extensive BM and bony metastases at diagnosis, obtained complete remission following CAdO regimen (cyclophosphamide 1.5 g/m² divided over 5 days; vincristine 1.5 mg/m² days 1 and 5; adriamycin 60 mg/m² day 5) and complete removal of the primary tumour. Subsequently, several courses of etoposide associated with cisplatin were delivered, but a relapse was observed 15 months from diagnosis. On admission, the patient had fever, anorexia and bone pain mostly confined to the arms. Physical examination showed enlarged right axillary lymph nodes. During the following days, these lymph nodes rapidly increased in size. Haematological findings included: haemoglobin level (Hb) 10g/dl, WBC 4500/mm³ with neutrophils 50%, platelet count 195,000/mm³. Ultrasound examination and CT scan of the abdomen and thorax were

Correspondence to Dr R. Mastrangelo at the Divisione di Oncologia Pediatrica, Università Cattolica, L.go A. Gemelli, 8-00168 Rome, Italy. R. Mastrangelo, A. Tornesello, R. Riccardi, A. Lasorella and S. Mastrangelo are at the Divisione di Oncologia Pediatrica; V. Rufini and L. Troncone are at the Istituto di Medicina Nucleare, Università Cattolica, Rome; and A. Mancini is at Clinica Pediatrica III, Università degli Studi, Bologna, Italy.

Table 1. Data of NB relapsed patients before and after combined therapy

Patient	Sex/Age (years)	Disease extent			Total [^{131}I]MIBG activity (mCi)	Total cisplatin dosage (mg/m ²)	Response (after 4–6 weeks)	Evolution from start of combined therapy (months)
		Soft tissues	Bone marrow infiltration	Cortical bony lesions				
1	M/4	Right paravesical mass, several bilateral para-aortic and inguinal lymph nodes, mediastinal mass	Massive	Skull, rachis, pelvis, long bones	200	100	CR	Relapse (3)
2	M/4	Right axillary lymph nodes	None	Right humerus, metacarpal bones, femoral metaphyses	240	120	CR	Relapse (3.5)
3	M/9	Supraclavicular, retroperitoneal, parailiac, intercavo-aortic, paravesical and inguinal lymph nodes	Massive	Pelvis, rachis, long bones	220	100	PR	Stable disease (7)

CR, complete response; PR, partial response.

negative. [^{131}I]MIBG revealed the presence of very large, right axillary lymph nodes and extensive bony metastases (Table 1). Radiological skeletal survey and technetium-99 scans were confirmatory. BM aspirations and biopsies showed no malignant cells. Catecholamines and catecholamine metabolites were within normal limits. 2 weeks after starting CO-TH, the physical examination was negative; 4 weeks later, re-evaluation with [^{131}I]MIBG scan showed disappearance of all bony lesions. Haematological toxicity was characterised by WHO grade 3–4 neutropenia and thrombocytopenia lasting 2 and 3 weeks, respectively. 2 months later, 3½ months from the beginning of CO-TH, a generalised relapse was observed.

Case 3

This was a 9-year-old boy with stage IV NB and relapsed progressive disease. At diagnosis, when 2 years old, the patient showed a large right abdominal mass and patchy BM involvement. After chemotherapy regimens, which included pep-tichemio, vincristine, cyclophosphamide and cisplatin (total of 200 mg/m² i.v.) and the total removal of the primary tumour, a complete remission was obtained. Several courses of the same regimen were subsequently administered. 5 years later, because of a relapse at the abdominal primary site, the presence of large abdominal lymph nodes and BM infiltration, a De-CECaT regimen, which included carboplatin, was administered with a partial remission. Following second-look surgery, the patient was referred to our Centre because of the persistence of abdominal lymph nodes. [^{131}I]MIBG therapy was administered (190 mCi i.v. in 6 h infusion) with no apparent response; 5 months later the same lymph nodes increased in size and a partial regression was obtained following 4 courses of CAAdO. While waiting for haematologic toxicity recovery, a reduced dose of cisplatin alone (3 daily fractions, i.v. 20 mg/m²/day) was attempted with no further reduction of the abdominal masses. 2 months later, because of rapid progression of the disease, CO-TH was administered. Before treatment, CT and [^{131}I]MIBG scans revealed extensive disease (Table 1). Technetium-99 scans confirmed bone lesions. BM aspirate revealed massive BM infiltration. Haematological findings included Hb 10.2 g/dl,

WBC 6600/mm³, absolute neutrophil count 4200/mm³, platelet count 95 000/mm³. Catecholamine levels were: 86 µg/day; VMA was 60.6 mg/day and HVA 47.7 mg/day. 6 weeks after the beginning of CO-TH, CT scan revealed reduction (> 50%) of abdominal and supraclavicular lymph nodes; [^{131}I]MIBG scan showed a marked reduction in uptake, at the level of the rachis, and of the bony metastases. BM aspirations and biopsy revealed patchy infiltration. Catecholamines were 44 µg/day, VMA was 32.6 and HVA 29.5 mg/day. No progression of the disease has been observed during the subsequent 5 months. Haematological toxicity is shown in Figure 1. There was a WHO grade 3 neutropenia and WHO grade 4 thrombocytopenia lasting, respectively, 1 week and 4 weeks, and 4 platelet transfusions were administered owing to occasional increases in the number of petechiae.

Case 4

A 36-month-old child was admitted to our hospital with a history of persistent fever and diffuse bone pain. Physical examination showed a left abdominal mass and a left orbital haemorrhagic lesion. Haematological findings included: Hb 6.3 g/dl, WBC 3900/mm³ (with 32% neutrophils), platelets 164,000/mm³. An abdominal CT scan showed a left retroperitoneal mass (6 × 8 cm). BM aspiration at two sites showed massive infiltration by malignant cells. Skeletal survey both by bone X-rays and bone scan with ^{99m}Tc-methylene diphosphate (^{99m}Tc-MDP) showed extensive bony lesions. [^{131}I]MIBG scan visualised the primary tumour located in the left adrenal, as well as multiple bony metastases in the skull and distal long bones; intense uptake of the radiopharmaceutical was also evident along the spine and pelvis, suggesting neoplastic BM infiltration. Catecholamines were within normal limits, but VMA was 52.5 mg/24 h (n.v. 1.5–3.5 mg/24 h), HVA 69.9 mg/24 h (n.v. <5).

During the clinical examination of approximately 1 week, rapid progression of the disease was evident, with the appearance of 2 new subcutaneous skull lesions in the left parietal region. 3 days later the subcutaneous masses increased markedly in size and two additional masses (3 × 3 cm and 2 × 3 cm) on the

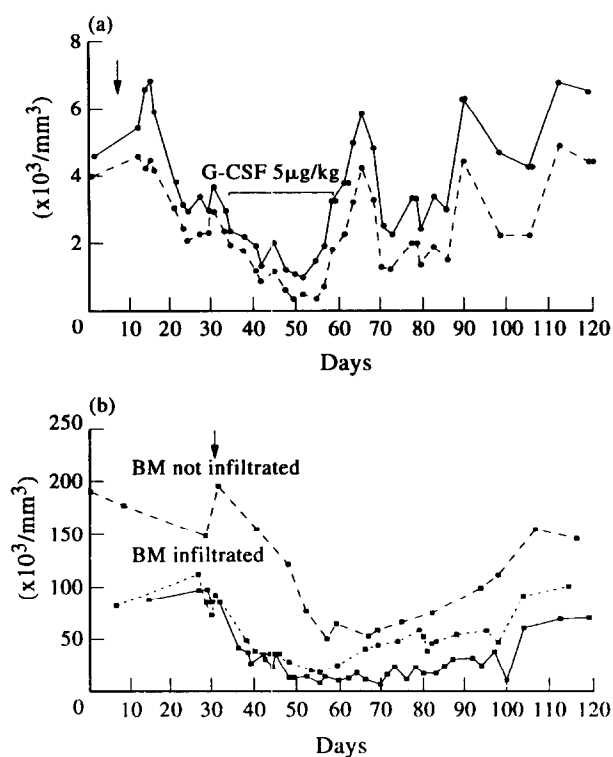


Figure 1. Case 3. Haematological toxicity. (a) Time course of white blood counts (●—●) and absolute neutrophil counts (○—○). The arrow indicates the day the combined treatment was started. (b) Time course of platelet counts after [^{131}I]MIBG alone (■—■) cisplatin alone (■···■) and combined therapy (■—■). The arrow indicates the day 3 different treatments were started.

same side were observed. Following a course of cisplatin 80 mg/m^2 i.v. over 4 days, his general condition improved and no further tumour growth was observed. 4 days later, at the time of radiometabolic treatment, no change was observed in the [^{131}I]MIBG uptake by tracer investigation (Figure 2a and b). 150 mCi of [^{131}I]MIBG at high specificity ($> 1.1 \text{ GBq}/\text{mg}$) split into two parts was administered by slow i.v. infusion (6–8 h)

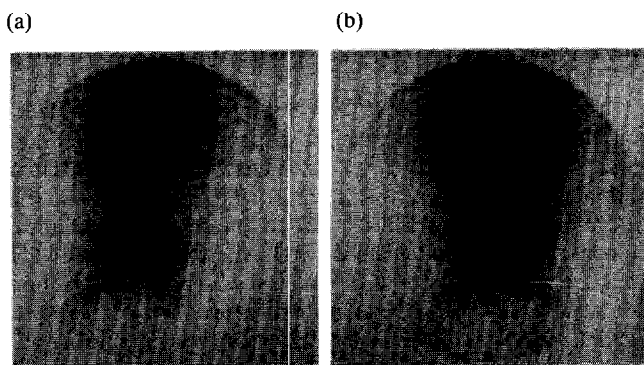


Figure 2. Case 4. [^{131}I]MIBG uptake before (a) and after treatment (b) with cisplatin alone.

with a 1-week interval. Subsequent [^{131}I]MIBG scintigraphic assessment 3–4 weeks later showed partial regression of all NB lesions, including a small reduction of the primary tumour and the complete disappearance of BM infiltration (also documented by 4 BM aspirations and biopsy). VMA and HVA were within normal limits. A second course of [^{131}I]MIBG (100 mCi i.v. 6 h infusion) was administered, and 3 weeks later a moderate reduction in size of the primary tumour on CT scan (a total of 40–50% reduction) allowed its surgical total removal. [^{131}I]MIBG scintigraphy performed immediately after surgery showed only mild uptake of the tracer in a confined area of the skull (Figure 3).

Two courses of chemotherapy (CAo) with vincristine (1.5 mg/m^2), cyclophosphamide (1.5 g/m^2 divided over 5 days) and doxorubicin (40 mg/m^2 in the first course, and the full dose of 60 mg/m^2 in the second course) were administered with a 5-week interval. The time course of platelet count, WBC and granulocyte count from diagnosis up to the completion of CAo chemotherapy is shown in Figure 4. A month from the last administration of CAo, physical examination continued to be unremarkable; CT scan of the abdomen and BM aspirations and biopsies showed no malignant cells. Skeletal survey showed no major changes; however, [^{131}I]MIBG scintigraphy still showed the small area of faint [^{131}I]MIBG uptake in the skull. The patient is being treated with conventional dosages of cisplatin and etoposide, with no significant haematological toxicity. No auditory, kidney, neurologic problems have been observed.

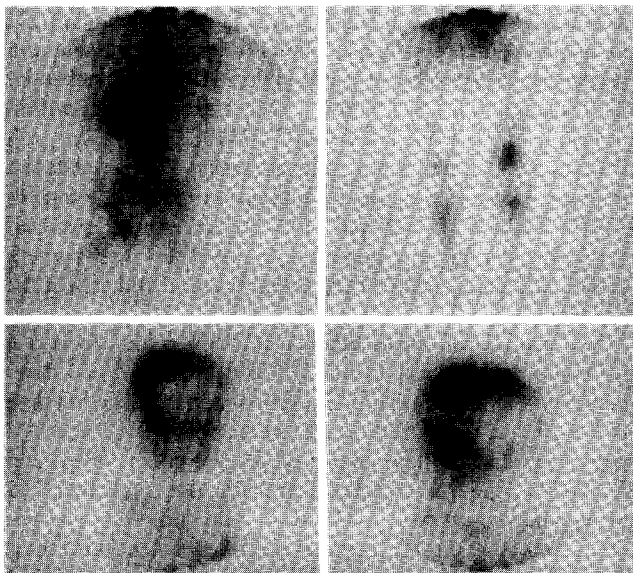
DISCUSSION

This pilot study was designed to test the tolerance and effectiveness of combining [^{131}I] MIBG and cisplatin in disseminated NB. The data presented are derived from work in progress and, obviously, more patients need to be treated to support general conclusions. However, some provisional conclusions may be drawn. The overall response rate in the first 3 relapsed cases investigated, including 2 complete remissions and 1 partial remission, suggests that the combined regimen [^{131}I]MIBG and cisplatin is most effective in pretreated stage IV NB, particularly in patients with BM infiltration and cortical bony metastases. These patients had received extensive prior chemotherapy which included cisplatin, and all had progressive disease at the time of CO-TH.

The response rate, with only a few complete remissions, using different intensive salvage chemotherapy regimens, has been in the order of 20–40% in similar subsets of patients, including 19 patients treated with several courses of high-dose cisplatin with etoposide administered over several months [12, 13]. Severe haematological and non-haematological toxicity also occurred. Effective responses were observed in less than 50% of stage IV resistant NB patients, most of these being partial remissions, after multiple courses of [^{131}I]MIBG administered alone, also over a period of several months [4]. Furthermore, with [^{131}I]MIBG alone, BM and cortical bony lesions very rarely showed any response [14, 15]. Therefore, when compared with similar patients treated with salvage chemotherapy or [^{131}I]MIBG alone, our 3 patients showed much better results, in terms of degree and rate of response, and with only one course of the CO-TH, with both cisplatin and [^{131}I]MIBG at “standard” dosage, administered over a short time. In these end-stage patients, the short duration of the complete remission, not maintained with further treatment, was not surprising.

The present treatment approach allowed the delivery of large, but not myeloablative, doses of combined [^{131}I]MIBG and

(a)



(b)

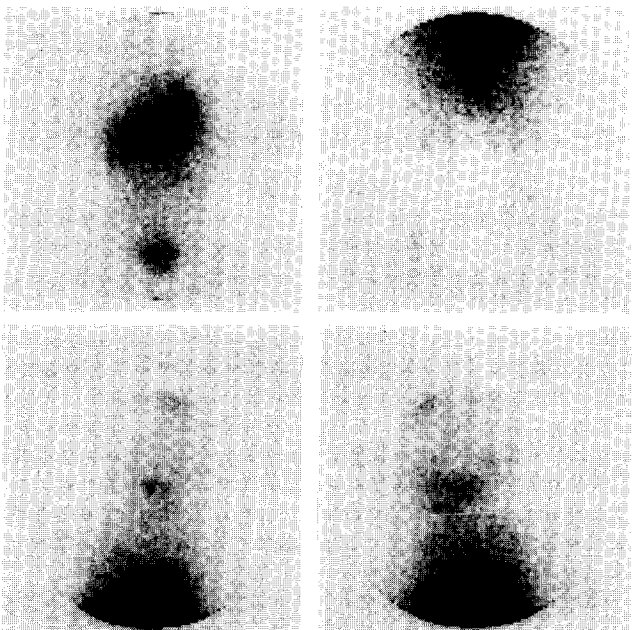


Figure 3. Case 4. ^{131}I MIBG uptake before (a) and after (b) combined therapy, following removal of primary tumour. A mild uptake of the tracer is evident only in a confined area of the skull after combined therapy.

cisplatin. The only toxicity was haematological, which was severe and relatively long-lasting, but not associated with any significant infections or bleeding tendency, despite initial haematological depression and BM infiltration in 2 of the 3 patients investigated. In case 3, even though synergistic "therapeutic" effects of the CO-TH could only be suspected, it appears that at least a "toxic" synergistic effect could be excluded, considering the time courses of the platelet counts (Figure 1). Furthermore, the general condition of these patients during the entire study period was excellent.

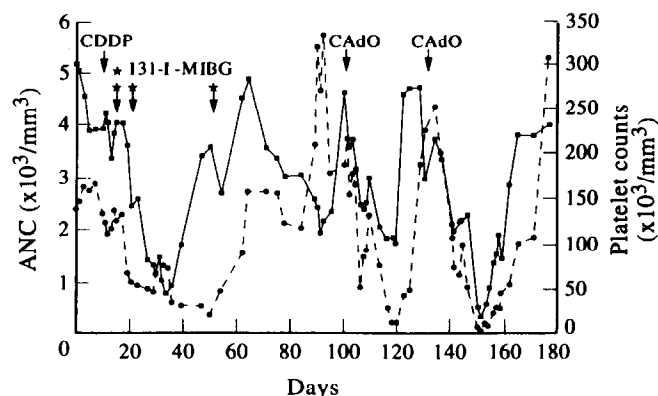


Figure 4. Case 4. Time course of absolute neutrophil (ANC ●—●) and platelet counts (■—■) with combined therapy, and during two courses with CAdO. The arrows indicate the days of cisplatin (CDDP), ^{131}I MIBG and CAdO administration.

We believe that ^{131}I MIBG combined with cisplatin should be attempted at an earlier stage of the disease, with the possibility of even better results and less haematological toxicity. Because of the virtual absence of non-haematological toxicity, there may be room for intensification of treatment with the addition of non-myelodepressive effective drugs, such as vincristine, to the CO-TH. CO-TH would be useful for patients with unsatisfactory initial conventional response and good MIBG uptake, with the aim of reducing the tumour burden some time before conditioning chemotherapy for autologous bone marrow transplantation (ABMT), since it has been observed that patients with a better pre-ABMT clinical response have a significantly lower relapse rate after ABMT [16]. The optimal use of CO-TH in the future treatment of stage IV NB may indeed derive from tentative therapeutic approaches at the time of diagnosis, whether BM infiltration is present or not. The only case treated so far at diagnosis (case 4) points in this direction. Although promising preliminary results have been obtained in children with disseminated NB treated with ^{131}I MIBG alone at diagnosis, these new lines of investigation have not been adequately pursued. There may be concern about the potential risk of BM toxicity of ^{131}I MIBG, used alone or, more so, in association with chemotherapy. In the presence of BM infiltration particularly, BM toxicity would also hamper the subsequent optimal delivery of conventional chemotherapy, because of the excessive BM depression due to the possible long-term BM toxicity from ^{131}I MIBG.

Our patient with stage IV NB and massive BM infiltration, was the first case ever treated at diagnosis with CO-TH and therefore, to be cautious, a less intensive, less concentrated and modified regimen was administered. Nevertheless, the integration of cisplatin with ^{131}I MIBG produced a good clinical response. The results obtained with a short course of CO-TH compare favourably with those obtained with the administration at diagnosis of ^{131}I MIBG alone, delivered in 2–5 courses over several months [8]. Haematological toxicity was mild; above all, the haematological toxicity from the subsequent CAdO regimen was comparable with that experienced by patients with NB treated at our Centre with an identical drug combination, but

without previous treatment with CO-TH (Figure 4). Following our experience using CO-TH in relapsed patients, we plan to gradually intensify the CO-TH, and reduce the administration time of the initial treatment.

The findings reported in case 4 also have two important clinical implications for the treatment of NB with CO-TH at diagnosis. The first point regards the unpredictable waiting time, sometimes up to a few weeks, to procure the drug for a disease which, even at diagnosis, may be rapidly progressive. The initial chemotherapy, as delivered to our patient, appeared very useful in controlling a rapidly progressive disease while waiting for the radiopharmaceutical. The second point concerns the fact that the biochemical and physiological integrity of the malignant cell wall appears to be essential for the optimal specific MIBG uptake [17], but our case showed that the [^{131}I]MIBG uptake by the NB cells is not altered by prior chemotherapy (Figure 2) and would not jeopardise the uptake of the therapeutic dose of [^{131}I]MIBG.

We believe that this new form of treatment combination deserves further extensive evaluation in stage IV NB, and several points need to be clarified, such as dosage, optimal infusion time, and the sequence relationship of [^{131}I]MIBG and cisplatin. More data are also needed on the pharmacological modulation of uptake and release of [^{131}I]MIBG in the tumour cells [18, 19]. In the future, no-carrier-added [^{131}I]MIBG, rather than the conventional low specific activity preparation, will probably result in an enhanced therapeutic ratio because of the different transport mechanisms in NB compared with normal tissue [20]. Finally, a better knowledge of the biochemical mechanisms of interaction of cisplatin with radiation would most likely lead to an optimal synergistic effect. All this information will probably help to determine the future role of this new treatment approach in the therapeutic strategy for one of the most frustrating malignant tumours of childhood.

- Philip T. Overview of current treatment of neuroblastoma. *Am J Ped Hematol Oncol* 1992, 14, 97–102.
- Helfre S, Habrand JL, Hartmann O, Bouhaouina N, Lemerle J. The role of radiation-therapy (RT) in the curative management of neuroblastoma (Nb). SIOP XXV Meeting, *Med Ped Oncol* 1993, 21, 583.
- Troncone L, Riccardi R, Montemaggi P, Rufini V, Lasorella A, Mastrangelo R. Treatment of neuroblastoma with [^{131}I]Metaiodobenzylguanidine. *Med Ped Oncol* 1987, 15, 220–223.
- Mastrangelo R. Editorial: the treatment of neuroblastoma with [^{131}I]MIBG. *Med Ped Oncol* 1987, 15, 157–158.
- Mastrangelo R, Troncone L, Lasorella A, Riccardi R, Montemaggi P, Rufini V. [^{131}I]Metaiodobenzylguanidine in the treatment of neuroblastoma at diagnosis. *Am J Ped Hematol Oncol* 1989, 11, 28–31.
- Mastrangelo R, Lasorella A, Iavarone A, et al. Critical observation on neuroblastoma treatment with 131-I-Metaiodobenzylguanidine at diagnosis. *Med Ped Oncol* 1993, 21, 411–415.
- Mastrangelo R, Voûte PA. Session on the treatment of neuroblastoma with radiiodinated metaiodobenzylguanidine. Chairmen's Report. *J Nucl Biol Med* 1991, 35, 260–262.
- De Kraker J, Hoefnagel CA, Caron H, Voûte PA, Tiel van Buul MMC, Valdes Olmos R. Targeted radiotherapy with iodine-131-metaiodobenzylguanidine (MIBG) as first line treatment of neuroblastoma advanced disease patients. SIOP XXVI Meeting, *Med Ped Oncol* 1994, 23, 179.
- Double EB, Richmond RC, O'Hara JA, Coughlin CT. Carboplatin as a potentiator of radiation therapy. *Cancer Treat Rev* 1985, 12 (suppl. A), 111–124.
- Dewit L. Combined treatment of radiation and cis-diamminedichloroplatinum (II): a review of experimental and clinical data. *Int J Rad Oncol Biol Phys* 1987, 13, 403–426.
- Double EB. Keynote address: platinum–radiation interactions. NCI Monographs 1988, 6, 315–319.
- Philip T, Ghalie R, Pinkerton R, et al. A phase II study of high-dose cisplatin and VP-16 in neuroblastoma: a report from the Société Française d'Oncologie Pédiatrique. *J Clin Oncol* 1987, 5, 941–950.
- Pinkerton R, Zucker JM, Hartmann O, et al. Short duration, high dose, alternating chemotherapy in metastatic neuroblastoma. (ENSG 3C induction regimen). *Br J Cancer* 1990, 62, 319–323.
- Matthay KK, Huberty JP, Hattner RS, et al. Efficacy and safety of [^{131}I]Metaiodobenzylguanidine therapy for patients with refractory neuroblastoma. *J Nucl Biol Med* 1991, 35, 244–247.
- Claudiani F, Garaventa A, Bertolazzi L, et al. 131-I-Metaiodobenzylguanidine therapy in advanced neuroblastoma. *J Nucl Biol Med* 1991, 35, 224–227.
- Matthay KK. An overview on the treatment of neuroblastoma. *J Nucl Biol Med* 1991, 35, 179–182.
- Beierwaltes WH. Treatment of neuroblastoma with 131-I-MIBG: dosimetric problems and perspectives. *Med Ped Oncol* 1987, 15, 188–191.
- Iavarone A, Lasorella A, Servidei T, et al. Uptake and storage of metaiodobenzylguanidine are frequent neuronal functions of human neuroblastoma cell lines. *Cancer Res* 1993, 53, 304–309.
- Smets LA, Rutgers M. Model studies on metaiodobenzylguanidine (MIBG) uptake and storage: relevance for 131-I-MIBG therapy of neuroblastoma. *J Nucl Biol Med* 1991, 25, 191–194.
- Mairs RJ, Cunningham SH, Russell J, et al. No-carrier-added [^{131}I]MIBG: evaluation of a novel preparation of a therapeutic radiopharmaceutical. EURONEU, Heidelberg, 9–11 June 1994, 21.

Acknowledgements—Supported by CNR, ACRO, Grant No. 94.01196 PF39 and by Associazione Italiana per la Ricerca sul Cancro (AIRC).