

Original Article

Secondary Myelodysplastic Syndrome and Leukemia Following ^{131}I-Metaiodobenzylguanidine Therapy for Relapsed Neuroblastoma

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Purpose: To describe three patients with secondary leukemia after treatment with ^{131}I-metaiodobenzylguanidine (MIBG) for neuroblastoma.

Methods: Of 95 children with refractory neuroblastoma treated with ^{131}I-MIBG at UCSF, 3 have been identified with secondary myelodysplasia/leukemia. The case records and bone marrow results were reviewed, along with a review of the literature.

Results: Three patients developed secondary myelodysplasia/leukemia, at 7, 11, and 12 months following ^{131}I-MIBG therapy. Cytogenetic abnormalities included −7q/−5, −7/+2q37, −11 and +12. Three additional cases were found in literature review of 509 reported patients treated with ^{131}I-MIBG for neuroblastoma.

Conclusions: Therapy with ^{131}I-MIBG may contribute to the risk of secondary leukemia in patients who have received intensive chemotherapy, thought the risk of this complication is far lower than the risk of disease progression. Further monitoring for this complication is indicated.

Key Words: acute myelogenous leukemia, ^{131}I-MIBG, myelodysplasia, neuroblastoma, secondary leukemia

Children over 1 year of age diagnosed with metastatic neuroblastoma have a long-term survival of less than 40%, even with intensive therapy including hematopoietic stem cell transplantation.[1] New approaches that do not increase undesirable toxicity are needed for these resistant tumors. ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) is similar in structure to norepinephrine and is taken up and stored in cells of the sympathetic nervous system. It has been shown to concentrate in neuroblastoma and therefore holds promise for cell-specific radiation treatment of this tumor. Multiple trials of ^{131}I-MIBG have shown significant response rates of 30% to 40% and apparent prolongation of survival in children treated after relapse.[2,3] More recently, some centers have begun testing the use of this agent in newly diagnosed patients and have shown good response rates and minimal toxicity.[4]

The intensity of therapy required to successfully treat neuroblastoma necessitates careful consideration of the possible serious late sequelae. Others have reported that increased dose intensity of alkylating agents and etoposide results in a significant percentage of children treated for neuroblastoma developing second malignant neoplasm (SMN), particularly myelodysplasia (MDS) and leukemia.[5] Alkylating agents, topoisomerase inhibitors, and irradiation are all currently important components of induction and myeloablative protocols for neuroblastoma, and all may increase the risk of SMN in long-term survivors. In the extensive literature reporting trials incorporating ^{131}I-MIBG in the treatment of neuroblastoma, SMNs are rarely associated with this novel therapy.[6,7] In this report, we present details of three children who developed MDS or secondary leukemia (t-AML) following treatment with ^{131}I-MIBG. The possible mechanism of leukemogenesis with the use of this agent is discussed.

METHODS

Ninety-five patients with refractory neuroblastoma have been treated on UCSF phase I and II trials of ^{131}I-MIBG between March 21, 1986, and May 31, 2002. The median follow-up for all patients at the time of this report is 30 months (range 1–136 months). Thirty-one patients survived more than 1 year; of these, 13 survived more than 2 years and 8 more than 3 years. The median activity of ^{131}I-MIBG administered was 358 mCi, or 16 mCi/kg. Patients were given ^{131}I-MIBG as a 2-hour infusion with appropriate thyroid blocking and radiation safety precautions. They were monitored for myelosuppression, and if the nadir of abso-

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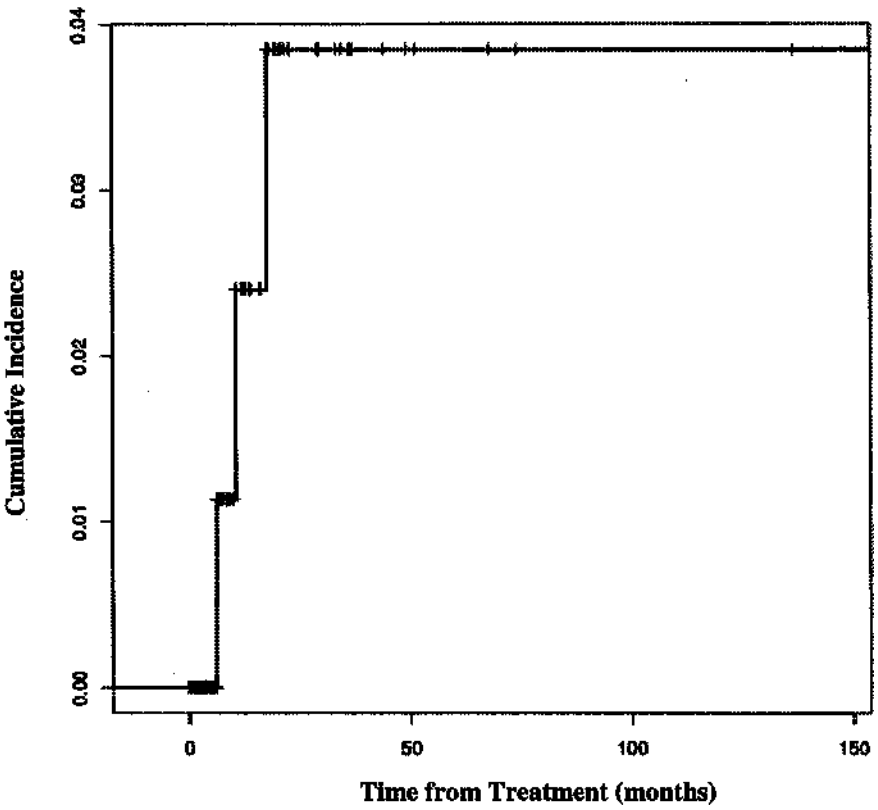

FIGURE 1. Cumulative incidence of therapy-related leukemia from ^{131}I-MIBG treatment.

lute neutrophils remained below 200/μL for more than 2 weeks, they received an infusion of previously collected, tumor-free autologous hematopoietic stem cells.[3,8] All patients or guardians signed appropriate informed consent, approved by the UCSF institutional review board. Details of the three patients who developed secondary MDS/t-AML are reported here. For the literature search, a Pubmed search was performed from 1977 to 2002 using the key words neuroblastoma, secondary leukemia, therapy-related leukemia, and MIBG.

RESULTS

Three of the 95 patients treated on UCSF protocols with ^{131}I-MIBG have developed secondary MDS/t-AML, at 7, 11, and 12 months after the targeted radionuclide therapy, for a cumulative incidence of 3.9% at 60 months after therapy (Fig. 1). In contrast, the cumulative incidence of disease progression was 75% at 18 months and 80% at 60 months after therapy. The chronology of the t-AML and cytogenetics are shown in Table 1, and the correlation with administered activity of ^{131}I-MIBG and red marrow dose is shown in Table 2.

Patient 1

A 13-year-old boy (UPN 37), diagnosed with stage 4 neuroblastoma with a primary abdominal mass, was treated with five cycles of chemotherapy following the N6 protocol containing vincristine, cyclophosphamide, doxorubicin, cisplatin, and etoposide. His bone and bone marrow metastases completely resolved with the chemotherapy. At the end of chemotherapy, surgery was attempted but the primary mass was unresectable. Five-and-a-half months after diagnosis, he was given 800 mCi (29.6 GBq) of ^{131}I-MIBG (14 mCi/kg), with a partial response in the primary tumor. This was followed by autologous (purged) bone marrow transplantation using a conditioning regimen consisting of carboplatin, melphalan, and etoposide. On recovery, the patient was also given anti-GD2 antibody (Ch 14.18) with IL-2. Two months later, gross total resection of the residual mass was accomplished, resulting in complete remission. After 6 months of mainte-

TABLE 1. *Chronology of secondary AML*

Patient	Dx NB to MIBG (months)	Chemotherapy duration (months)	MIBG to MDS (months)	Cytogenetic abnormalities
1	6	5	12	−7q/−5
2	86	67	11	−7/+2q37
3	36	24	7	−11 and +12

TABLE 2. *^{131}I-MIBG activity and red marrow dose*

Patient	^{131}I-MIBG/kg GBq/kg (mCi/kg)	Cumulative ^{131}I-MIBG GBq (mCi)	Red marrow dose (cGy)
1	0.529 (14.3)	29.6 (800)	217
2	1.339 (36.2)	32.5 (879)	690
3	0.692 (18.7)	21.1 (570)	502

nance therapy with 13-cis-retinoic acid, the patient developed refractory anemia with ringed sideroblasts (RARS) and abnormal cytogenetics with monosomy of chromosome 7q and chromosome 5 (−7q/−5). Allogeneic matched sibling bone marrow transplantation was performed after conditioning with busulfan and cyclophosphamide. Three months after transplantation, a bone marrow examination showed the patient had progressed to acute myeloblastic leukemia with monosomy 5 (−5) (Fig. 2). One hundred days after transplantation, he died of pulmonary edema/ARDS.

Patient 2

A 6-month-old girl (UPN 23) was diagnosed with stage 4S neuroblastoma, *MYCN* non-amplified, with disease confined to the liver, and was observed. After 1 year 7 months, her liver mass was increased in size and she was found to have abdominal 1ymphadenopathy on a computed tomography scan. She was treated with monthly cycles of cyclophosphamide, cisplatin, etoposide, and doxorubicin[1] and given 1,000 cGy of radiotherapy to the liver. On surgical evaluation, she was found to have viable tumor in the liver and adjacent lymph nodes. She was given further therapy with dactinomycin and vincristine, then cisplatin and 13-cis-retinoic acid, then melphalan. On evaluation, she still had viable unresectable tumor in the liver. She was given more melphalan, alternating with cyclophosphamide and doxorubicin. Approximately 7 years after diagnosis, she was given 439 mCi (16.2 GBq) of ^{131}I-MIBG (18 mCi/kg) therapy after autologous bone marrow harvest and cryopreservation. Since she seemed to have a minor response to the first MIBG therapy, with decrease in pain and urinary catecholamines, a second dose of ^{131}I-MIBG, 440 mCi (16.2 GBq), was given 3 months later. Four months after her first ^{131}I-MIBG therapy, she developed persistent thrombocytopenia and a paucicellular bone marrow with trilineage hematopoiesis. She received her autologous bone marrow but remained pancytopenic. Seven months later, she presented with frank AML with cytogenetic studies showing monosomy 7(45XX, +2q37, −7). She died with AML 14 months after her original ^{131}I-MIBG therapy.

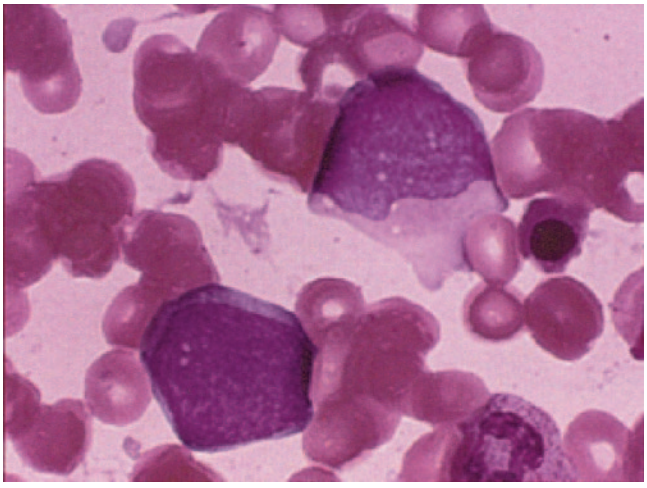

FIGURE 2. Bone marrow aspirate (×1,000) from patient 1. Myeloblasts with diffuse chromatin and multiple nucleoli.

Patient 3

A 9-year-old boy (UPN 55), diagnosed with stage 3 neuroblastoma with *MYCN* gene amplification, was initially treated on CCG-321P1 with cyclophosphamide, DTIC, vincristine, cisplatin, etoposide, and doxorubicin. At the end of chemotherapy, he had two surgeries resulting in complete removal of the primary tumor. Six months later, he had local recurrence and bone marrow metastases. He was treated with cisplatin and 13-cis-retinoic acid for 3 months, during which time the tumor grew. Topotecan and cyclophosphamide were given for two cycles with no response, then two cycles of buthionine sulfoximine with melphalan were given without response. Radiotherapy to the abdomen was given twice, 3,060 cGy and 2,340 cGy respectively, 3 months apart. Fenretinide, an apoptotic agent, was given for eight cycles, but the patient eventually developed progressive disease in the abdomen. Three months after this, approximately 3 years after diagnosis, he was treated with 570 mCi (21.1 GBq) of ^{131}I-MIBG therapy (18 mCi/kg). The abdominal tumors remained stable for 6 months and then progressed. Seven months after MIBG therapy, he was diagnosed with refractory anemia that progressed to blasts in the peripheral blood. Cytogenetic study showed two different clones, one with trisomy 12 and another with monosomy 11. He was given thalidomide, cisplatin, and 13-cis-retinoic acid without response. He died 4 months after the diagnosis of MDS, 10 months after ^{131}I-MIBG therapy, due to his secondary MDS.

Literature Review

A review of all available publications reporting treatment of patients with neuroblastoma with ^{131}I-MIBG was performed. A total of approximately 500 patients have been reported in the literature as having received ^{131}I-MIBG treatments. This includes 44 at diagnosis, 390 with refractory or relapsed disease, and 50 treated with a combination of ^{131}I-MIBG and high-dose chemotherapy with stem cell rescue. Only three patients, in addition to the three reported here, were reported to have developed secondary leukemia, including one patient with M5 subtype, one with M1, and one with chronic myelomonocytic leukemia.[6,7] All three patients had refractory heavily pretreated neuroblastoma, with heavy exposure to alkylating agents, etoposide, and radiotherapy. Cytogenetics were normal in one patient, showed trisomy of chromosome 8 in another, and were not done in the third. There has also been one case of secondary leukemia[9] reported out of more than 150 patients treated with ^{131}I-MIBG for neuroendocrine tumors.[10,11] This patient developed M6 t-AML with del (5q) 8 years after receiving 800 mCi of ^{131}I-MIBG for medullary thyroid carcinoma.

DISCUSSION

We have reviewed the literature regarding ^{131}I, the radionuclide with which MIBG is tagged, and the incidence of SMNs, in particular secondary leukemias. We found only three other patients with neuroblastoma mentioned in the literature who developed secondary acute leukemia following ^{131}I-MIBG therapy.[6,7] All had heavy prior exposure to alkylating agents, epipodophyllotoxins, and radiotherapy. Secondary MDS or AML is rare after treatment with ^{131}I alone for thyroid cancer. Dottorini et al treated 627 patients with ^{131}I for thyroid diseases without a single second neoplasm.[12] Similarly, Hall et al reviewed the Swedish experience of over 46,988 patients exposed to ^{131}I for diagnostic or therapeutic reasons and found the incidence of leukemia in this population mirrored that of the general population, with leukemia rarely seen except after high doses of ^{131}I exceeding 800 mCi.[13] It would appear that the bone marrow dose of radiation accumulated by our patients, which was considerably larger than in the usual ^{131}I treatment of thyroid cancer, may have contributed to the development of t-AML, but to what extent is unknown.

Therapy-related malignant myeloid disorders have emerged as serious late complications of cancer treatment in as many as 5% to 10% of patients who are apparently "cured" of a primary neoplasm with aggressive multimodal regimens. In 1977, Rowley et al published the first report of a group of patients who developed t-AML or MDS as a second neoplasm after treatment of another cancer.[14] Since then, distinctive clinical and cytogenetic patterns have been associated with medical exposure to specific agents. Most patients with therapy-related AML and MDS previously received chemotherapeutic agents that alkylate DNA (with or without radiation). These cases typically involve a latency of 3 to 7 years between genotoxin exposure and disease onset, a myelodysplastic prodrome, and frequent loss of chromosomes 5 and/or 7 (−5 and/or −7) or deletions involving the long arms of these chromosomes {del(5q)/del(7q)}.[15] Another subtype of therapy-related AML develops after therapy with drugs that inhibit topoisomerase II, such as etoposide. These cases are characterized by a shorter interval between cytotoxic therapy and clinical signs, overt leukemia at presentation, and balanced translocations that usually involve the *MLL* gene located on 11q23.[16] Both subtypes of therapy-related myeloid disease carry a poor prognosis. Therapy-related MDS and AML are growing in clinical importance as increasingly aggressive multiagent chemotherapeutic regimens are being used to treat many common malignancies.

Certainly, our small group of patients was exposed to a significant dose of alkylators and epipodophyllotoxins prior to (and, in one case, after) ^{131}I-MIBG therapy. In addition, Kushner et al[5] observed a higher incidence of t-AML in children treated for neuroblastoma with increasing chemotherapy dose intensity. While none of 50 low-risk neuroblastoma patients with minimal disease treated without cytotoxic chemotherapy developed t-AML, 7% of 53 previously untreated patients given high-dose cyclophosphamide, with doxorubicin, etoposide, and cisplatin, developed t-AML, a cumulative incidence almost double that of our patients treated with ^{131}I-MIBG. Cytogenetic analysis of leukemic cells demonstrated monosomy 7 in many of these patients, a finding that strongly implicates alkylator exposure in leukemogenesis.

However, radiation therapy has also been linked to secondary malignancies in the literature. Radiation represents waveform energy with electrical and magnetic properties. Most radiation sources used for cancer therapy involve high-energy photons, which displace electrons from their orbit, thereby producing ions. Although x-rays can cause direct damage to cellular components, most damage occurs indirectly when x-rays ionize water to generate reactive species, including H_2O_2, O_2^-, and hydrated electrons that generate most of the cellular damage. Radiation causes DNA single-strand breaks, which disrupt the phosphodiester bond in the backbone of the DNA and sometimes result in point mutations and double-strand breaks, and thus to large-scale genomic changes including chromosomal deletions, rearrangements, and homologous recombination.

A possible causal relationship between x-rays and cancer was described shortly after the discovery of x-rays. Radiation exposure was subsequently implicated in the observed increased risk of AML and MDS among radiologists and atomic bomb survivors. Limited cytogenetic data from some of these cases revealed chromosome 7 deletions (−7). While therapeutic exposure to radiation or alkylating agents is independently associated with an excess risk of SMN, important similarities and differences are known.

Both radiation and alkylating agents are strongly implicated in the subsequent development of t-MDS and t-AML, and the myeloid malignancies that are detected after radiotherapy and alkylator therapy share morphologic, cytogenetic, and biologic features.[17] Most cases of t-MDS/t-AML diagnosed in patients who received multimodal therapy are attributable to alkylating agents, and the incidence is related to alkylator dose intensity. In contrast, radiotherapy is most strongly associated with treatment-induced sarcomas (particularly arising in the radiation field) but has been linked to many other solid tumors. For example, long-term survivors of Hodgkin disease show a 5- to 18-fold increased risk of developing any SMN, with AML being the most common.[18] The risk of leukemia is limited primarily to the first 10 years following treatment, while solid tumors typically occur later, with the risk continuing to rise up to 30 years later.[18]

Studies addressing whether combined modality therapy confers a greater risk for t-MDS/t-AML than either modality alone have arrived at opposing conclusions. This discrepancy may arise from multiple confounding factors such as the cumulative dose of chemotherapy, volume irradiated, and patient age at the time of treatment. In a cooperative study of late effects of childhood cancer, all patients with t-AML or t-MDS had received radiation and/or alkylator

therapy. While the mean bone marrow dose of radiation was 1,000 cGy, no statistically significant difference in the risk of secondary leukemia was identified based on radiation dose. However, a dose-response was observed in relation to alkylator exposure.[19] Similarly, Kuttesch et al[20] described the incidence of secondary malignancy and secondary sarcomas in childhood survivors of Ewing sarcoma, a cancer treated with a dose-intensive regimen using drugs and radiation comparable to that used in the treatment of neuroblastoma. While several patients in this retrospective study developed secondary leukemias (both ALL and AML), only the cumulative incidence rate of secondary sarcoma was dependent on the radiation dose.

CONCLUSIONS

The three patients all received high-dose alkylator and etoposide therapy plus external beam radiation in addition to ^{131}I-MIBG therapy. Two of the patients had the typical cytogenetic changes seen after alkylating agents and radiotherapy. Whether radiation adds to the risk of developing therapy-related leukemia is currently debated in the literature. Given our report and that of other groups, this potential complication of targeted radionuclide therapy should be carefully monitored, though it would appear that the risk of death from progressive disease in this relapse population far outweighs the risk of death from second malignant neoplasm.

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