Korean Journal of Pediatrics Vol. 51, No. 2, 2008
DOI : 10.3345/kjp.2008.51.2.214 □ Case Report □

Palliative effect of ^{131}I-MIBG in relapsed neuroblastoma after autologous peripheral blood stem cell transplantation

Yong Jik Lee, M.D. and Jeong Ok Hah, M.D.

Department of Hematology/Oncology, Yeungnam University College of Medicine

Neuroblastoma is one of the most common extracranial solid tumor of childhood, and treatment of refractory neuroblastoma remains a significant clinical problem. Iodine-131-metaiodobenzylguanidine (^{131}I-MIBG) therapy is an alternative approach to treat stage Ⅳ neuroblastoma. We report the palliative effect of ^{131}I-MIBG in three cases of relapsed neuroblastoma after autologous peripheral blood stem cell transplantation. ^{131}I-MIBG is an effective and relatively nontoxic palliative therapy resulting in reduction of pain and prolongation of survival. **(Korean J Pediatr 2008;51:214-218)**

Key Words : Relapsed neuroblastoma, ^{131}I-MIBG, Palliative therapy

Introduction

Neuroblastoma accounts for 8-10% of all childhood malignancies. The prognosis of neuroblastoma is highly variable depending on the age at diagnosis, stage of the disease, and tumor biology. High risk is defined as neuroblastoma occurring in children over 1 year of age with an amplification of the MYCN oncogene or distant metastasis[1]. Despite recent improvements in outcome with intensification of therapy for metastatic neuroblastoma, the long-term prognosis of advanced neuroblastoma remains poor with current survival probability of less than 40%[1, 2].

Multiply relapsed patients have been treated with ^{131}I-MIBG over the last 2 decades for palliative effects[3, 4]. We report the palliative effects of ^{131}I-MIBG in three cases of relapsed neuroblastoma after autologous peripheral blood stem cell transplantation.

Case Report

Case 1

A 4-year-old male presented with fever, generalized weakness with easy fatigability, and left cervical lymph node swelling for 2 weeks. Physical examination revealed a 3×2 cm sized, firm, immobile and non-tender mass in the left cervical area. Laboratory findings were as follows: WBC 9,800/μL, hemoglobin 7.9 g/dL, platelet count 374,000/μL, lactate dehydrogenase (LDH) 602 U/L, serum ferritin 609.19 ng/mL, serum neuron-specific enolase (NSE) 79 ng/mL, 24hr-urine vanillylmandelic acid (VMA) 18.3 mg/day, 24hr-urine homovanillic acid (HVA) 36.6 mg/day. Computed tomography (CT) of chest showed a 3×3 cm sized mass in the paravertebral area. Bone scan revealed hot uptake of the paravertebral area and right femur involving bone marrow. The patient was diagnosed with stage Ⅳ neuroblastoma of paravertebral area. After chemotherapy was given every 4 weeks for 5 cycles (cisplatin 20 mg/m^2 on day 1-4, etoposide 125 mg/m^2 on day 1-3, ifosfamide 2,000 mg/m^2 on day 1-3, adriamycin 10 mg/m^2 on day 1-3), surgical resection of the residual paravertebral mass was performed. The follow-up 24hr-urine VMA and HVA were 1.24 mg/day and 2.51 mg/day and bone scan showed no hot spots in the whole body. An autologous peripheral blood stem cell transplantation (auto-PBSCT) with purging technique using magnetic beads was performed after carboplatin (400 mg/m^2 on days -7, -6, -5, -4), etoposide (200 mg/m^2 on days -7, -6, -5, -4), and melphalan (90 mg/m^2 on days -3, -2). Therapy with all-trans-retinoic acid (ATRA) for 2 weeks every month was given for one and a half years, when the patient complained of hip and lower back pain. An MIBG scintigram showed multiple metastases in the left supraclavicular area and the right acetabulum. Bone marrow

접수 : 2007년 12월 15일, 승인 : 2008년 1월 19일
책임저자 : 하정옥, 영남대학교 의과대학 소아과학교실
Correspondence : Jeong Ok Hah, M.D.
Tel : 053)620-3530 Fax : 053)629-2252
E-mail : johah@med.yu.ac.kr

examination disclosed bone marrow involvement of tumor cells. After 3 cycles of chemotherapy with carboplatin (400 mg/m^2 on day 1 through 3), etoposide (100 mg/m^2 on day 1 through 5), ifosfamide (1,800 mg/m^2 on day 1 through 3), and adriamycin (30 mg/m^2 on day 4), follow-up MIBG scintigram showed hot uptake of left supraclavicular lymph node. The patient was treated with ^{131}I-MIBG at a dose of 4 mCi/kg. Bone pain subsided and he did well for several months. However, residual lesions on the left supraclavicular and right inguinal lymph nodes were shown on MIBG scintigram. Eight months later, he was treated again with ^{131}I-MIBG at the same dose.

Six months after the second ^{131}I-MIBG radiotherapy, the patient developed headache, vomiting and seizure. The MRI of the brain showed a 5×6 cm sized mass with hemorrhage into the left temporal lobe. The mass was entirely surgically resected and histologically was found to be neuroblastoma. Postoperative irradiation of the brain with 3 Gy was followed by a local irradiation of the left supraclavicular metastatic lesion with 3 Gy. The patient was treated with temozolamide (200 mg/m^2/day, for 5 days a month) for 6 months. For the following one year, MIBG scintigram showed no hot uptakes. He has been doing well without any gross evidence of residual lesion.

Case 2

A 5-year-old male presented with intermittent episodes of chest pain. On physical examination, a bean-sized left supraclavicular lymph node was palpable. Laboratory examination showed elevations of the LDH (1,593 U/L), NSE (218 ng/mL), 24hr-urine VMA (31.2 mg/day) and HVA (31.6 mg/day). CBC and serum ferritin were normal. A CT scan of the chest revealed a 3×3 cm sized mass in the posterior mediastinum. A bone scan showed diffuse hot-uptake in the skull, left humerus, right 7th and 10th rib, 4th lumbar spine, and bilateral femurs. Bone marrow examination revealed rosette formed tumor cells. He was diagnosed with stage Ⅳ neuroblastoma. The patient received induction chemotherapy as case 1 followed by surgical resection of posterior mediastinal mass and auto-PBSCT after purging. The follow up 24hr urine VMA, HVA, and serum NSE were 2.1 mg/day, 3.36 mg/day, and 8.98 ng/mL. He had been doing well for 8 months after auto-PBSCT, when he developed a headache and bilateral lower leg pain. MIBG scan showed multiple metastatic lesions of skull, rib, spine, and both femurs. The patient was treated again with induction chemotherapy for 3 cycles. The MIBG scintigram showed no interval change compared with the prechemotherapy scan. Therefore chemotherapeutic regimens were changed to a regimen including carboplatin (500 mg/m^2 on day 1 and 2), etoposide (120 mg/m^2 on days 1-3), ifosfamide (1,800 mg/m^2 on days 1-3), and dacarbazine (250 mg/m^2 on day 1 and 2) for 2 cycles. However, he continued to complain of headache and bone pain as well as persistent metastatic lesions on MIBG scintigram. After receiving ^{131}I-MIBG radiotherapy at 7.5 mCi/kg, bone pain subsided. Another ^{131}I-MIBG radiotherapy was given after one year for persistent metastatic lesions on following up MIBG scintigram. Three and a half years after the recurrence, the patient remained relatively stable and bone pain disappeared. Platelet count was suppressed for 2 months after ^{131}I-MIBG radiotherapy. One year later, third ^{131}I-MIBG radiotherapy at 10 mCi/kg was performed as the multiple lesions of hot uptakes on MIBG scintigram were persistent. The recent follow-up MIBG scintigram showed mild hot uptake of the skull, anterior chest, and bilateral femurs. However, the patient no longer complained of bone pain and was able to resume daily life including school attendance.

Case 3

A 7-year-old male was admitted for abdominal pain and distension for several days. Laboratory findings were as follows: WBC 14,500/μL, hemoglobin 9.7 g/dL, platelet 268,000/μL, LDH 332 U/L, ferritin 134.75 ng/mL, NSE 36 ng/mL, 24hr urine VMA 6.7 mg/day, 24hr urine HVA 5.7 mg/day. CT scan of the abdomen showed an 8×5 cm solitary mass with calcification in left suprarenal area. Bone scan and bone marrow examination demonstrated no metastatic lesions and no bone marrow involvement. Fine needle aspiration confirmed the diagnosis of ganglioneuroblastoma. The patient received complete surgical resection of the tumor followed by postoperative chemotherapy including cisplatin (60 mg/m^2 on day 0), etoposide (100 mg/m^2 on day 2 and 5), cyclophosphamide (900 mg/m^2 on day 3 and 4), and adriamycin (30 mg/m^2 on day 2) for one year. Eleven months later, a recurrent tumor was found in the left kidney as shown on a routine surveillance CT scan. He was treated with left nephrectomy and chemotherapy as in case 1 followed by auto-PBSCT without purging. Two years later, PET-CT showed hot upkake in the left renal area and left humerus. Local irradiation of the left humerus and left renal area with 3 Gy for each area were performed. A year later,

however, the patient complained of abdominal pain and bilateral lower leg pain. MIBG scintigram showed multiple metastases in the liver and lung. The patient was treated with ^{131}I-MIBG at 7.5 mCi/kg once. The patients pain subsided but pancytopenia persisted after ^{131}I-MIBG radiotherapy for 2 months with no interval change on MIBG scintigram.

Discussion

Neuroblastoma is a disease of the sympathicoadrenal lineage of the neural crest, and therefore tumors can develop anywhere along the sympathetic nervous system. Patients with neuroblastoma suffer from the structural effects of abdominal or thoracic tumors and the consequences of the metastases, including bone pain, difficult walking, proptosis or periorbital bruising, and anemia or pancytopenia caused by marrow invasion.

Treatment depends on tumor staging and risk groups. Neuroblastoma can show widely varying courses, such as a spontaneous regression of the tumor or differentiation into either ganglioneuroma or neuroma, or an aggressive progression with widespread metastases. Clinically, infant patients tend to show a favorable prognosis, slow tumor growth or a spontaneous regression, or a high response to chemotherapies, whereas older patients often show rapid tumor growth, metastases, and poor outcomes[5]. Standard treatment programs for patients with high risk neuroblastoma include strongly myelosuppressive induction and consolidation chemotherapy regimens using combinations of alkylating agents, platinum compounds, and topoisomerase II inhibitors. All-trans-retinoic acid and 13-cis-retinoic acid decrease proliferation and induce differentiation in neuroblastoma cell lines, established from refractory tumors, or residual tumor cells that are resistant to cytotoxic agents[1]. However, despite advances in treatment, the prognosis for patients with advanced neuroblastoma in older children is poor because of early metastasis and recurrence[6].

^{131}I-MIBG is radioiodinated analogue of norepinephrine. The chemical structure of MIBG includes the benzyl portion of bretylium with the guanidine group of guanethidine[7]. Any malignant neural crest tumor, showing sufficient uptake and retention of the ^{131}I-MIBG in a tracer study, is a candidate for radionuclide therapy. Standard indications for ^{131}I-MIBG therapy are malignant pheochromocytoma, paraganglioma, neuroblastoma stage III and IV, medullary thyroid carcinoma and symptomatic, metastatic carcinoid tumors.

Treatment with ^{131}I-MIBG has been used in children with neuroblastoma for palliative and recently curative purposes[8, 9]. According to the cumulative experience of several centers abroad, the overall objective response rate is approximately 35% in patients with chemoresistant neuroblastoma after induction chemotherapy or at relapse[10]. There are currently four major methods for determining the therapeutic dose to be delivered: by dosimetry using a tracer dose of MIBG, by dose per body weight, by fixed dose, and by dose escalation in which hematopoietic tissue is harvested for stem cell transplant[11].

Tracer doses of ^{131}I- or ^{123}I-MIBG are now used routinely for neuroblastoma staging and response evaluations. In general, at much higher doses (3-18 mCi/kg), ^{131}I-MIBG shows effect against refractory neuroblastoma, with response rates of 20-50%[12]. ^{131}I-MIBG infusion as a single agent in a phase I dose-escalation study showed a response rate of 37% in children with relapsed neuroblastoma. At doses of 15 mCi/kg or higher, response rates were apparently greater. In some patients, delayed effects were shown with significant responses at 12 months after treatment with ^{131}I-MIBG. However, almost half of the patients required autologous hematopoietic stem cell infusion with bone marrow or peripheral blood stem cell support due to the prolonged myelosuppression[9]. In addition many patients with stage IV neuroblastoma may not tolerate grade 4 hematopoietic toxicity or do not have a stem cell product available. Howard et al[9] suggested that increasing the infusion amount improved overall response. Therefore multiple infusions of high dose ^{131}I-MIBG were feasible and effective in refractory neuroblastoma, but were limited by hematologic toxicity, especially thrombocytopenia. Matthay et al[8] demonstrated that 12 mCi/kg was the maximum tolerated dose due to protracted grade 4 hematopoietic toxicity at higher dose levels. Kang et al[13] reported that a single infusion of ^{131}I-MIBG at 12 mCi/kg or less was an effective and relatively nontoxic method for palliative treatment of neuroblastoma. In our cases, patients received multiple infusions of ^{131}I-MIBG at 4-10 mCi/kg and showed substantial clinical improvement, including resolution of pain from progressive tumor without severe hematologic toxicities.

Thrombocytopenia in excess of neutropenia has frequently been described as a complication of MIBG therapy even with a single infusion[8, 14]. In our cases, neutropenia was usually transient and without associated infection. Matthay et al[15] reported that despite myelosuppression, the incidence

of grade 3 to 4 proven infection was low (11%) and the acute toxic death rate was only 1%.

Acute non-hematologic grade 3 and 4 toxicities were infrequent. Cardiovascular toxicities included arrhythmia, capillary leak syndrome, edema, hypotension, and hypertension. Pulmonary toxicities included acute respiratory distress syndrome, dyspnea, and hypoxia. Some cases had gastrointestinal toxicity which was related to mucositis and had low glomerular filtration rate (GFR). Hepatic toxicities included hepatomegaly, hypoalbuminemia, and elevations in bilirubin, alkaline phosphatase, gamma-glutamyltransferase levels, AST, and ALT[16]. Myelodysplastic syndrome and leukemia have been reported rarely as a late complication of ^{131}I-MIBG radiotherapy. Weiss et al[17] reported that ^{131}I-MIBG radiotherapy may contribute to the risk of secondary leukemia in patients who have received previous intensive chemotherapy. Hall et al[18] reported that the incidence of leukemia was increased after cumulative doses of 800 mCi. In our report, only thrombocytopenia of grade 2 toxicity was developed in 2 patients, and pancytopenia of grade 3 toxicity persisting for 2 months was observed in the other patient. Non-hematologic side effects were not seen.

In conclusion, submyeloablative dose of ^{131}I-MIBG is effective and safe in providing palliative therapy for recurrent refractory neuroblastoma patients. Its clinical applicability is limited to the patients with no hope for cure at present. Possible future clinical trials to improve the therapeutic index of this unique targeted agent may focus on adequate dose escalation and interval and combining ^{131}I-MIBG with conventional chemotherapy or other potential radiosentitization agents.

한 글 요 약

자가 말초혈조혈모세포이식 후 재발된 신경모세포종 3예에서 ^{131}I-MIBG의 고식적 치료 효과

영남대학교 의과대학 소아과학교실

이 용 직 · 하 정 옥

신경모세포종은 소아에서 발생하는 흔한 두개외 고형 종양 중 하나로서 진행된 경우 고용량 항암요법 및 자가 말초혈조혈모세포이식 후에도 재발이 잘 되어 예후가 매우 나쁘다. Iodine-131 metaiodobenzylguanidine (^{131}I-MIBG)는 치료에 잘 반응하지 않는 신경모세포종 4기 환자를 위한 대증적 치료 요법으로 제한적으로 이용되어 왔다. 저자들은 자가 말초혈조혈모세포이식 후 재발된 신경모세포종 3례에서 ^{131}I-MIBG를 이용하여 통증을 경감시키고 생존 기간을 늘이는 고식적인 치료 효과를 얻어 이들에 대한 증례 보고를 하는 바이다.

References

1) Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. N Engl J Med 1999;341:1165-73.
2) Klingebiel T, Bader P, Bares R, Beck J, Hero B, Jürgens H, et al. Treatment of neuroblastoma stage 4 with ^{131}I-meta-iodo-benzylguanetidine, high dose chemotherapy and immunotherapy. A pilot study. Eur J Cancer 1998;34:1398-402.
3) Garaventa A, Guerra P, Arrighini A, Bertolazzi L, Bestagno M, De Bernardi B, et al. Treatment of advanced neuroblastoma with I-131 meta-iodobenzylguanidine. Cancer 1991;67:922-8.
4) Yanik GA, Levine JE, Matthay KK, Sisson JC, Shulkin BL, Shapiro B, et al. Pilot study of iodine-131-metaiodobenzylguanidine in combination with myeloablative chemotherapy and autologous stem-cell support for the treatment of neuroblastoma. J Clin Oncol 2002;20:2142-9.
5) Riley RD, Heney D, Jones DR, Sutton AJ, Lambert PC, Abrams KR, et al. A systematic review of molecular and biological tumor markers in neuroblastoma. Clin Cancer Res 2004;10:4-12.
6) Matthay KK, Atkinson JB, Stram DO, Selch M, Reynolds CP, Seeger RC. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. J Clin Oncol 1993;11:2226-33.
7) Hickeson MP, Charron M, Maris JM, Brophy P, Kang TI, Zhuang H, et al. Biodistribution of post-therapeutic versus diagnostic ^{131}I-MIBG scans in children with neuroblastoma. Pediatr Blood Cancer 2004;42:268-74.
8) Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, et al. Phase I dose escalation of ^{131}I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. J Clin Oncol 1998;16:229-36.
9) Howard JP, Maris JM, Kersun LS, Huberty JP, Cheng SC, Hawkins RA, et al. Tumor response and toxicity with multiple infusions of high dose 131I-MIBG for refractory neuroblastoma. Pediatr Blood Cancer 2005;44:232-9.
10) Troncone L, Galli G. The role of [131I]Metaiodobenzylguanidine in the treatment of neural crest tumors. Proceedings of an international workshop. Rome, Italy, September 6-7, 1991. J Nucl Biol Med 1991;35:177-363.
11) Tepmongkol S, Heyman S. 131I MIBG therapy in neuroblastoma: mechanisms, rationale, and current status. Med Pediatr Oncol 1999;32:427-31.
12) Klingebiel T, Berthold F, Treuner J, Schwabe D, Fischer M, Feine U, et al. Metaiodobenzylguanidine (MIBG) in treatment of 47 patients with neuroblastoma: results of the German Neuroblastoma Trial. Med Pediatr Oncol 1991;19:

84-8.
13) Kang TI, Brophy P, Hickeson M, Heyman S, Evans AE, Charron M, et al. Targeted radiotherapy with submyeloablative doses of ^{131}I-MIBG is effective for disease palliation in highly refractory neuroblastoma. J Pediatr Hematol Oncol 2003;25:769-73.
14) De Kraker J, Hoefnagel CA, Caron H, Valdes Olmos RA, Zsiros J, Heij HA, et al. First line targeted radiotherapy, a new concept in the treatment of advanced stage neuroblastoma. Eur J Cancer 1995;31:600-2.
15) Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng SC, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol 2007;25:1054-60.
16) Matthay KK, Tan JC, Villablanca JG, Yanik GA, Veatch J, Franc B, et al. Phase I dose escalation of iodine-131-metaiodobenzylguanidine with myeloablative chemotherapy and autologous stem-cell transplantation in refractory neuroblastoma: a new approaches to Neuroblastoma Therapy Consortium Study. J Clin Oncol 2006;24:500-6.
17) Weiss B, Vora A, Huberty J, Hawkins RA, Matthay KK. Secondary myelodysplastic syndrome and leukemia following 131I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. J Pediatr Hematol Oncol 2003;25:543-7.
18) Hall P, Holm LE. Cancer in iodine-131 exposed patients. J Endocrinol Invest 1995;18:147-9.