Secondary childhood acute myeloid leukemia with complex karyotypic anomalies including monosomy 7, monosomy 5 and translocation (1;10) after $^{131}$I-metaiodobenzylguanidine therapy for relapsed neuroblastoma

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The prognosis for relapsing or refractory neuroblastoma (NB) remains dismal, with a five-year disease-free survival of <20%, and no effective salvage treatment has been identified so far. $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) has come to play an essential role in the imaging and therapy of NB over the past 30 years. The role of $^{131}$I-MIBG in the treatment of NB is continually expanding. $^{131}$I-MIBG treatment together with cumulative doses of other alkylating agents has potential serious late side effects such as myelodysplasia and leukemia, although rare. We describe a secondary acute myeloid leukemia case with complex karyotypic anomalies that included monosomy 5, monosomy 7 and translocation (1;10) in a child with relapsed NB who received therapeutic $^{131}$I-MIBG.

Key words: $^{131}$I-metaiodobenzylguanidine, monosomy 5 and 7, neuroblastoma, secondary myeloid leukemia, translocation (1;10).

High-risk neuroblastoma (NB) continues to have a high mortality rate in developing and underdeveloped countries despite extensive research and treatment. $^{131}$I-metaiodobenzylguanidine ($^{131}$I-MIBG) therapy has mainly been used for the treatment of refractory or relapsed NB. Since this patient population has a dismal prognosis, little is known about the late effects of $^{131}$I-MIBG therapy on these young patients. The contribution of radiolabeled $^{131}$I-MIBG to a specific late effect can also be difficult to ascertain since these patients have been heavily pretreated with other toxic therapies. Despite these limitations, several groups have reported their experience with secondary malignancies in patients treated with $^{131}$I-MIBG for NB.

We describe a secondary acute myeloid leukemia (AML) with complex karyotypic anomalies that included translocation (1;10), monosomy 5 and monosomy 7 in a child with relapsed NB who received therapeutic $^{131}$I-MIBG.

Case Report

A 15-month-old girl was diagnosed as having a left localized, unresectable, thoracic-paraspinal ganglioneuroblastoma of the stroma-rich, intermixed subtype. The left-sided thoracic ganglioneuroblastoma showed infiltration of the intervertebral foramina and spinal canal without spinal cord compression. She was treated with chemotherapy according to the Turkish Society of Pediatric Oncology protocol (TPOG NBL 93). There was no reduction in tumor size after administration of eight courses of chemotherapy, consisting of vincristine sulfate, ifosfamide (total cumulative dose 36 g/m²), cyclophosphamide (6 g/m²), dacarbazine...
(5 g/m²), doxorubicin (240 mg/m²), etoposide (1.2 g/m²), and cisplatin (600 mg/m²). The tumor was then subtotally excised. The patient received 3060 cGy of radiotherapy and six courses of maintenance chemotherapy postoperatively. She received 100 mCi of ¹³¹I-MIBG therapy for local recurrence four months later. Her condition seemed stable following treatment. However, she developed anemia and thrombocytopenia due to hypocellular bone marrow with trilineage hematopoiesis without any evidence of dysplasia or macrocytosis in the fifth month of follow-up after ¹³¹I-MIBG therapy and then AML with M1 subtype at the end of two years. Her bone marrow cytogenetic analysis showed multiple chromosomal anomalies that included monosomy 5, monosomy 7 and translocation (1;10) (Fig. 1). She died due to the secondary AML 27 months after the ¹³¹I-MIBG therapy.

Discussion

Neuroblastoma (NB) has an incidence of about 10 cases per million children aged 0-14 years, and it is the most common pediatric extracranial solid tumor. It accounts for 7.8% of all childhood malignancies, and is the third leading cause of death because of cancer. The treatment of NB depends upon a patient’s estimated risk of relapse, based upon identified clinical and biological prognostic features. The combination of chemotherapy and surgical resection is the standard approach with excellent outcomes for patients with locally aggressive tumors (International Neuroblastoma Staging System 3) but favorable biology. Patients with metastatic disease at initial diagnosis who are older than 18 months of age and patients with MYCN-amplified locoregional tumors are treated with intensive multimodal therapy with chemotherapy, surgical resection, local radiation, and consolidation with high-dose therapy with autologous hematopoietic stem cell rescue. While this intensive approach has been shown to improve outcome, patients with high-risk disease frequently relapse and fewer than 50% of these patients will be long-term survivors. High-dose chemotherapy and autologous hematopoietic stem cell rescue seems to be a good treatment option for children with high-risk NB. It results in higher overall and event-free survival rates than conventional therapy, although possible higher levels of adverse effects should be kept in mind.

¹³¹I-metaiodobenzylguanidine (¹³¹I-MIBG) has come to play an essential role in the imaging and therapy of NB over the past 30 years. The role of ¹³¹I-MIBG in the therapy of NB is continually expanding. It has proven to be one of the most effective therapies in patients with relapsed and refractory disease with a response rate close to 40%. Matthay et al. and Troncone et al. reported that the objective response rate was 18% in the treatment of patients with refractory NB with ¹³¹I-MIBG. In a German study that included 12 patients with relapsed or refractory NB treated with ¹³¹I-MIBG, the objective response rate was 66% and the median survival was 369 days after ¹³¹I-MIBG therapy. In the United Kingdom Children’s Cancer Study Group study, the objective rate was 33% and the median survival was 1 year. Hoefnagel et al. reported this rate as 56%. However, the response rates varied between 27% and 80% in combination studies of ¹³¹I-MIBG in patients with relapsed or refractory NB. The main reported toxicity of ¹³¹I-MIBG therapy in these studies was myelosuppression. DuBois et al. reported that 36% of their patients required stem cell support for prolonged myelosuppression in their series. Little is known about the late effects of ¹³¹I-MIBG therapy in patients with NB. The risk of a second cancer will have to be taken into consideration should ¹³¹I-MIBG treatment become more broadly employed in
the therapeutic strategy for NB\textsuperscript{17}. A report by Weiss et al.\textsuperscript{3} details the development of secondary leukemia in three of 95 patients with refractory neuroblastoma. These three cases were detected 7, 11 and 12 months after \textsuperscript{131}I-MIBG therapy, and they were characterized by variable losses of chromosome 5, 7 or 11 or by gain of chromosome 12. The cumulative incidence of developing a secondary leukemia or myelodysplastic syndrome (MDS) was less than 4% at five years. In addition to leukemia, Garaventa et al.\textsuperscript{17} documented the occurrence of schwannoma and rhabdomyosarcoma following \textsuperscript{131}I-MIBG therapy. All had heavy prior exposure to alkylating agents, epipodophyllotoxins and radiotherapy\textsuperscript{3}. It is known that numerous studies have confirmed that treatment with topoisomerase II inhibitors and alkylating agents increases the probability of secondary AML. The risk of secondary AML is influenced by treatment factors, including the schedule of administration and concomitant medications\textsuperscript{18}. Our patient was certainly exposed to a significant dose of alkylators and epipodophyllotoxins prior to \textsuperscript{131}I-MIBG therapy. It is therefore difficult to understand the contribution of \textsuperscript{131}I-MIBG therapy to the development of AML.

Patients diagnosed with AML or myelodysplasia that includes monosomy 5 plus monosomy 7 or monosomy 5 plus more than three karyotypic anomalies have been shown to have a worse prognosis\textsuperscript{19-21}. On the other hand, acute leukemia including t(1;10) is rarely reported in the literature. Wan et al.\textsuperscript{22} reported an adult patient with AML with M4 subtype including t(1;10)(p34;p15), but there was no information about the prognosis of the patient. Funato et al.\textsuperscript{23} reported a seven-month-old girl with AML including t(1;10) who underwent bone marrow transplantation because of relapse. She had no local or systemic signs of disease recurrence 12 months after bone marrow transplantation.

In conclusion, \textsuperscript{131}I-MIBG is an alternative treatment for patients with relapsed or refractory NB. Despite its rarity, \textsuperscript{131}I-MIBG treatment with cumulative doses of the other alkylating agents has potential serious late side effects such as myelodysplasia and leukemia. All children who have received \textsuperscript{131}I-MIBG therapy therefore need long-term follow-up because of these side effects.

REFERENCES


