Case Report

Treatment of Advanced Retinoblastoma with Syngeneic Bone Marrow Transplantation

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Abstract: High dose multiagent chemotherapy followed by syngeneic bone marrow rescue was used in the treatment of two patients with advanced bilateral retinoblastoma. The first patient presented with classical heritable retinoblastoma and his identical twin was also affected. He received multi-modality treatment including radiotherapy, chemotherapy and enucleation. The disease recurred and locally invaded 42 months after diagnosis. The second patient underwent enucleation after diagnosis of a large mass of retinoblastoma with vitreous seeding and retinal detachment. No additional treatment was given. The disease recurred 11 months after diagnosis in the other eye and metastasized to liver and bone marrow. Although he received intensive chemotherapy, CNS metastases developed. Syngeneic BMT was used in the treatment of both patients. The preparative regimen consisted of carboplatin, etoposide, and cyclophosphamide. A self-limited clinical syndrome grade II-GVHD was observed in both patients. The transplant course was complicated by reversible renal insufficiency, and elevated liver transaminase in the second patient. The first patient remains progression free to date. The second patient had recurrent CNS disease and expired 3 months after bone marrow transplantation.

Key Words: Retinoblastoma Syngeneic bone marrow transplantation

ably unilateral and solitary. Tumors are bilateral in 20-30% of patients. Retinoblastoma usually has a favorable prognosis. The survival rate at 5 years is more than 90%. Current treatment for retinoblastoma aims to save lives and preserve useful vision. Therapies include enucleation, radiation, cryotherapy, photocoagulation and chemotherapy. Although in general, the results of treatment of retinoblastoma are very good, extraocular spread still carries a poor prognosis, particularly with hematogenous metastases. Dissemination of tumors is virtually the sole cause of mortality in unilateral retinoblastoma and also accounts for a majority of early deaths in the genetically determined variety. Intensive chemotherapy is recommended in this setting. Several multiagent regimens offer some promise. Because the dose-limiting toxicity of the effective chemotherapy is myelosuppression, hematopoietic rescue may allow dose escalation, which in turn may provide better efficacy. Successful treatment of advanced retinoblastoma by high-dose chemotherapy in combination with purged or unpurged autologous bone marrow transplantation (BMT) has been reported.

This is the first report, to our knowledge, of the treatment of advanced retinoblastoma with syngeneic BMT. One of two such patients is well and disease-free over 3 1/2 years after transplantation. Unfortunately, the other patient died of recurrent disease three and a half months after transplantation.

CASE 1

The patient presented with strabismus and was diagnosed as having bilateral retinoblastoma at 20 months of age. More than 20 and 10 foci were noted on ocular examination in the left and right eyes respectively. Notably, he was diagnosed at the same time as his twin brother. At diagnosis, bone marrow and spinal fluid were clear of tumor cells. At that time he was treated with multiple courses of cryotherapy to both eyes. He also received 4,600 cGy extended beam radiation therapy to both eyes and initially had a fair response.

Five months after the diagnosis, examination under anesthesia revealed persistent large lesions larger than 10 disk diameters in the right eye. There was no progression in the left eye. Therefore, he received brachytherapy with at a dose of 3,920 cGy for a total of 49 hours to the right eye. Afterward, he also received a course of chemotherapy consisting of vincristine 2 mg/m² IV and etoposide 75 mg/m² PO for 3 days every 3 weeks. Two months after the start of chemotherapy, an MRI showed new extensive tumor in the left eye. He then received cryotherapy to the left eye. Restaging revealed no progression of tumor. Of note, he demonstrated no significant vision at that time in the right eye and the left eye demonstrated minimal vision. He had a slow but stable response to the chemotherapy which resulted him in regaining vision in his right eye. However, after 3 months of chemotherapy, an MRI showed bilateral retinoblastoma with progression in the
left eye. He then underwent left eye enucleation with a clear surgical margin. The pathology confirmed the diagnosis. During that time, he continued to receive chemotherapy with vincristine and etoposide and completed 21 courses over 18 months. There was no residual tumor in the right eye. He was followed by an ophthalmologist and was noted to have some residual vision in the right eye and was in a state of good health.

The patient had a twin brother who was also found to have bilateral retinoblastoma shortly after the diagnosis of the first twin patient. This second twin had a solitary lesion of the right eye and two lesions in the left eye. All lesions were behind the equator. Metastatic work-up was negative. He received radiation of 4,400 cGy to both eyes. There was no residual tumor in both eyes. He has done well after treatment.

The study of the retinoblastoma gene in the family revealed heritable transmission pattern. (Figure 1) Genetic identity of these twins was verified by DNA microsatellite typing, HLA class I and II typing as well as major and minor blood group typing. There was no other family history of cancer or ocular disease.

Four and a half years after diagnosis, the first patient returned with a right temporal mass. A CT scan showed a right infratemporal fossa mass without brain parenchymal extension. An MRI revealed a 2.5x6 cm mass as well as a 2.4x3 cm right-sided lymph node at the angle of the mandible. Biopsy of the mass showed small, round blue cell tumor which was pathologically confirmed to be retinoblastoma by immunoperoxidase staining and electron microscopy. Evaluation for distant metastases, including a CT scan of the chest and abdomen, bone scan, spinal fluid cytology, and bone marrow aspiration and biopsy was negative.

The patient was then started on chemotherapy according to POG Protocol #9341 consisting of 5 courses of chemotherapy. Each course was 3 weeks apart. The first course
consisted of cyclophosphamide 1 gm/m² day 1, 2; Adriamycin 60 mg/m² day 1; and vincristine 1.5 mg/m² day 1, 8, 15; the second course consisted of high-dose cisplatinum 40 mg/m² day 1-5, and etoposide 100 mg/m² day 2-4; the third course consisted of ifosfamide 2 gm/m² day 1-5, and etoposide 75 mg/m² BID day 1-3; and the fourth and fifth courses consisted of carboplatin 500 mg/m² day 1 and etoposide 75 mg/ m² BID day 1-3. After the third course of chemotherapy, an MRI showed near complete resolution of the soft tissue mass in the right temporal area, a persistent enhancing nodule in the right globe, and a marked decrease in size of the enlarged lymph nodes behind the right mandibular angle. After the completion of chemotherapy, a repeat MRI showed resolution of the lymph node enhancement but persistently minimal gadolinium enhancement remained in the area of tumor in the right globe. He, then, received 1,980 cGy extended beam irradiation to this lesion. The bone marrow and cerebrospinal fluid work-ups remained negative for tumor.

The patient was considered to undergo syngeneic bone marrow transplantation after completion of chemotherapy 6 months after the recurrence of tumor. The twin donor has been free of disease for over 4 years. The preparative regimen consisted of carboplatin, etoposide and cyclophosphamide. (Table 1) He was transfused with unprocessed bone marrow containing 6x10⁹ cells/kg nucleated cells. Engraftment, defined as an absolute neutrophil count more than 500/mm³, was documented on day +9. The platelet count more than 20,000/mm³, was documented on day +12. He was discharged home on day +13. During first few weeks, he came for the follow-up twice weekly. The patient did not require any transfusion. His only complication was a self-limited clinical syndrome of acute graft versus host disease, which was manifest by a diffuse erythematous maculopapular rash, as well as diarrhea, lasting from day 9 to 11, with more than 800 mL of liquid stool per day. No biopsy was obtained. The symptoms resolved without therapy. Repeat MRIs at 4 and 8 months post BMT showed a tiny focus in the right globe inferolaterally consistent with calcification. The follow-up MRI at 14 months post BMT showed enhancement in the region of calcific focus. No specific treatment was offered. Subsequent MRIs at 17, 20, and 27 months post BMT were normal.

The patient is now progression free more than 3 1/2 years post-BMT and continues to do

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**Table 1** Preparative regimen

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/m²)/day</th>
<th>Days before transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide</td>
<td>800 mg/m², IV</td>
<td>-6, -5, -4</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>725 mg/m², IV</td>
<td>-6, -5, -4</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>60 mg/kg, IV</td>
<td>-3, -2</td>
</tr>
</tbody>
</table>
Treatment of Advanced Retinoblastoma

well except for poor vision. No further recurrence has been observed by ophthalmologic or examination more than 3 years since the completion of BMT. The hearing test revealed normal hearing sensitivity through 1,500 Hz sloping to a severe hearing loss thereafter. Besides hearing loss, the patient has not suffered from any long-term complication.

**CASE II**

A 3 1/2-year-old white male was noted to have an absent red reflex in the left eye. The examination under anesthesia confirmed opacification of the left eye by a mass larger than 10 disk diameters. Vitreous seeding and retinal detachment were identified, classified as Reese-Ellsworth group V. He therefore underwent left eye enucleation, and pathology was consistent with retinoblastoma. There was infiltration of the retina with invasion of the optic nerve head within 2 mm of the lamina cribosa. No extrasceral extension was noted. A metastatic work-up including CSF and bone marrow studies was negative. He received no further treatment at that time.

Notably, the patient had an identical twin sibling who was not affected by the disease. Genetic identity of these twins was verified by DNA microsatellite typing, HLA class I and II as well as major and minor blood group typing. The retinoblastoma gene was studied by RFLP from blood samples in family members and tumor sample from the patient. (Figure 2) The results do not formally exclude a germ-line mutation of the Rb gene in this family, although the unilateral presentation at age 3 1/2 years, with an unaffected identical twin makes this possibility remote. There was no history of retinoblastoma in the family.

One year after resection, the patient returned with bone pain and was noted to have anemia with marked hepatomegaly. A bone marrow aspirate and biopsy were positive for recurrent tumor. An abdominal CT showed liver involvement and an MRI of the head and orbit showed a mass in the right orbit suspicious for retinoblastoma. The brain and CSF were free of tumor. A bone scan was negative. A biopsy of
the orbital mass was compatible with retinoblastoma. He then received one course of chemotherapy consisting of cisplatinum 90 mg/m² day 1, etoposide 200 mg/m² day 3, cyclophosphamide 600 mg/m² day 7, and Adriamycin 35 mg/m² day 10 (CECA).

His chemotherapy course was complicated by fluid overload, tumor lysis syndrome and renal insufficiency. The tumor in the right globe was surgically removed. Afterward, the patient was switched to a regimen which consisted of vincristine 1.5 mg/m² day 1, 8, 15; ifosfamide 1.8 gm/m² day 1-5; and etoposide 100 mg/m² day 1-5 (VIE). He received 4 courses every 3 weeks apart. After 2 courses of VIE, a repeated abdominal CT showed that the liver metastases had markedly decreased in size and number. An MRI of brain and orbit showed no evidence of persistent or recurrent tumor. Bone marrow and CSF were free of tumor cells. After 4 courses of VIE, abdominal CT showed continued response of the liver metastases. Brain imaging and CSF studies were normal. However, 2 months later, an MRI done to evaluate persistent headache and vomiting showed that the patient had multiple new lesions in the basal ganglia. CSF cytopathology was positive for tumor. Bone scan and bone marrow studies were negative. At this time, the patient received etoposide 200 mg/m² day 1; and cyclophosphamide 600 mg/m² day 2, 3. One month later he received etoposide 200 mg/m² day 1-3, and carboplatin 500 mg/m² day 1-2. Thereafter, he received a course of irradiation with 4,140 cGy to brain, 4,360 cGy to spinal cord; and 1,050 cGy to liver. However, his spinal fluid after irradiation was persistently positive for abundant tumor cells.

Three months after the onset of central nervous system metastases, he was admitted for syngeneic bone marrow transplantation. He received a preparative regimen consisting of etoposide, carboplatin, and cyclophosphamide. (Table 1) The patient had received 3 doses of intrathecal thiotepa on day -19, -12, and -5 prior to BMT. A spinal tap done on day -4 was still positive for 3 tumor cells/mm³ of CSF. Engraftment, defined as ANC >500/mm³, was documented on day +8 and platelet count more than 20,000/mm³ was on day +11.

On day +16 CSF was free of tumor cell. The patient received 5 additional doses of intrathecal cytosine arabinoside weekly as consolidation. This transplant course was complicated by epistaxis, renal insufficiency, elevated transaminase and mucositis, which resolved completely in 2 weeks. The patient had a generalized maculopapular rash on day 2 to 18. The symptoms resolved without any therapy. His twin brother was diagnosed with fifth disease. Parvovirus PCR and serology of the patient were negative. Skin biopsy done on day +8 showed mild basal vacuolization with perivascular infiltration which was compatible with acute GVHD. On day +30 his CSF and bone marrow were clear of malignant cells. Two months after BMT, CT scans of chest, abdomen, and head were normal.
Three months after transplantation, the patient was suffering from persistent nausea and emesis. An MRI showed multiple metastases at the brain stem, cerebellum and cerebral cortex. He received Taxol twice a week with palliative intent. A week later, the patient clinically deteriorated and a CT scan revealed rapid disease progression with hydrocephalus, cerebral edema and herniation. A VP shunt was placed. He was discharged home to hospice care and expired 3 1/2 months after BMT.

Discussion

Retinoblastoma (RB) is the most common ocular tumor in childhood. The heritable variant of this tumor is usually bilateral and multifocal whereas nonheritable RB is invariably unilateral and solitary. Bilateral presentation was found 34-38% of RB cases in some reports. In this report, the first patient had characteristic of germ line mutation RB, with early bilateral presentation and multiple tumors; and in addition, both identical twins were affected. The second patient was found to have RB at older age. The RFLP analysis of the RB gene in this family could not exclude germ line mutation, although the presentation was typical of nonheritable RB. This patient developed advanced RB in the second eye 15 months after initial diagnosis of the first eye.

In those patients who present with unilateral RB, especially sporadic cases, it is difficult to define the incidence of RB development in the contralateral eye. There was a case in this report developed RB in the second eye as late as 6 years after the first eye.

The management of RB can be extremely complex, and establishing firm treatment guideline is impossible. In bilateral cases, the eye with more advanced tumor has traditionally been enucleated, and the less involved eye is managed with irradiation or other methods. Indications for chemotherapy are not clearly established. Most authorities agree that if a child with RB has known metastatic disease, chemotherapy should be part of the treatment regimen. If orbital involvement or extensive optic nerve involvement is evident after enucleation or if tumor recurs in the ophthalmic socket, chemotherapy should be initiated along with a course of orbital irradiation. Chemotherapy also may be indicated for children with bilateral RB particularly if one or both eyes are treated by methods other than enucleation. The adjuvant chemotherapy for selected patient with RB with high risk of dissemination is recommended. The most widely accepted regimen is the combination of cyclophosphamide and vincristine. In bilateral or early unilateral cases, the aim of chemotherapy could be either initial tumor shrinkage or concurrent, preferably synergistic interaction with other modalities.

We approached the first patient by treating him conservatively with sequential cryotherapy, radiotherapy with initially fair response of the tumors and later he was treated with brachytherapy to the residual tumors. Chemotherapy with vincristine and oral etoposide was added to,
which he had slow but steady response, resulting him in regaining vision in one eye. The other eye was enucleated for failure of the mass to respond. Chemotherapy with vincristine and oral etoposide was continued and temporarily controlled the disease. The patient did well for almost 3 years before recurrence.

Although the results of treatment of RB are very good in general, extraocular RB still carries a poor prognosis particularly after hematogenous metastasis and in cases with metastatic CNS involvement. There are two strategies that offer the potential for cure to patients with disseminated RB either at presentation or relapse. The first is an intensive combination of multiagent chemotherapy as well as radiation therapy in manner comparable to that utilized in other similar poor prognostic tumors of childhood such as neuroblastoma and brain tumors. The second strategy of promise use of BMT after remission or minimal disease status is achieved in such patients. There was a report of a patient with bone marrow involvement by RB documented long-term survival after a regimen consisted of cyclophosphamide, adriamycin, cisplatinum, vincristine, DTIC and nitrogen mustard (MADDOC). Orbital and cranial irradiation were also given. The tumor remained in remission 18 months after completion of chemotherapy. Thereafter, a preleukemic syndrome was diagnosed, and allogeneic BMT was done. Except for this patient, there are no reports of long term survival in patients with RB metastatic to bone marrow. Ishii also reported a successful treatment of bilateral retinoblastoma with vitreous seeding by combination of ranimustine and carboplatin. No recurrence has been observed for over 4 years. From the study of the Societe Francaise d’Oncologie Pediatrique, etoposide and carboplatin were shown highly effective in treatment of extraocular retinoblastoma with response rate for 20 patients was 85%; there were nine complete responses and eight partial responses.

The treatment of chemotherapy regimen varies center to center, especially in metastatic RB. The first patient in our report was successfully treated with one course of cyclophosphamide, adriamycin and etoposide followed by 5 courses of cisplatinum and etoposide; and local irradiation additionally. The second patient received intensive chemotherapy with cisplatinum, etoposide, cyclophosphamide and adriamycin (CECA) and then followed by vincristine, ifosfamide and etoposide (VIE). The treatment schedule was interrupted and complicated by myelosuppression and infections. Although the patient received aggressive chemotherapy, he developed CNS involvement refractory to radiation therapy and aggressive conventional chemotherapy.

In the past, patients who had systemic metastases either at initial diagnosis or at later relapse, were not curable, although transient response could be achieved. The presumed cause of failure to either achieve or maintain remission in disseminated retinoblastoma is emergence of drug resistance in the tumor. The
most appealing strategy for curing disseminated retinoblastoma is the use of bone marrow transplant after achieving remission or minimal disease status. Fortunately, both of our patients were identical twins to be considered for syngeneic bone marrow transplant.

We considered that the first patient should have syngeneic bone marrow transplant since his sibling, who used to have bilateral retinoblastoma, was doing well and was free of the disease for over 4 years. Moreover, there was a chance to reinfuse tumor cells in case of autologous bone marrow transplantation even though his bone marrow was negative for tumor cells in light microscopy. Saarinen reported a case that tumor cells were detected in bone marrow by indirect immunofluorescent of CD 2 positive cells 2 months after initiation of chemotherapy consisting of VP-16 and cisplatinum, whereas the bone marrow was normal in light microscopy. Although special studies to detect tumor cell contamination for our patient and donor were not done, it is more likely that the donor’s bone marrow was free of tumor cells than the patient since the donor had never had dissemination or progression.

A novel anti-neoplastic combination chemotherapy myeloablative preparative regimen was developed at the Johns Hopkins Oncology Center. Results from this trial determined maximally tolerated doses (MTD) of etoposide (2,400 mg/m²) and carboplatin (2,175 mg/m²) in combination with a fixed, relatively conservative dose of cyclophosphamide (60 mg/kg/day x 2 days). The limiting toxicity was stomatitis in essentially all patients. Most patients had transient, clinically elevated hepatic transaminase several days after the chemotherapy regimen. In children with refractory solid tumors, the use of this preparative regimen with autologous bone marrow rescue was tolerated and achieved response. The first patient in this report tolerated preparative chemotherapy well but the second patient suffered complications which included renal insufficiency, elevated liver enzymes and mucositis, which resolved completely. In a study of SFOP and SFGM with high-risk retinoblastoma, 25 patients received high-dose chemotherapy including carboplatin (1,500-2,100 mg/m²), etoposide (2,100 mg/m²), and cyclophosphamide (4.8 gm/m²) [CARBOPEC] followed by autologous hematopoietic stem cells rescue. The main toxicities were bone marrow suppression, mucositis, and diarrhea. Two of the 13 evaluable patients had grade 3 and 4 ototoxicity. One patient had an acute grade 1 reversible cardiotoxicity. Retinoblastoma with CNS involvement carries a bad outcome of treatment. In a study of 51 patients with retinoblastoma in Argentina, all six patients died had relapsed initially with CNS involvement rather than systemic metastasis. Patients with distant metastasis, especially in the bone, bone marrow without central nervous system involvement is seldom cured with conventional chemotherapy. In the second patient who had CNS, liver and bone marrow involvement, complete response
was achieved after the transplant but unfortunately was of short duration. He had recurrence of tumor three months post-bone marrow transplant.

A GVHD-like syndrome can occur after marrow transplantation is performed between identical twins (syngeneic) or after autologous bone marrow transplant\textsuperscript{25,27}. It is believed that disruption of both central and peripheral mechanism governing self tolerance leads to autologous/syngeneic GVHD. Autoregulation system is sensitive to irradiation and cyclophosphamide. Among immunosuppressive drugs, cyclosporin A is commonly used to induce autoagression syndrome. Both cases in this report received cyclophosphamide in preparative regimen. Interestingly, both patients developed syngeneic GVHD which confined to the skin and resolved spontaneously. The first patient developed acute GVHD, which manifested by maculopapular eruption (grade 1) and diarrhea (grade 2) which lasted for 3 days. The diagnosis of GVHD was clinically based and no biopsy was obtained. The second patient had only maculopapular eruptions (grade 2) which were pathologically confirmed. Autoagression GVHD was found to have significant antitumor activity in high grade NHL, breast cancer\textsuperscript{26}. Moreover, the antitumor effects appeared to be enhanced by the administration of gamma-interferon. To our knowledge, there is no evident report of autologous or syngeneic GVHD effect on retinoblasts. Thus, the induction of autologous or syngeneic GVHD may be used to enhance the efficacy of autologous or syngeneic BMT in treatment of retinoblastoma.

In the limited number of reported cases treated with autologous bone marrow transplant, the patients received different chemotherapy and preparative regimens and the follow-ups were in short periods. Thus, the optimal therapy and the best conditioning regimen remain unclear. There were two reported cases of stage IV retinoblastoma treated with immunomagnetic purged autologous bone marrow transplant\textsuperscript{9,11}. One patient was symptom-free and disease-free over 18 months while another case had relapsed 2 months post-bone marrow transplant. Ekert\textsuperscript{11,12} reported 4 cases of stage IV retinoblastoma treated with unpurged autologous bone marrow transplant in which 3 patients remained disease-free over 2, 5 and 47 months. The disease still progressed post-bone marrow transplant in one child. Namouni 21 reported 25 cases of high-risk retinoblastoma who received CARBOPEC followed by unpurged autologous bone marrow transplant. The 3-year DFS was 67%. The central nervous system was the main site of failure. There was only one report of autologous bone marrow transplant in one patient that TBI was included in the preparative regimen\textsuperscript{8}. The patient was disease-free over 17 months post-bone marrow transplant.

Because patients with a constitutional abnormality of the retinoblastoma gene are at high risk for sarcoma and other secondary malignancies, long-term follow-up is needed in the patient. However, the only effect of chemo-
therapy in the survivor in this report so far has been hearing loss.

We conclude that syngeneic bone marrow transplant, after intensive chemotherapy and a preparative regimen consisting of high-dose carboplatin, etoposide and cyclophosphamide, is a potentially curative approach in patients with widespread metastatic retinoblastoma. The patients with retinoblastoma, particularly bilateral retinoblastoma, should have careful follow-up.

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บทคัดย่อ: รายงานผู้ป่วยเป็นมะเร็งจอประสาทที่สองข้างซ้ายและขวา 2 ราย ที่ได้รับยาเคมีบำบัดขนาดสูงหลายชนิดแล้วตามด้วยการปลูกถ่ายไขกระดูกจากไขกระดูกของคู่แฝดเพียง 1 ราย ป่วยรายแรกมีอาการของโรครั้วที่ผิดแผนการทำตามทางพันธุกรรมซึ่งผู้ป่วยได้รับการรักษาต่อมาด้วยมิวิบัคต, การฉายรังสีและการผ่าตัด แต่โรคก็ยังเป็นแหล่งหลังรักษาราย 42 เดือน ผู้ป่วยรายที่สอง พบเม็ดเซล์ประสานศักยภาพจากการเข้ารับรูมาตาและมีอัตราประสานดี ผู้ป่วยได้รับการรักษาต่อมาด้วยแหล่งหลังการผ่าตัด 11 เดือนในทางถ้าอาการดังกล่าว รวมถึงแสดงแนวโน้มการกระจายไปที่ระบบประสาท กลาง ผู้ป่วยทั้งสองรายได้รับการปลูกถ่ายไขกระดูกจากไขกระดูกของคู่แฝดเพียง 1 ราย พบการเตรียมผู้ป่วยก่อนการปลูกถ่ายไขกระดูกด้วยการใช้ ciclophosphamide, etoposide และ carboplatin มีผลephyค่อนข้างดีจากการปลูกถ่ายไขกระดูกที่มี GVHD grade II ในผู้ป่วยทั้งสองราย และผู้ป่วยรายที่สอง ที่มีเพียงเนื้องอกของตับและยังไม่มีการขยายตัวไปที่ระบบประสาทกลาง ผู้ป่วยรายแรกมีชีวิตอยู่และมีระยะเวลาที่ติดอยู่สูงกว่าจากเม็ดเซล์ประสานศักยภาพไปที่ระบบประสาทกลาง รายหลังการปลูกถ่ายไขกระดูก 3 เดือน

Key Words : Retinoblastoma Syngeneic bone marrow transplantation

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