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Successful second autologous peripheral blood stem cell transplantation conditioned with total body irradiation for progressive neuroblastoma after recurrence

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A girl with recurrent neuroblastoma was successfully treated with second autologous stem cell transplantation (SCT) conditioned with total body irradiation (TBI). This patient was diagnosed as stage IV neuroblastoma at the age of 18 months. Pathological finding was stroma-poor unfavorable histology and amplification of MYCN gene was extremely high (153 copies). In spite of autologous SCT with non-TBI regimen in the status of disease-free, neuroblastoma relapsed at the primary site 6 months later. Second autologous SCT conditioned with TBI and melphalan was performed although the tumor was progressive. Over 3 years after second SCT, she has been well with no evidence of further recurrence of neuroblastoma, but she was complicated with permanent atrophy of left kidney.
TBI might be effective for relapsed neuroblastoma who previously received SCT with non-TBI regimen.

Key words: neuroblastoma, stem cell transplantation, total body irradiation, renal atrophy

INTRODUCTION

Neuroblastoma is one of common solid tumors in childhood. Recently, aggressive multi-agents chemotherapy with surgical resection and/or radiotherapy and subsequent myeloablative chemotherapy followed by autologous stem cell transplantation (SCT) have improved the outcome of neuroblastoma with poor prognostic factors such as Stage IV, age over 1 year, high amplification of MYCN gene. However, about 40-60% of these patients have recurrence and progression of the tumor at local or distant lesions [1-4]. In case of recurrence, long-term survival is quite difficult, and adequate salvage treatment remains unclear.

We experienced a girl with recurrent neuroblastoma who was successfully treated with second autologous SCT conditioned with total body irradiation (TBI) although the disease was progressive.

CASE REPORT

An 18 month-old girl was admitted to the hospital because of abdominal distention. The radiological findings on admission revealed massive intra-abdominal tumor with ascites, and additionally with pleural effusion. Pathological diagnosis of the tissue obtained by open-biopsy was neuroblastoma (stroma-poor, unfavorable Shimada's histology), and cytological analysis of the pleural effusion revealed intrathoracic invasion of neuroblastoma cells. Southern blot analysis for MYCN gene in tumor cells revealed extremely high amplification for 153 copies. Although distant metastasis to bone or bone marrow was absent, the clinical stage was evaluated as stage IV according to International Neuroblastoma Staging System (INSS) because of the intrathoracic dissemination across the diagram.

Induction chemotherapy containing vincristine (VCR), cisplatin (CDDP), cyclophosphamide (CPM), and tetrahydropyranyl adriamycin (THP-ADR) was effective, so that the tumor mass was dramatically reduced and pleural effusion was diminished.

As the result of consolidation chemotherapy with CPM, CDDP, THP-ADR, and VCR according to the Japan National Protocol [5] for 4 cycles, the primary retroperitoneal tumor became resectable.

After complete resection of the residual primary tumor, in the status of disease-free, myeloablative chemotherapy with calboplatin 1500 mg/m^2, etoposide 500 mg/m^2, and melphalan 200 mg/m^2 followed by non-purged autologous peripheral blood stem cell transplantation (PBSCT) was performed without any complications. For maintenance therapy, 13-cis-retinoic acid was initiated 2 months after completion of SCT.

However, 6 months later, computed tomography (CT) showed the localized tumor at the primary site overlying on the left kidney. After removal of this tumor with dissection of regional lymph nodes, alternative chemotherapy was introduced with ifosfamide, irinotecan, topotecan and others. Pathological findings and MYCN gene amplification were the same as those at the initial diagnosis.

Eleven months after the first recurrence, the second recurrence of neuroblastoma at the same site was found. Although the recurrent tumor was removed completely, abdominal CT on seventh day after operation showed additional multiple tumors in her left abdominal site (10th thoracic para-vertebra, left kidney,

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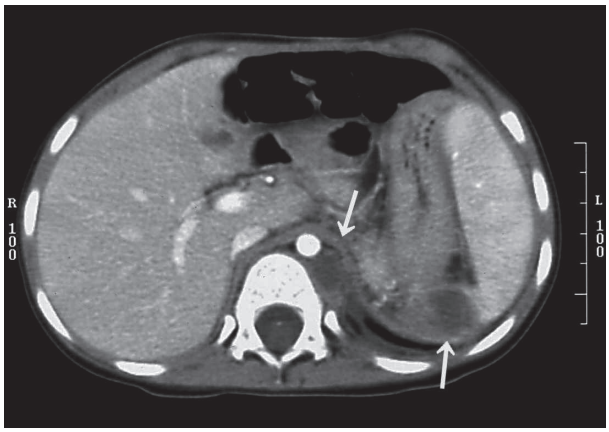

Fig. 1 Recurrent multiple tumors in the left abdominal area before second SCT.

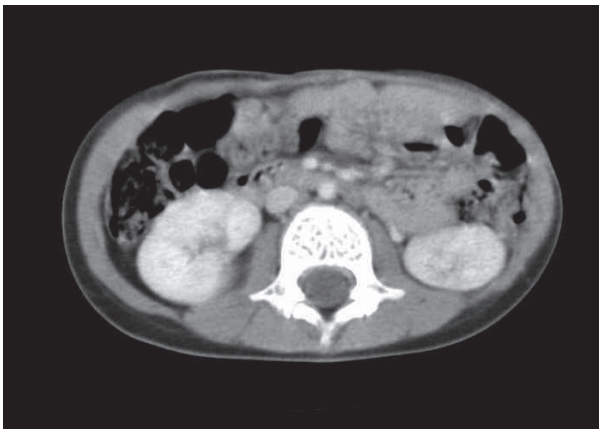

Fig. 2 Computed tomography revealed atrophy of left kidney without neuroblastoma after second SCT.

and near the descending aorta). We planned irradiation therapy of 19.8 gray (Gy; 1.8 Gy/dose × 11 times) at the affected hemi-abdominal area (including left kidney), followed by subsequent second autologous PBSCT conditioned with 10 Gy of TBI (2.0 Gy/dose × 5 times) and melphalan 180 mg/m^2. 2.9×10^8/kg of non-purged peripheral blood stem cells (2.4×10^6/kg of CD34 positive cells) collected in second remission was infused 48 hours after conditionings. As acute toxicity, she developed grade II gastrointestinal symptoms without prolonged nutritional support, and grade IV hematological effect, especially delayed recovery of platelet counts requiring transfusion of platelet concentration until the day of 90 after the second SCT.

Although the acute toxicity was tolerated, the left kidney gradually became atrophic about a half in size compared with the previous CT image before the second SCT. Another kidney remains intact and parameters of renal function such as glomerular filtration rate and serum creatinine level are within normal ranges.

Over three years after the second SCT, the patient has been well without evidence of tumor, and with good performance status of her life. Although the left kidney remains atrophic on the radiological findings, her renal function has been wholly preserved within normal limits.

DISCUSSION

Although stage III and IV neuroblastoma with poor prognostic factors seems to be curable by myeloablative therapy with hematopoietic stem cell support, 40-60% of these patients have recurrence and progression at primary lesion or distant sites. Treatment strategy for such recurrent neuroblastoma is not established yet, and the prognosis of these children is quite miserable.

It is controversial that TBI is indicated as a part of conditioning regimen for myeloablative treatment with SCT or not. Some of the studies concluded that TBI for SCT regimen was beneficial for cure of neuroblastoma patients [4, 6, 7]. Other studies reported that SCT with non-TBI regimen resulted in survival rates which were not significantly different from that of SCT with TBI containing regimen [8-11].

Our case of stage IV neuroblastoma had frequent recurrences at the primary site and finally extended in her abdomen after non-TBI regimen SCT. In spite of the progressive nature of the tumor, we tried subsequent second SCT with TBI-containing regimen after local irradiation. As a result, tumor cells were successfully eradicated and long-term disease-free-survival was achieved. Second SCT with TBI could possibly be a salvage therapy for recurrent neuroblastoma after SCT with non-TBI regimen.

Based on the reports that local irradiation to the primary site would attribute to the improvement of over-all survival [12, 13], it would be reasonable to speculate that our patient might have been in first or second remission if local irradiation had been performed before recurrence.

Our patient was complicated with irreversible renal atrophy after treatment. Fortunately, her renal function is not severely affected as to require additional care for renal dysfunction. Both aggressive surgical intervention and radiotherapy as the cause of renal atrophy were reported in a few literatures [14-17]. Tanabe *et al.* reported that, out of fifty-eight neuroblastoma patients who received aggressive surgical intervention with regional lymph nodes dissection, six patients were complicated with unilateral renal atrophy [15]. As regards to irradiation effect, Jenkins *et al.* reported two patients with renal atrophy who underwent irradiation therapy of 30 Gy or more to the kidney [18]. Cohen *et al.* mentioned that fractionated irradiation of 23-30 Gy will injure the kidney tissue [19].

Although the cause of renal atrophy in our patient is not determined, both aggressive surgical intervention and irradiation of 29.8 Gy (local; 19.8 Gy, TBI; 10 Gy) for cure might contribute to the development of unilateral renal atrophy. Additionally, high cumulative doses of chemotherapeutic agents (especially platinum and anthracyclines), might at least in part be attributed to her permanent renal damage.

CONCLUSION

Autologous SCT with TBI regimen might be effective not only for the newly diagnosed patients but also for recurrent neuroblastoma after SCT with non-TBI regimen. And we have to pay attention to renal atrophy as a long-term complication in the patients who received aggressive treatments combined with surgery, radiotherapy, and chemotherapy.

REFERENCES

1) Ikeda H, August CS, Goldwein JW, Ross III AJ, D'Angio GJ, Evans AE. Sites of relapse in patients with neuroblastoma following bone marrow transplantation in relation to preparatory "debulking" treatments. J Pediatr Surg 1992; 27: 1438-1441.
2) Matthay KK, Atkinson JB, Stram DO, Selch M, Reynolds CP. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. J Clin Oncol 1993; 11: 2226-2233.
3) Verdeguer A, Munoz A, Canete A, Pardo N, Martinez A, Donat J, *et al*. Long-term results of high-dose chemotherapy and autologous stem cell rescue for high-risk neuroblastoma patients: a report of the Spanish working party for BMT in children (Getmon). Pediatr Hematol Oncol 2004; 21(6): 495-504.
4) Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, *et al*. Treatment of high-riswk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. N Engl J Med 1999; 341: 1165-1173.
5) Kaneko M, Tsuchida Y, Mugishima H, Ohmura N, Yamamoto K, Kawa K, *et al*. Intensified chemotherapy increases the survival rates in patients with Stage 4 neuroblastoma with MYCN amplification. J Pediatr Hematol Oncol 2002; 24: 613-621.
6) Haas-Kogen DA, Swift PS, Selch M, Haase GM, Seeger RC, Gerbing RB, *et al*. Impact of radiotherapy for high-risk neuroblastoma: a Children's Cancer Group study. Int J Radiat Oncol Biol Phys 2003; 56: 28-39.
7) von Allmen D, Grupp S, Diller L, Marcus K, Fcklund K, Meyer J, *et al*. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. J Pediatr Surg 2005; 40(6): 436-441.
8) F Berthold, J Boos, S Burdach, Erttmann R, Henze G, Hermann J, *et al*. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomized controlled trial. Lancet Oncology 2005; 6: 649-658.
9) Valteau-Couanet D, Benhamou E, Vassal G, Stambouli F, Lapierre V, Couanet D, *et al*. Consolidation with a buslfan-containing regimen followed by stem cell transplantation in infants with poor prognosis Stage 4 neuroblastoma with MYCN amplification. Bone Marrow Transplant 2000; 25: 937-942.
10) Kushner BH, O'Reilly RJ, Mandell LR, Gulati SC, LaQuaglia M, Cheung NV. Myeloablative combination chemotherapy without total body irradiation for neuroblastoma. J Clin Oncol. 1991; 9: 274-279.
11) Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, and Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. Pediatr Blood Cancer 2005; 44(4): 348-357.
12) SM Bradfield, JG Douglas, DS Hawkins, Sanders JE, Park JR. Fractionated low-dose radiotherapy after myeloablative stem cell transplantation for local control in patients with high-risk neuroblastoma. Cancer 2004; 100: 1268-1275.
13) Kushner BH, Wolden S, LaQuaglia MP, Kramer K, Verbel D, Heller G, *et al*. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. J Clin Oncol 2001; 19: 2821-2828.
14) Day DD, Johnson RT, Ordrezin GT, Woods WG, Alford BA. Renal atrophy or infarction in children with neuroblastoma. Radiology 1991; 180: 493-495.
15) Tanabe M, Ohmura N, Iwai J, Yoshida H, Takahashi H. Renal impairment after surgical resection of neuroblastoma. J Pediatr Surg. 31: 1252-1255. 1996.
16) Tokiwa K, Fumino S, Ono S, Iwai N. Results of retroperitoneal lymphadenectomy in the treatment of abdominal neuroblastoma. Arch Surg 2003; 138(7): 711-715.
17) Kubota M, Yagi M, Kanada S, Okuyama N, Kinoshita Y, Yamazaki S, *et al*. Long-term follow-up status of patients with neuroblastoma after undergoing either aggressive surgery or chemotherapy - a single institutional study. J Pediatr Surg 2004; 39(9): 1328-32.
18) Jenkins PJ, Plowman PN. Case report: renal morbidity and compensatory renal responses associated with flank radiotherapy in two children. Br J Radiol Jul 1994; 67(799): 651-653.
19) Cohen EP, Robbins MEC. Radiation nephropathy. Semin Nephrol 2003; 23(5): 486-499.