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Case Report

Peripheral Blood Stem Cell Transplantation for Hepatoblastoma with Microscopical Residue: A Therapeutic Approach for Incompletely Resected Tumor

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Department of Pediatrics, [1]Department of Pediatric Surgery, [2]Department of Pathology, Tohoku University School of Medicine, Sendai 980-8574, and [3]Department of Pediatrics, Hachinohe City Hospital, Hachinohe 031-8555

YOSHINARI, M., IMAIZUMI, M., HAYASHI, Y., SATO, A., SAITO, T., SUZUKI, H., SAISHO, T., ABUKAWA, D., OGAWA, E., AIKAWA, J., GOTO, K., SATOH, T., OHI, R. and IINUMA, K. *Peripheral Blood Stem Cell Transplantation for Hepatoblastoma with Microscopical Residue: A Therapeutic Approach for Incompletely Resected Tumor*. Tohoku J. Exp. Med., 1998, **184** (3), 247-254 —— We report a nine-month-old boy with stage III B hepatoblastoma of caudate lobe origin. Surgical resection was attempted following six courses of chemotherapy, but viable tumor cells remained microscopically at resection margins. Subsequently, he received peripheral blood stem cell transplantation (PBSCT), whose preparative regimen being consisted of carboplatin, etoposide, tetrahydropyranyl adriamycin, and melphalan. Since then, the patient shows no relevance of local relapse or distant metastasis without any chemotherapy. PBSCT for patients with post-operative residue may improve the outcome of advanced hepatoblastoma and worth of a further clinical investigation. ———— microscopic residual hepatoblastoma; caudate lobe origin; megatherapy; peripheral blood stem cell transplantation

Hepatoblastoma (HB) is the most important liver tumor of childhood. Its resectability has increased to 90%, owing to the improvement of better chemotherapeutic regimens and surgical approach (Stringer et al. 1995; von Schweinitz et al. 1995). Even those who remain in an irresectable state, some were rescued

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by liver transplantation (Lockwood et al. 1993; Stringer et al. 1995; von Schweinitz et al. 1995). It is now essential to draw attention to management of incompletely resected tumors regarding duration, intensity, and drug combination of chemotherapy or application of radiotherapy. Although prolonged chemotherapy would increase the frequency of severe side effects such as cardiomyopathy (Stringer et al. 1995), develop drug resistance (von Schweinitz et al. 1995), and disturb children's mental development, it is difficult to determine the endpoint of post-operative chemotherapy. Recently, a supportive technique for peripheral blood stem cell transplantation (PBSCT) has remarkably improved even in very young children (Takaue et al. 1995; Shen et al. 1997; Urban et al. 1997). Megatherapy supported by autologous stem cell transplantation may enable to shorten the duration of post-operative chemotherapy without worsening the outcome. The efficacy and adequacy of PBSCT for incompletely resected HB should be strictly discussed.

We report an infant with stage III B HB of caudate lobe origin, the resection of which was incomplete owing to this special location. He received PBSCT in a state with microscopic residure of HB, and is free of disease for 24 months after surgical resection.

Case Report

A nine-month-old boy was referred to Hachinohe City Hospital in August 1995 with complaints of abdominal distension, vomiting, and failure to thrive. A serum a-Fetoprotein (AFP) level was markedly elevated to 226 689 ng/ml. An abdominal computed tomography (CT) and magnetic resonance imaging (MRI) revealed a huge tumor originating from the caudate lobe and expanding into both lobes (Fig. 1A). No metastatic disease was seen by bone scintigraphy and CT of the chest. Open biopsy was carried out at our hospital and the pathological diagnosis was HB of fetal type. According to the pretreatment grouping system used in the International Society of Pediatric Oncology (SIOP) study, known as SIOPEL 1 (MacKinlay and Pritchard 1992), the tumor was inoperable and classified as group IV.

From August 1995 to January 1996, he received six courses of chemotherapy every four week according to the Japanese Study Group for Pediatric Liver Tumor (JPLT) (Uchino et al. 1995). The chemotherapy regimen consisted of 80 mg/m^2 of cisplatin in an intravenous continuous infusion (CI) over 24 hours on day 1; and 30 mg/m^2 of tetrahydropyranyl adriamycin in CI over 24 hours on days 2 and 3. Because he was younger than one year old, chemotherapeutic agents were reduced to half doses in the first course, and three-quarters in the following three courses, respectively, according to the protocol (Fig. 2). Surgical resection was not attempted until the sixth course of chemotherapy, because frequent imaging studies revealed the huge tumor surrounded by major vessels that were thought to be difficult of resection. When the sixth course of chemo-

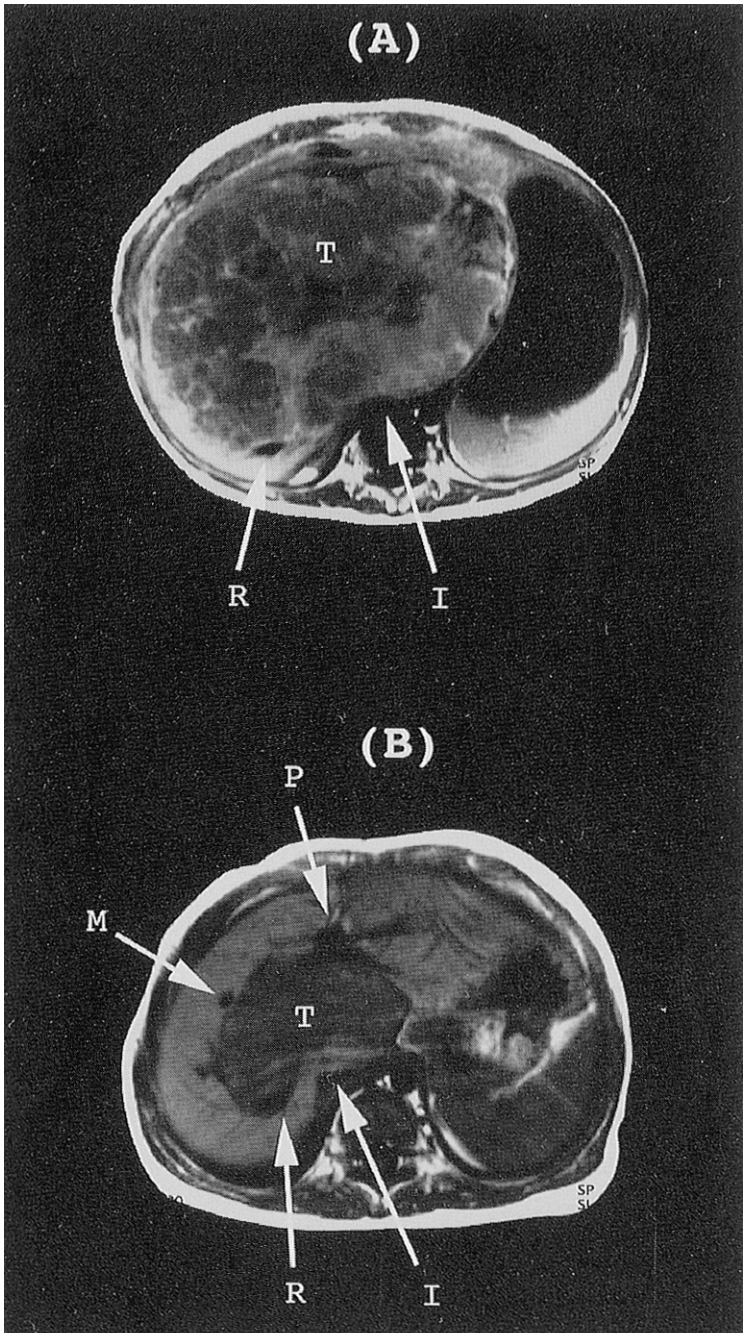

Fig. 1. Abdominal MRI.
A: At onset, before the chemotherapy. The tumor (T) of $13 \times 9 \times 10$ cm in size, occupied almost the entire liver and the normal liver was hardly recognized. The IVC (I) was compressed to flat, whereas right hepatic vein (R) was dilated.
B: After six courses of chemotherapy, just before surgical resection. The tumor (T) was reduced to size of $6 \times 6 \times 4$ cm, but was surrounded by portal vein (P), middle hepatic vein (M), right hepatic vein (R), and IVC (I).

therapy was accomplished, AFP level was decreased to 2000 ng/ml, and the findings of MRI (Fig. 1B), ultrasonography, and angiography indicated that the tumor was next to, but not invading into, inferior vena cava (IVC) or hepatic veins. Thus, left trisegmentectomy of the liver was performed.

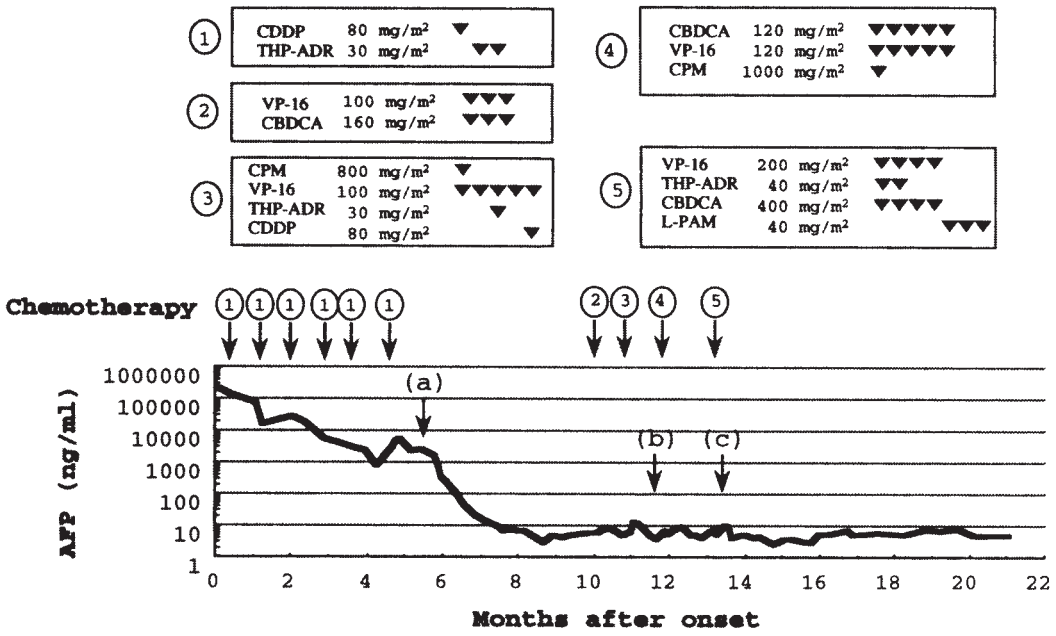

Fig. 2. Change of AFP levels in relevance to chemotherapy regimens (1–5) and surgical resection (a), PBSC collection (b), and PBSC infusion (c). CDDP, cisplatin; THP-ADR, tetrahydropyranyl adriamycin; VP-16, etoposide; CBDCA, carboplatin; CPM, cyclophosphamide; L-PAM, melphalan.

The tumor was carefully separated from IVC or right hepatic vein using intraoperative ultrasonography. Left trisegmentectomy was achieved en bloc with resection of the entire caudate lobe. However, histological examinations revealed the residue of viable tumor cells at resection margins (Fig. 3). Subcostophrenic abscess and postoperative bile leakage were the major complications, which were relieved by drainage within four months.

Three courses of post-operative chemotherapy including carboplatin and etoposide were performed (Ohmizono et al. 1995; Oue et al. 1995; Tokuda et al. 1995) (Fig. 2). Serum AFP levels and imaging study did not show signs of local relapse or distant metastases. His cardiac or renal functions were normal according to the examinations of cardiac ejection fraction or renal creatinine clearance. His liver size has shown remarkable regeneration following resection according to the abdominal MRI (data not shown). Liver scintigraphy using ^{99m}Tc-pyridoxyl-5-methyltriptophan or ^{99m}Tc-DTPA-galactosyl-human serum albumin revealed normal function of his liver. Moreover, he never showed any symptoms of liver disfunction following three courses of post-operative chemotherapy, and his biochemical examinations always remained in normal range. Thus, he was considered to be eligible of myeloablative chemotherapy.

PBSC collections were performed safely as described elsewhere (Takaue et al. 1995; Shen et al. 1997; Urban et al. 1997). Because he weighed only 10 kilograms and was 17 months old at the time of PBSC collection, the procedure was paid attentions as follows. PBSCs were mobilized by application of granulocyte

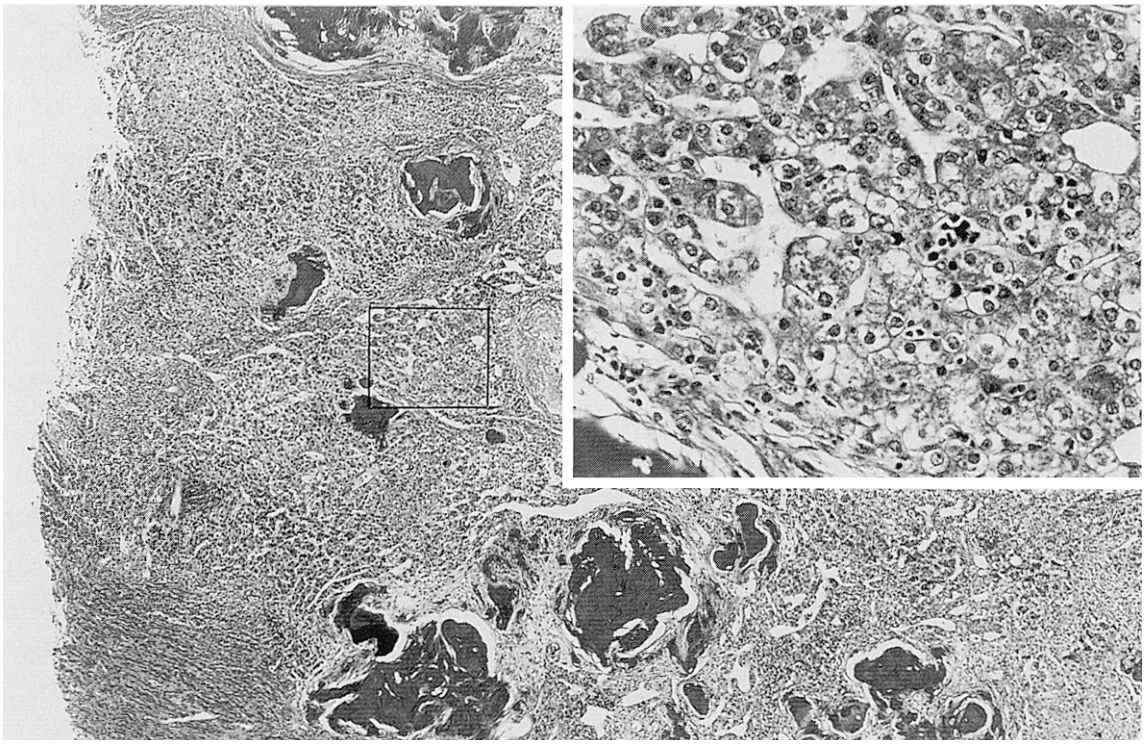

Fig. 3. Histology of the resected liver specimen. Left side is the resection margin containing hepatoblastoma cells composed of fetal hepatocyte-like tumor cells and osteoids (magnification $\times 10$). Inset shows larger magnification appearance of the boxed area (magnification $\times 50$).

colony stimulating factor (G-CSF) at a dosage of 5 μg/kg body weight intravenously by 24 hours CI. PBSCs were collected through a double-lumen central venous catheter inserted at the time of diagnosis. Leukapheresis was performed with a COBE Spectra Blood Component Separator (COBE, Lakewood, CO, USA), whose extracorporeal line was primed with concentrated red blood cells and normal saline to avoid acute blood volume loss. During leukapheresis, calcium gluconate was administered continuously to prevent hypocalcemia. He was not sedated, otherwise entertained with toys. Leukapheresis was performed safely for two times and PBSCs with 3.5×10^5 colony forming unit granulocyte/macrophage (CFU-GM)/kg of the patient weight were collected.

The megatherapy consisted of carboplatin, 400 mg/m^2/day as a CI over 24 hours on days -7 to -4; etoposide, 200 mg/m^2/day as a CI over 3 hours on days -7 to -4; tetrahydropyranyl adriamycin, 40 mg/m^2/day as a CI over 20 hours on days -7 and -6; and melphalan, 40 mg/m^2/dose three times every 12 hour by intravenous infusion on days -3 and -2 (Tokuda et al. 1995). After one day of rest, 2.0×10^5 CFU-GM/kg of PBSCs were infused on day 0. Supportive or prophylactic administrations with aciclovir, antifungal drugs, γ-globulin with high anti-cytomegalovirus titers, antibiotics, and G-CSF were performed. Granulocyte engraftment ($>0.5 \times 10^9$/liter) was achieved on day 10, and final platelet transfusion was on day 31 with no serious complications.

Since his discharge on day 46 after PBSCT, he has been followed as an outpatient without any chemotherapy. AFP levels and imaging studies show no relevance of local relapse or distal metastases. Recent examinations of his cardiac ejection fraction, hearing ability and renal creatinine clearance were within normal range. The patient is fine as of February 1998, 30 months following his presentation and 24 months following surgical resection.

Discussion

Reduction of chemotherapy-related morbidity and prevention of long-term adverse effects, such as cardiotoxicity of anthracyclines and ototoxicity or nephrotoxicity of cisplatin, are essential goals in the treatment of very young children. It has been reported that one child died from doxorubicin cardiotoxicity one month after completing eight courses of post-operative chemotherapy, and the other child has undergone cardiac transplant for cardiomyopathy eight years after chemotherapy (Stringer et al. 1995). Aiming to reduce cardiotoxicity of doxorubicin, SIOP Group (Ninane et al. 1991) and Childrens Cancer Study Group (Ortega et al. 1991) recommend the administration of cisplatin and doxorubicin in CI. Pediatric Oncology Group (POG) uses the regimen, which is consisted of cisplatin, vincristine, and fluorouracil, to avoid cardiotoxicity of anthracyclines (Douglass et al. 1993). Our patient received pre-operative chemotherapy in CI according to JPLT (Uchino et al. 1995), and post-operative chemotherapy plus megatherapy consisted of several other agents, the cumulative doses of which were 395 mg/m^2 for tetrahydropyranyl adriamycin, 460 mg/m^2 for cisplatin, and 2680 mg/m^2 for carboplatin, respectively. His cardiac and renal function is normal, but obviously further follow-up is essential.

HB of caudate lobe origin is uncommon and often adherent to IVC and/or portal vein, indicating a probability of early vascular invasion and dissemination, and a technical difficulty of complete resection (Takayama et al. 1990, 1991). Owing to this special location of the tumor, our patient needed six courses of pre-operative chemotherapy and surgical resection was incomplete. Although microscopic residues were apparent, he has benefited by this resection in reducing residual tumor, which were demonstrated by normalization of AFP level after resection (Fig. 2).

The strategy for treating HB with post-operative microscopic residue has not been established. The disease free survival for patients with a complete tumor resection was 89%, whereas it was reduced to 50% for patients with microscopic residual tumor and 0% for patients with gross residual tumor (von Schweinitz et al. 1997). These results indicate that post-operative chemotherapy may be needed in patients with incomplete resection, but it is difficult to determine the optimal duration and intensity of chemotherapy due to rarity of those cases. A survey conducted by SIOP Liver Tumour Study Group has shown an efficacy of radiotherapy when tumor size was reduced to small volume before radiotherapy

(Habrand and Pritchard 1991), but it has not gained wide acceptance yet.

Recently, megatherapy supported by autologous stem cell infusion has been performed for HB in state of progressive disease or pulmonary metastases (Kato et al. 1995; Matsushita et al. 1995). The report of PBSCT for microscopic residual HB is rare (Yamaguchi et al. 1995). The reason we applied PBSCT to this patient is as follows: (1) Many viable tumor cells existed microscopically at resection margins; (2) an involvement of portal vein, hepatic veins, or IVC suggested a high risk of local tumor relapse in the liver or pulmonary metastasis (von Schweinitz et al. 1995); (3) a prolonged chemotherapy and hospitalization would be less beneficial for an infant; and (4) an improved technique and safety of PBSCT procedure in our hospital. Consequently, PBSCT was accomplished without any severe complication, and since then he has been fine and free from disease.

We consider that PBSCT is effective and tolerable treatment for advanced HB, especially in a state with microscopic residure. Further study with uniform conditioning regimen will be essential for evaluating the efficacy of PBSCT for these patients with a residual HB.

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