**131I-metaiodobenzylguanidine (131I-MIBG) therapy for residual neuroblastoma: a mono-institutional experience with 43 patients**

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**Summary**

Incomplete response to therapy may compromise the outcome of children with advanced neuroblastoma. In an attempt to improve tumour response we incorporated 131I-metaiodobenzylguanidine (131I-MIBG) in the treatment regimen of selected stage 3 and stage 4 patients. Between 1986 and 1997, 43 neuroblastoma patients older than 1 year at diagnosis, 13 with stage 3 (group A) and 30 with stage 4 disease (group B) who had completed the first-line protocol without achieving complete response entered in this study. 131I-MIBG dose/course ranged from 2.5 to 5.5 Gbq (median, 3.7). The number of courses ranged from 1 to 5 (median 3) depending on the tumour response and toxicity. The most common acute side-effect was thrombocytopenia. Later side-effects included severe interstitial pneumonia in one patient, acute myeloid leukaemia in two, reduced thyroid reserve in 21. Complete response was documented in one stage 4 patient, partial response in 12 (ten stage 3, 15 stage 4) and disease progression in five (one stage 3, four stage 4). Twenty-four patients (12/13 stage 3, 12/30 stage 4) are alive at 22–153 months (median, 59) from diagnosis. 131I-MIBG therapy may increase the cure rate of stage 3 and improve the response of stage 4 neuroblastoma patients with residual disease after first-line therapy. A larger number of patients should be treated to confirm these results but logistic problems hamper prospective and coordinated studies. Long-term toxicity can be severe. © 1999 Cancer Research Campaign

**Keywords:** neuroblastoma; radiometabolic therapy; 131I-metaiodobenzylguanidine

One of the major goals of cancer treatment is to develop therapies affecting cancer cells while causing little or no damage to the normal counterparts. In this perspective numerous attempts have been made to bind anti-tumour compounds or radioactive isotopes to molecules specifically taken up by tumour cells. One example of these molecules is benzylguanidine, a structural analogue of noradrenaline, which is selectively taken up by cells of neural crest origin including tumours such as pheochromocytoma and neuroblastoma (Jaques et al, 1987; Montaldo et al, 1991). Linking radioactive iodine to benzylguanidine has led to the synthesis of 123I- and 131I-metaiodobenzylguanidine (*I-MIBG), which at low doses have become an important tool for both diagnosis and follow-up of these tumours (Buck et al, 1985; Geatti et al, 1985). Moreover, given at higher doses 131I-MIBG has proven to be active against these tumours, especially neuroblastoma (Schwabe et al, 1987; Klingebiel et al, 1989). Most clinical studies have been carried out on patients in advanced stages of the neoplasia (Italian MIBG Workshop, 1987; Klingebiel et al, 1989; Lashford et al, 1992), although recently 131I-MIBG has been administered to poor-risk patients as up-front therapy in an attempt to improve their outcome (Mastrangelo et al, 1993, 1998; Weber et al, 1996).

Despite all this information the precise role of 131I-MIBG in the overall therapeutic strategy of neuroblastoma is far from being defined. In particular, it is still unclear whether 131I-MIBG might improve the tumour response of patients who did not achieve complete remission with conventional therapy and are therefore predisposed to disease progression and death. Since 1986 it has been the policy of our institute to use 131I-MIBG as therapy for stage 3 and 4 neuroblastoma patients with MIBG-positive residual disease after front-line protocol. We have thus accumulated considerable experience in this area.

The results of this experience are hereby reported. They suggest that 131I-MIBG may provide additional therapeutic benefits for some of these patients, although related toxicity may occasionally be severe.

**MATERIALS AND METHODS**

**Patients**

Patients were registered in this study between March 1986 and December 1996. They were diagnosed with inoperable or disseminated neuroblastoma (INSS stage 3 and stage 4 respectively) (Brodeur et al, 1993) in ages ranging from 1 to 15 years. Diagnosis of neuroblastoma and evaluation of disease extent was carried out according to standard clinical and pathologic criteria of the Italian Cooperative Group for Neuroblastoma (ICGNB) (De Bernardi et al, 1992). Treatment was given according to ICGNB protocols (De Bernardi et al, 1992). In order to be eligible for this study...
patients had to have either (a) stage 3 disease with residual tumour positive at the $^{123}$I- or $^{131}$I-MIBG scintigraphy at end of first-line therapy (group A), or (b) stage 4 disease partially responsive to first-line therapy with residual tumour at the level of primary tumour and/or skeleton (no more than four lesions) and/or bone marrow (only if infiltration was of minimal entity) with at least one lesion clearly uptaking $^{123}$I- or $^{131}$I-MIBG (group B). The cohort of 43 patients in this study (13 stage 3 and 30 stage 4) represents all the patients with these characteristics treated in our institution. This accounts for approximately one-third of the patients enrolled in the Italian protocols between 1985 and 1996 who reached partial response to first-line therapy (28 out of 76 stage 3 and 102 out of 281 stage 4 patients). In the same period we diagnosed and treated 36 stage 3 and 112 stage 4 patients aged more than 1 year.

Further eligibility criteria included recovery of haematopoiesis from previous chemotherapy, and normal renal, hepatic and thyroid functions. Parents or guardian were informed of the experimental nature of this treatment and requested to give written consent. The study was approved by the Ethical Committee of the Giannina Gaslini Children’s Hospital.

### Evaluation of tumour response

Tumour response was defined as follows (Brodeur et al, 1993): complete response (CR), disappearance of primary tumour and of all metastatic lesions with normalization of urine catecholamines; very good partial response (VGPR), > 90% volume reduction of the primary tumour with clearing of all measurable metastatic lesions with the exception of residual changes at skeletal scintigraphy, normalization of urine catecholamines; partial response (PR), > 50% volume reduction of the primary tumour and of all measurable metastatic lesions, residual marrow infiltration in only one site; mixed response (MR), > 50% reduction of any measurable lesion (primary or metastases) with < 50% reduction in any other and < 25% increase in any existing lesion; no response (NR), < 50% reduction but < 25% increase in any existing lesion; progressive disease (PD), increase > 25% of any measurable lesion or appearance of a new lesion(s). The isolated decrease of $^{131}$I-MIBG uptake was not considered evidence of tumour response. Response was evaluated 4–8 weeks following each $^{131}$I-MIBG course. The best response achieved is reported in the Results section of the article and in the Tables. Some patients underwent further improvement several months after completion of $^{131}$I-MIBG therapy and the best status achieved is reported in the outcome.

### $^{131}$I-MIBG therapy

The administered doses of $^{131}$I-MIBG ranged from 2.5 to 5.5 GBq according to body weight: 2.5–3.7 GBq for patients weighing less than 15 kg; 3.7–4.7 GBq for patients weighing 15–20 kg; 5.5 GBq for those weighing more than 20 kg. Specific activity ranged from 1.1 to 2.8 GBq mg⁻¹ (median 1.6). Doses were determined attempting to give at least 2000 cGy to the tumour and possibly less than 200 cGy to the whole body (Beirewaltes, 1987).

Thyroid gland uptake of radiiodine was blocked by oral administration of iodine (2–3 mg kg⁻¹ day⁻¹ of iodine as Lugol’s solution) given for 5 days before and 8 days after $^{131}$I-MIBG.

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### Table 1: Stage 3 patients (group A)

| Case no. | Sex, age (yrs) | Primary tumour site | NMYC copies | Time (months) from diagnosis to $^{131}$I-MIBG therapy | Tumour lesion at $^{131}$I-MIBG therapy | $^{131}$I-MIBG therapy courses | Tumour response after $^{131}$I-MIBG therapy | Clinical course and outcome |
|----------|----------------|---------------------|-------------|------------------------------------------------------|----------------------------------------|------------------------------|---------------------------------------------|---------------------------|
| 1        | F, 2           | Thorax              | 1           | 7                                                    | Yes                                    | E 2                          | NR Alive 131 months, SD                      |                           |
| 2        | M, 3           | Thorax              | 1           | 6                                                    | Yes                                    | E 4                          | PR Alive 107 months, CR                       |                           |
| 3        | F, 2           | RPG                 | 1           | 5                                                    | Yes                                    | E 3                          | NR Alive 98 months, SD                       |                           |
| 4        | M, 12          | Adrenal             | 1           | 14                                                   | Yes                                    | E 2                          | NR Alive 89 months, SD                       |                           |
| 5        | F, 1           | RPG                 | ND          | 1                                                    | Yes                                    | E 4                          | PR Alive 78 months, CR                       |                           |
| 6        | F, 2           | RPG                 | 32          | 7                                                    | Yes                                    | E 3                          | PR Alive 77 months, SD                       |                           |
| 7        | M, 3           | RPG                 | 1           | 7                                                    | Yes                                    | E 4                          | NR Alive 77 months, SD                       |                           |
| 8        | F, 3           | Thorax              | 1           | 8                                                    | Yes                                    | E 3                          | NR Alive 71 months, SD                       |                           |
| 9        | M, 1           | RPG                 | 1           | 5                                                    | Yes                                    | E 4                          | MR Alive 56 months, SD                       |                           |
| 10       | F, 1           | Adrenal             | 1           | 5                                                    | Yes                                    | E 4                          | NR Alive 56 months, SD                       |                           |
| 11       | F, 4           | RPG                 | 14          | 8                                                    | Yes                                    | E 3                          | PD Dead 17 months, PD                        |                           |
| 12       | M, 2           | Adrenal             | 1           | 6                                                    | Yes                                    | E 1                          | NR Alive 47 months, CR                       |                           |
| 13       | M, 1           | RPG                 | 1           | 8                                                    | Yes                                    | E 2                          | NR Alive 34 months, SD                       |                           |

RPG, retroperitoneal ganglia; B, bone; (s), single lesion; (m), multiple lesions; BM, bone marrow; LN, distant lymph node; CR, complete remission; PR, partial remission; MR, minor response; NR, no response; SD, stable disease; PD, progressive disease; N normal, E elevated, ND, not done. *Acute myeloid leukaemia presently in remission. **Acute myeloid leukaemia under treatment.
infusion. During hospitalization patients were kept in single rooms. Close relatives actively participated in nursing care and were provided with film dosimetry. Once discharged patients were checked weekly for haematological indices and at longer intervals for other organic functions.

Toxic effects attributable to $^{131}$I-MIBG therapy were evaluated according to WHO criteria (WHO, 1979). The duration of $^{131}$I-MIBG treatment depended on tumour response and toxicity. In case of either disease improvement or stability after the first $^{131}$I-MIBG course, additional courses up to a maximum of 5 with an interval of 4–6 weeks between courses were administered unless evidence of progressive disease was documented or excessive myelotoxicity had occurred.

**RESULTS**

Group A consisted of 13 stage 3 disease patients who had had partial tumour response to first-line regimen. Before $^{131}$I-MIBG therapy 11 patients underwent second-look surgery consisting of partial tumour resection in four and of a biopsy only in seven with histological evidence of viable tumour cells in all surgical specimens. At the time of entry into this study all patients but one had abnormal urinary catecholamine excretion. All showed pathological scintigraphic $^{123}$I-MIBG uptake at the site of the primary.

Main patients' data including characteristics at diagnosis, interval from diagnosis to $^{131}$I-MIBG therapy, number of courses of $^{131}$I-MIBG administered, tumour response to $^{131}$I-MIBG and outcome are listed in Table 1. In all but one patient NMYC gene

| Case no. | Sex, age (years) | Primary tumour site | NMYC copies | Time (months) from diagnosis to $^{131}$I-MIBG therapy | Tumour lesions at $^{131}$I-MIBG therapy | $^{131}$I-MIBG therapy courses | Tumour response after $^{131}$I-MIBG | Clinical course and outcome |
|----------|------------------|---------------------|--------------|---------------------------------------------------|---------------------------------------|---------------------------------|---------------------------------|---------------------------|
| 1        | F, 3             | RPG                 | ND           | 25                                                 | Yes, No                              | E                               | 4                              | PR                        | Alive 153 months, CR*     |
| 2        | M, 4             | RPG                 | 1            | 10                                                 | Yes, No                              | N                               | 2                              | NR Dead 21 months, PD      |
| 3        | M, 2             | Adrenal             | ND           | 11                                                 | Yes, No                              | E                               | 3                              | NR Death 22 months, PD     |
| 4        | M, 2             | RPG                 | 32           | 7                                                  | Yes, No                              | N                               | 3                              | PR Alive 67 months, CR    |
| 5        | F, 1             | Adrenal             | 9            | 7                                                  | Yes, No                              | N                               | 1                              | PR Alive 65 months, CR    |
| 6        | F, 17            | RPG                 | 1            | 21                                                 | Yes, No                              | E                               | 2                              | NR Alive 57 months, SD    |
| 7        | F, 3             | RPG                 | 1            | 13                                                 | Yes, No                              | N                               | 2                              | PR Alive 47 months, SD    |
| 8        | M, 1             | RPG                 | 1            | 12                                                 | Yes, No                              | N                               | 2                              | NR Alive 36 months, SD    |
| 9        | M, 2             | Adrenal             | 1            | 9                                                  | Yes, No                              | E                               | 2                              | NR Dead 21 months, PD     |
| 10       | M, 14            | Adrenal             | 1            | 18                                                 | Yes, No                              | N                               | 2                              | NR Alive 30 months, SD    |
| 11       | F, 2             | RPG                 | 1            | 5                                                  | Yes, O(m), MO                        | E                               | 3                              | NR Dead 10 months, PD     |
| 12       | M, 3             | Adrenal             | 20           | 6                                                  | Yes, O(m), MO                        | E                               | 5                              | NR Dead 14 months, PD     |
| 13       | M, 4             | Adrenal             | ND           | 16                                                 | Yes, O(m)                            | E                               | 1                              | PD Dead 19 months, PD     |
| 14       | M, 2             | Adrenal             | ND           | 9                                                  | Yes, LN                              | E                               | 2                              | PD Dead 12 months, PD     |
| 15       | M, 6             | RPG                 | ND           | 14                                                 | Yes, MO                              | E                               | 2                              | NR Dead 20 months, PD     |
| 16       | F, 1             | RPG                 | ND           | 13                                                 | Yes, O(m), MO                        | E                               | 3                              | PR Dead 19 months, PD     |
| 17       | F, 4             | RPG                 | 1            | 11                                                 | Yes, O(m), MO                        | E                               | 3                              | PR Alive 39 months, SD*   |
| 18       | M, 4             | RPG                 | 1            | 12                                                 | Yes, LN                              | E                               | 3                              | NR Dead 20 months, PD     |
| 19       | M, 16            | RPG                 | 1            | 12                                                 | Yes, LN                              | E                               | 2                              | NR Alive 48 months, SD    |
| 20       | M, 11            | RPG                 | 14           | 9                                                  | Yes, O(m)                            | N                               | 2                              | NR Dead 13 months, PD     |
| 21       | M, 1             | RPG                 | 3            | 10                                                 | Yes, LN                              | N                               | 3                              | NR Toxic death, 13 months |
| 22       | M, 2             | RPG                 | 20           | 10                                                 | Yes, MO                              | E                               | 3                              | PR Dead 14 months, PD     |
| 23       | M, 4             | Adrenal             | ND           | 12                                                 | Yes, B(m), BM                        | N                               | 3                              | PR Dead 16 months, PD     |
| 24       | M, 5             | Adrenal             | ND           | 17                                                 | Yes, B(m), BM                        | N                               | 1                              | PD Dead 24 months, PD     |
| 25       | F, 4             | Adrenal             | ND           | 14                                                 | Yes, B(m), BM                        | E                               | 2                              | NR Alive 24 months, PD    |
| 26       | M, 4             | RPG                 | 1            | 10                                                 | Yes, B(s), BM                        | N                               | 1                              | NR Alive 22 months, SD    |
| 27       | M, 2             | Adrenal             | 1            | 8                                                  | No, BM                               | N                               | 4                              | PD Dead 9 months, PD      |
| 28       | F, 1             | Adrenal             | 1            | 12                                                 | No, B(s)                             | E                               | 3                              | PR Alive 60 months, CR    |
| 29       | F, 3             | Adrenal             | 1            | 17                                                 | No, B(m)                             | N                               | 1                              | CR Alive 68 months, CR    |
| 30       | M, 2             | Adrenal             | 3            | 21                                                 | No, BM                               | E                               | 2                              | PR Alive 45 months, PD    |

RPG, retroperitoneal ganglia; B, bone; (s), single lesion; (m), multiple lesions; BM, bone marrow; LN, distant lymph node; CR, complete remission; PR, partial remission; MR, minor response; NR, no response; SD, stable disease; PD, progressive disease; N normal, E elevated, ND, not done. *Acute myeloid leukaemia presently in remission. **Acute myeloid leukaemia under treatment.
was studied, and in two patients an abnormal copy number was present.

One patient received one $^{131}$I-MIBG course, three patients received two courses, four received three courses and five received four courses. The interval between courses ranged from 4 to 8 weeks (median, 7). Two patients had partial and one had mixed response (< 25% reduction of tumour volume with return to normal of catecholamines). The disease remained stable in nine patients and progressed in one alone.

No further antitumour therapy was administered and four patients became progressively disease-free including normal $^{13}$I-MIBG scan despite some ‘irregularity’ detected by imaging studies at level of primary tumour and interpreted as possible scar tissue. They are now alive at 47–107 months (median, 78) from diagnosis (case nos 2, 5, 6, 12). Eight patients are alive with stable disease (residual tumour persisting at imaging and MIBG scan) at 24–131 months (median, 74). Four of them underwent biopsy of the residual tumour with histological findings of ganglioneuroblastoma in two (case nos 3, 7) and of ganglioneuroblastoma in the other two (case nos 4, 9). The only case (no. 11) who developed PD after $^{131}$I-MIBG therapy died 9 months later. He was one of the two patients with an amplified NMYC gene. The 5-year event-free survival (EFS) of this group is 92% (± 0.07) with follow-up of 34–131 months (median, 78) (Figure 1).

Group B consisted of 30 patients with stage 4 disease who achieved partial response with first-line therapy. Twenty-one received $^{131}$I-MIBG therapy within 2 months from completion of their chemotherapy protocol ending in a course of myeloablative therapy, while in the remaining nine patients $^{131}$I-MIBG therapy was not preceded by myeloablative therapy due to (a) inoperable primary tumour (five patients), (b) bone marrow infiltration by tumour preventing autologous stem cell harvest (two patients), and (c) lack of adequate harvest (two patients). Scintigraphy performed before $^{131}$I-MIBG therapy was positive at one site in 11 patients (at level of primary in ten, a unique bone lesion in one), two sites in five, three or more sites in 14.

Main patient data are summarized in Table 2. Five patients received one $^{131}$I-MIBG course of therapy, 13 received two courses, nine received three courses, two received four courses and one received five courses. Intervals between courses ranged from 4 to 16 weeks (median, 7).

One patient (case no. 29) achieved CR (clearing of two bone lesions) and is presently alive disease-free 50 months later. Eleven patients had PR involving the primary tumour (the only tumour lesion) in four cases (nos 1, 4, 5, 7), a single bone lesion in one case (case no. 28), bone marrow in one (case no. 30), bone marrow plus primary in one (case no. 22), and bone plus bone marrow and primary in three (case nos 16, 17, 23). Eight of them are alive at 36–153 months (median, 53) among whom four are in CR (case nos 1, 4, 5, 28) including case no. 1 who developed myeloid leukaemia and is presently in CR after allogeneic bone marrow graft, two cases who had no further disease change (case nos 8, 17) including case no. 17 who developed myeloid leukaemia and is still alive after 14 months and one (case no. 30) who is alive with PD. Fourteen patients did not respond. Among them one is alive with PD at 24 months (case no. 25) and five are alive with stable disease (case nos 6, 8, 10, 19, 26) at 22–88 months (median, 42) from diagnosis, while the remaining nine patients died, among whom seven of disease at 13–21 months (median, 20) and two of toxicity.

The last four patients (case nos 13, 14, 24, 27) experienced early PD and died within a few months. The 5-year EFS of this group is 40% (± 0.08) (Figure 1).

Patients having a single tumour lesion positive at $^{13}$I-MIBG scan had better chance of survival with eight out of 11 surviving, four of whom in CR. Of the four patients with two positive lesions, two are presently alive with non-progressive disease and one is alive in CR. Of the 14 with three or more $^{13}$I-MIBG-positive lesions, only three are currently alive among whom two with stable disease and one with PD.

Bone marrow infiltration at time of $^{131}$I-MIBG therapy was prognostically unfavourable, since only three of 11 such patients are presently alive, one with stable disease and two with PD.

Of the 18 patients with normal NMYC copy number, 11 are alive; out of four patients with amplified NMYC only one survives, and two out of seven patients not evaluated for this gene survive.

The majority of patients who responded to $^{131}$I-MIBG therapy and survive are those who received $^{131}$I-MIBG after myeloablative therapy. In fact, out of 21 such patients nine responded (one CR, eight PR), nine had no disease change (one died of toxicity and eight progressed) and three developed progressive disease. On the contrary, in the group of nine patients who were not eligible for such a therapy only one responded, although a total of four are alive with stable disease.

**Toxicity**

**Acute toxicity**

No noticeable reaction was registered during or shortly after the administration of $^{131}$I-MIBG courses.

**Haematological toxicity (Table 3)**

Among the group A patients the main toxicity of this type attributable to $^{131}$I-MIBG was thrombocytopenia. However, out of 32 evaluable courses only two patients had grade 4 thrombocytopenia and three others had grade 3 toxicity which did not worsen with subsequent courses. Six patients, for a total of 24 courses, manifested no haematological toxicity.

In group B patients 58/72 courses were evaluable. Only one patient had no marrow toxicity. Grade 4 thrombocytopenia occurred after 19 course* grade 3 leukopenia occurred after 18 courses. None of the 21 patients who received therapeutic $^{131}$I-MIBG after myeloablative chemotherapy and autologous stem cell rescue had grade 4 haematological toxicity, although 12 developed grade 3 and seven grade 2 thrombocytopenia, which was often long-lasting (2–7 months; median 5).

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**Table 3 Haematological toxicity after $^{131}$I-MIBG therapy**

| Course             | I   | II  | III | >IV | Total |
|--------------------|-----|-----|-----|-----|-------|
| Stage 3: evaluable course | 12  | 11  | 7   | 2   | 32    |
| Leukopenia: grade 3 | –   | –   | 3   | –   | –     |
| Thrombocytopenia: grade 3 | –   | –   | 3   | –   | –     |
| Stage 4: evaluable courses | 25  | 21  | 9   | 3   | 58    |
| Leukopenia: grade 3 | –   | 5   | 1   | –   | 8     |
| Thrombocytopenia: grade 3 | 9   | 3   | 1   | 1   | 13    |
|                  | 4   | 8   | 7   | 3   | 19    |

*Grade 3 and 4 toxicity was often long-lasting (2–7 months; median 5).
Both thrombocytopenia and leukopenia occurred in most cases
3–5 weeks following administration of 131I-MIBG therapy.
Lymphocytopenia below 1 x 10^9 L^{-1} was found only after nine of
50 evaluable courses and appeared earlier (7–10 days after
131I-MIBG infusion) than other haematological toxicities.

Other toxicities
One stage 4 disease patient (case no. 21) treated with megatherapy
and autologous bone marrow rescue, followed by three courses of
131I-MIBG therapy, developed interstitial pneumopathy 1 month
after the last course and died. One stage 4 patient (case no. 17)
developed acute myeloid leukaemia (FAB M2) 1 year after the last
(third) 131I-MIBG course. She had previously received carboplatin
for a total dose of 4.4 g m^{-2}, cyclophosphamide for 14.4 g m^{-2},
etoposide for 1.5 mg m^{-2} and melphalan for 140 mg m^{-2}, plus
27 Gy radiation therapy to the primary tumour site. Another stage
4 disease patient (case no. 1) who had received 1.8 g m^{-2} of peptici-
chemio, 600 mg m^{-2} of cisplatin and only one course of 131I-MIBG,
developed myeloid leukaemia 6 years later, which was success-
fully treated by an unrelated marrow graft. This patient is presently
dead of interest. Both 125I- and 131I-labelled MIBG seemed suitable
much higher doses for therapeutic purposes brought about a great
optimize the therapeutic tools at his disposal (Castleberry et al,
Philip et al, 1997). Thus, until innovative and more effective ther-
erapeutic use of radioactive MIBG has been limited to 131I-MIBG.
abandoned with few exceptions (Sisson et al, 1996) and the thera-
therapy modality. The difficulties in design such studies include
the rarity of neuroblastoma, the fact that many centres do not
possess the facilities to deliver the treatment to young patients,
the high cost of the drug and, not least, the psychological burden of
keeping patient in a radiation protected environment with limited
parental contact extended for several days.

In a previous study we reported on 31 patients treated after
relapse or progression: the rate and degree of responses were lower
in the presence of bulky disease, a high number of MIBG-positive
lesions, long duration of previous therapy and overt bone marrow
infiltration (Garaventa et al, 1991).

In the present study we administered 131I-MIBG as therapy to
children with high-risk neuroblastoma who responded to first-line
therapy without achieving CR, provided that the residual primary
tumour and/or metastase(s) were clearly uptaking MIBG. Our
objective was to increase knowledge on toxicity of repeated cycles
and the possibly to improve the outcome of these children. Our
results indicate that stage 3 disease patients did benefit from this
treatment. Despite the fact that only two out of 13 of them had a
greater than 50% decrease of the residual primary tumour at short-
term evaluation after completion of 131I-MIBG therapy, two others
later experienced a progressive decrease in tumour size until its
disappearance without receiving further anti-tumour therapy. The
disease has remained stable for a median of 75 months in eight
other patients. Four of these eight patients eventually underwent
biopsy of the residual tumour, which turned out to be ganglio-
neuroma in two cases and ganglioneuroblastoma, with marked
evidence of differentiation in the other two. The disease progressed in only one patient after 131I-MIBG therapy. It is of
interest that this patient had abnormal MYCN gene copy number,
although a similar patient is a long survivor. Presently, 12 out of 13
patients are alive either disease-free or with stable disease with an
observation period of several years in most cases (Figure 1).

Since several authors have reported that incomplete tumour
excision in stage 3 disease is associated with a worse survival rate
(Garaventa et al, 1993; Haase et al, 1995; Powis et al, 1996), we
believe that our results should be considered worthy of interest
despite the fact that only one of our long-term survivors had ampli-
fication of MYCN gene.

The possible benefit of 131I-MIBG therapy for stage 4 disease
patients is more difficult to prove in this study. Among 30 such
patients only one achieved a CR and survives. However, ten other
patients experienced a PR and six of them are alive. No tumour
change was seen in 15 patients, six of whom are alive despite the
absence of additional treatment. Four patients developed early
progression and died. Tumour response and outcome correlated
with the extent of the disease at the time of 131I-MIBG therapy.
In fact, of 11 patients with a single positive lesion at 121I-MIBG
scintigraphy eight survive with stable disease, while of 19 with
two or more positive lesions only five survive. This last group
includes 12 patients with bone marrow involvement of whom only
two survive without tumour progression.

DISCUSSION

Long-term survival of children with inoperable or disseminated
neuroblastoma diagnosed after the age of 1 year remains largely
unsatisfactory mainly because current treatment commonly fails to
eradicate the disease (Garaventa et al, 1993; Haase et al, 1995;
Philip et al, 1997). Thus, until innovative and more effective ther-
apies are developed the paediatric oncologist dealing with refrac-
tory or partially responsive neuroblastoma must struggle to
optimize the therapeutic tools at his disposal (Castleberry et al,
Gaze et al, 1995; Leavey et al, 1997).

When radioiodinated benzylguanidine became available for the
diagnosis of neural crest-derived tumours the possibility to use it at
much higher doses for therapeutic purposes brought about a great
deal of interest. Both 125I- and 131I-labelled MIBG seemed suitable
due to their different physical characteristics. The former emits
short-range energy making it theoretically suitable to destroy small
tumour aggregates (Buck et al, 1985), while the long-range radia-
tion emitted of 131I could be more effective to induce damage of
larger tumour lesions (Weber et al, 1996). However, since residual
neuroblastoma is usually not homogeneous, 125I short-range
radioactivity might miss part of the tumour and was consequently
abandoned with few exceptions (Sisson et al, 1996) and the therape-
etic use of radioactive MIBG has been limited to 131I-MIBG.

Initial phase I–II studies with 131I-MIBG therapy, dating back to
the late 1980s, showed good tolerance and demonstrated objective
tumour responses in 20–60% of patients failing to respond to
modern therapies (Italian MIBG Workshop, 1987; Schwabe et al,
1987; Klingebiel et al, 1989; Lashford et al, 1992). In addition,
significant pain relief was noticed even in patients who did not
exhibit objective responses (Klingebiel et al, 1989). Since the
anti-tumour effect is dose-dependent with a maximum tolerated
dose of 12 mCi kg^{-1}, autologous stem cell rescue has been used to
allow dose escalation up to 18 mCi kg^{-1} (Matthay et al, 1998).
Lastly, attempts are being made to evaluate whether 131I-MIBG
given as front-line therapy may improve the outcome of these
patients without causing excessive toxicity (Van Hasselt et al,
1996; Mastrangelo et al, 1998). No prospective study has been
carried out so far to the true potential value of MIBG therapy and
to identify the group of patients who may profit best from this
treatment modality. The difficulties in design such studies include
the rarity of neuroblastoma, the fact that many centres do not
possess the facilities to deliver the treatment to young patients,
the high cost of the drug and, not least, the psychological burden of
keeping patient in a radiation protected environment with limited
parental contact extended for several days.

In a previous study we reported on 31 patients treated after
relapse or progression: the rate and degree of responses were lower
in the presence of bulky disease, a high number of MIBG-positive
lesions, long duration of previous therapy and overt bone marrow
infiltration (Garaventa et al, 1991).

In the present study we administered 131I-MIBG as therapy to
children with high-risk neuroblastoma who responded to first-line
therapy without achieving CR, provided that the residual primary
tumour and/or metastase(s) were clearly uptaking MIBG. Our
objective was to increase knowledge on toxicity of repeated cycles
and the possibly to improve the outcome of these children. Our
results indicate that stage 3 disease patients did benefit from this
treatment. Despite the fact that only two out of 13 of them had a
greater than 50% decrease of the residual primary tumour at short-
term evaluation after completion of 131I-MIBG therapy, two others
later experienced a progressive decrease in tumour size until its
disappearance without receiving further anti-tumour therapy. The
disease has remained stable for a median of 75 months in eight
other patients. Four of these eight patients eventually underwent
biopsy of the residual tumour, which turned out to be ganglio-
neuroma in two cases and ganglioneuroblastoma, with marked
evidence of differentiation in the other two. The disease progressed in only one patient after 131I-MIBG therapy. It is of
interest that this patient had abnormal MYCN gene copy number,
although a similar patient is a long survivor. Presently, 12 out of 13
patients are alive either disease-free or with stable disease with an
observation period of several years in most cases (Figure 1).

Since several authors have reported that incomplete tumour
excision in stage 3 disease is associated with a worse survival rate
(Garaventa et al, 1993; Haase et al, 1995; Powis et al, 1996), we
believe that our results should be considered worthy of interest
despite the fact that only one of our long-term survivors had ampli-
fication of MYCN gene.

The possible benefit of 131I-MIBG therapy for stage 4 disease
patients is more difficult to prove in this study. Among 30 such
patients only one achieved a CR and survives. However, ten other
patients experienced a PR and six of them are alive. No tumour
change was seen in 15 patients, six of whom are alive despite the
absence of additional treatment. Four patients developed early
progression and died. Tumour response and outcome correlated
with the extent of the disease at the time of 131I-MIBG therapy.
In fact, of 11 patients with a single positive lesion at 121I-MIBG
scintigraphy eight survive with stable disease, while of 19 with
two or more positive lesions only five survive. This last group
includes 12 patients with bone marrow involvement of whom only
two survive without tumour progression.

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Twenty-one of the 30 stage 4 disease patients received therapeutic $^{131}$I-MIBG within 3 months from myeloablative therapy. Although we expected severe and long-lasting haematological toxicity in these patients, they tolerated the radioiodinated treatment surprisingly well. In particular no severe haemorrhagic episodes were recorded, though three patients required several platelet transfusions.

However, important non-haematological toxicity which was not encountered in stage 3 disease, did occur in stage 4, possibly due to the overall greater amount of chemotherapy usually given to these patients as well as occasional irradiation to large proportions of the bone marrow and skeleton. One example was the early occurrence of fatal interstitial pneumonia that one patient developed within 2 months after the last $^{131}$I-MIBG therapy course. The precocity of this complication suggests that the elevated concentration of the radioactive compound in the pulmonary bloodstream during $^{131}$I-MIBG therapy may aggravate a pre-existing immune deficiency favouring the growth of opportunistic micro-organisms. This hypothesis is confirmed by the increased risk of pneumopathy reported in lymphoma patients treated with $^{131}$I-charged monoclonal antibodies (Press et al, 1995). According to these authors, after bone marrow, the organs which are most likely to develop toxicity from radioiodinated therapy are the lungs. This should therefore be taken into consideration when planning doses and duration of this type of treatment. Even more concern raises the early occurrence of leukaemia in two out of 30 stage 4 disease patients since it could represent the result of a combined chemoroadiotherapeutic effect on bone marrow precursor cells. A similar case has recently been reported in a series of 30 children enrolled in a therapeutic $^{131}$I-MIBG dose-finding study (Matthay et al, 1998). If the risk of secondary leukaemia in neuroblastoma patients subjected to $^{131}$I-MIBG therapy proved true, then the limits of this treatment would have to be more clearly defined. Subclinical hypothyroidism was frequent with residual disease after first-line therapy proved true, then the limits of this treatment would have to be more clearly defined. Subclinical hypothyroidism was frequent with residual disease after first-line therapy and this may translate into an overall improved outcome. This favourable result has been reached with the only side-effects being tolerable haematological and thyroid toxicity. In our opinion, the fact that 12 out of 13 such patients alive could justify a prospective study of $^{131}$I-MIBG therapy in this particular subset of patients. $^{131}$I-MIBG exhibited antitumour activity in approximately one-third of stage 4 patients. Interestingly enough, the haematological toxicity of this treatment was of moderate entity even for patients who had previously received myeloablative therapy. Overall, our results suggest that the addition of $^{131}$I-MIBG at therapeutic dosages to the conventional regimens for high-risk neuroblastoma may implement tumour response in some patients and this might translate in better chance of cure for some of them. Controlled clinical trials should be considered to define the true potential of this new therapeutic tool. However, since trials aiming to respond such an important question would imply the long lasting commitment of highly specialized centres and a potential severe toxicity the cost–benefit ratio of such a study deserves to be carefully evaluated.

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