exposure are at a significantly greater risk for abnormal cardiac function than are older patients[20]. Recent studies have examined whether genetic factors affect anthracycline processing[21], but no conclusive findings have been obtained.

The precise mechanism underlying anthracycline-induced cardiotoxicity is not understood. Most evidence shows that anthracycline therapy generates free radicals through an enzymatic mechanism using the mitochondrial respiratory chain and through a nonenzymatic pathway incorporating iron. Both free radicals and iron can damage cells. Cardiac cells are more vulnerable to free radical damage. Furthermore, anthracycline has a high affinity for cardiolipin and a phospholipid in the inner mitochondrial membrane of cardiomyocytes, resulting in the accumulation of anthracycline inside cardiac cells[22]. The free radicals may continue to be generated after anthracycline treatment has been completed and could account for late cardiotoxic effects of this therapy. Once cardiomyocytes are damaged by anthracycline, the cells might not recover their function. Loss of cardiomyocytes leads to progressive left ventricular dilatation, left ventricular wall thinning, and decreased contractility.

Serial monitoring of cardiac function in children receiving anthracycline allows early identification of cardiac damage. There are many methods to monitor anthracycline-induced cardiotoxicity, including echocardiography, electrocardiography, and radionuclide ventriculography. Fractional shortening and ejection fraction are reliable echocardiographic measures of left ventricular systolic function. Some reports suggest that exercise testing is useful for detecting cardiac function abnormalities that were not significant at rest[23,24]. Signal-averaged echocardiography is another useful tool for early detection of anthracycline-induced cardiotoxicity[25]. Cardiac markers are an accurate and convenient means of monitoring the cardiac health of patients during and after cancer therapy. For example, brain natriuretic peptide and troponin T are markers of cardiomuscular function.

The best treatment for cardiotoxicity is prevention. Although early reports in adults have suggested a lower prevalence of cardiotoxicity with continuous infusion of anthracycline than with bolus administration, more recent reports in children show that the method of administration does not provide cardioprotection[26]. One recent approach to preventing or minimizing chemotherapy-induced cardiotoxicity is to add a cardioprotectant to the treatment regimen. Dexrazoxane (Ziecard; Phamacia & Upjohn, Peapack, NJ) is a cardioprotectant that has been proven to be effective in adult patients. Dexrazoxane was approved in 2002 by the United States Food and Drug for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who had received a cumulative doxorubicin dose of at 300 mg/m^2 and continued to receive anthracycline treatment to maintain tumor control[21]. Clinical trials with dexrazoxane in children have been encouraging. For example, children who received dexrazoxane before doxorubicin were significantly less likely to have cardiac injury during treatment as measured by elevated serum levels of cardiac troponin T[27]. An association between the use of dexrazoxane and the risk of SMN in children with Hodgkin's disease has also been reported[28]. However, a recent report found the absence of an association of secondary malignant neoplasm in children with acute lymphoblastic leukemia who had received dexrazoxane[29].

Conclusions

The number of long-term survivors of childhood cancer will continue to increase, and almost 75% will have a chronic health problem resulting from cancer therapy. More than 40% will have a severe, disabling, or life-threatening condition or will die of because of a chronic condition resulting from cancer therapy[30]. The most important method for preventing these problems is a follow-up survey of cancer survivors. It is important to recognize that patients are not necessarily best categorized by primary diagnosis in such a follow-up survey and that strategies for surveillance of survivors must be based on the treatment each patient received. Therefore, we are establishing a follow-up system

for survivors of childhood cancer that includes an individual treatment summary and follow-up notebook for patients.

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Ewing Sarcoma/Primitive Neuroectodermal Tumor of the Kidney in a Child

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A 6-year-old female was admitted with abdominal pain and a mass in the right abdomen. Her lactose dehydrogenase level was 1,200 IU/L, and neuron specific enolase was 120 ng/ml. Computed tomography scan confirmed a large right renal mass with necrosis. A right radical nephrectomy was performed. The tumor was completely encapsulated. Based on small round cell histology, strong MIC-2 (CD99) positive tumor cells, and EWS-FLI-1 fusion transcript, Ewing sarcoma/primitive neuroectodermal tumor of the kidney was diagnosed. Induction and follow-up with seven cycles of chemotherapy were given after surgery. She has had no evidence of recurrence 90 months from diagnosis. Pediatr Blood Cancer 2008;50:180–183. © 2006 Wiley-Liss, Inc.

Key words: electron microscopy; Ewing sarcoma/primitive neuroectodermal tumor; EWS-FLI-1; immunohistochemistry; kidney

INTRODUCTION

Ewing sarcoma/primitive neuroectodermal tumor (ES/PNET) of the kidney is a rare and highly malignant neoplasm. It affects young adults, and only a few pediatric cases (younger than 15 years) have been reported [1–9]. ES/PNET arising in the kidney act aggressively and show poor response to therapy [1]. ES/PNET of the kidney needs to be differentiated from other small round cell tumors of the kidney, because each type of tumor is treated differently. The diagnosis of this neoplasm is currently based on a combination of light microscopy, immunohistochemistry, electron microscopy, chromosomal analyses, and specific chimeric transcripts. Our patient, who was diagnosed by histochemistry and molecular biology analysis of the resected kidney and treated with chemotherapy, has remained alive more than 90 months after diagnosis.

CASE

A 6-year-old female was admitted to our hospital with abdominal pain and an abdominal mass. On physical examination, a large and firm mass was evident in the right abdomen. Laboratory evaluation showed a lactate dehydrogenase level of 1,200 IU/L (normal 218–411 IU/L), a neuron specific enolase level of 120 ng/ml (normal <10 ng/ml), and ferritin level of 160 ng/ml (normal 15–89 ng/ml). Urine catecholamine levels were within normal limits. Abdominal computed tomography (CT) scan confirmed a large right renal mass with areas of necrosis and bleeding. There was no obvious lymphadenopathy and no intra-abdominal metastasis. Bone scintigraphy and CT scan of the thorax did not detect metastasis.

A right radical nephrectomy was performed. The tumor involved a large portion of the lower part of the kidney. The tumor was completely encapsulated and was 5.0 × 4.5 × 4.5 cm. Lymph nodes were negative for malignancy. Histologic examination revealed a small round cell tumor with massive necrosis, but no rosette formations. Periodic acid-Schiff (PAS) staining revealed diastase sensitive material in the tumor cell cytoplasm. Immunohistochemistry revealed that tumor cells were strongly positive for MIC-2 (CD99) as well as vimentin. The tumor cells were negative for chromogranin A, neurofilament, and synaptophysin. Electron microscopic examination showed a high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm (Fig. 1A). A higher magnification of tumor cells showed neurosecretory-type granules, microtubules, and desmosome-like structures (Fig. 1B). The expression of EWS-FLI-1 fusion transcript was demonstrated by molecular biology (Fig. 2). A single 330 base pair cDNA product was detected by ethidium bromide staining, corresponding to the EWS-FLI-1 as previously reported by Sorensen et al. [10]. Direct DNA sequencing confirmed the presence of a fusion of EWS exon 7 to the FLI-1 exon 6. Unfortunately chromosomal findings failed because proliferation of the tumor cells was poor. According to results on small round cell histology and immunohistochemical profiles, electron microscopic findings, and EWS-FLI-1 fusion transcript, the tumor was diagnosed as an ES/PNET of the kidney. Therapy was initiated with 1.5 gm/m^2 vincristine on days 1, 8, 15, 22, 29, and 36; 500 mg/m^2 cyclophosphamide on days 2, 9, 30, and 37; and 0.45 mg/m^2 dactinomycin on days 16–20 for induction and then a total of seven cycles of 4-drug chemotherapy, consisting of 1.5 gm/m^2 vincristine on days 1, 15, 22, 29, 36, and 43; 0.45 mg/m^2 dactinomycin on days 1–5; 500 mg/m^2 cyclophosphamide on days 16, 23, 30, 37, and 44; and 60 mg/m^2 doxorubicin on day 44 after surgery. She had no serious adverse effects during chemotherapy. She had no evidence of recurrence after 90 months from diagnosis and no late effects have been noted.

DISCUSSION

Though the existence of renal PNET was reported in 1975 in a review of pediatric PNETs [11], only a small number of cases have been reported. Recently, Parham et al. [12] from National Wilms Tumor Study Group Pathology Center reported that 79 of 146 cases of primary malignant neuroepithelial tumors of the kidney in adults and children were considered to be ES/PNET. Follow-up information, however, was only provided for 14 of 146 cases, and it is unclear which, if any, of those were actually ES/PNET [8]. Pediatric cases (younger than 15 years old) of ES/PNET of the kidney are extremely rare, and only ten cases have been reported previously [1–9]. Clinical characteristics, pathologic features, treatments, and outcomes of those cases are summarized in Table I.

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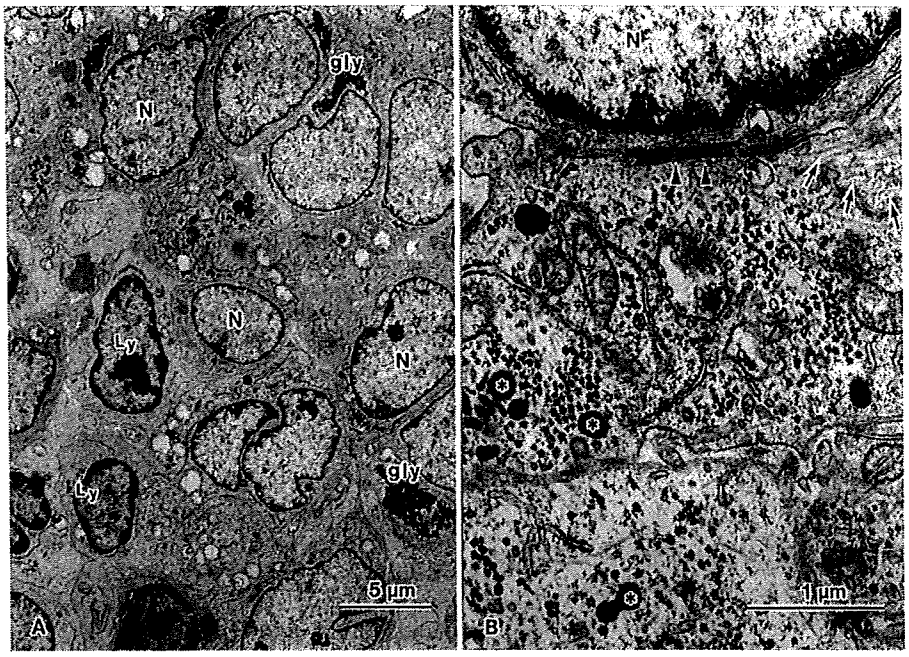

Fig. 1. Ultrastructural findings in the tumor cells. **A**: Tumor cells are oval and small (about 8–10 μm in a diameter). Nuclear-cytoplasm ratio is high. Nucleus has a few heterochromatin. Aggregated glycogen granules (gly) are observed in the cytoplasm. Ly, lymphocytes; N, nuclei. **B**: Neurosecretory granules (asterisks), microtubules (arrows), and desmosome-like structures (arrowheads) are observed in the tumor cells under higher magnification.

Several approaches can be used to arrive at a diagnosis of ES/PNET. The first approach is light microscopic examination of tumor tissue including immunohistochemistry. These tumors consist of primitive-appearing round cells with high nucleus to cytoplasmic ratios. The immunohistochemical features of ES/PNET are positive for CD99 (MIC2); however, expression of CD99 is by no means specific for ES/PNET among round cell tumors [13]. Although FLI-1 is a variable histochemical marker for ES/PNET, it is also positive in lymphoblastic lymphoma [14]. In contrast, WT-1 is a positive marker of Wilms tumor and desmoplastic round cell tumors, whereas it is a negative marker for ES/PNET, neuroblastoma and rhabdomyosarcoma. The second approach is electron microscopic examination of tumor tissue. Electron microscopic features include a specific high nuclear-cytoplasm ratio and aggregated glycogen granules in the cytoplasm. Neural differentiation appears on some cells with polar processes, which may contain microtubules or neurosecretory glands [15]. The third approach is chromosomal translocation, such as t(11;22) (q24;q12) which is positive in 88–95% of ES/PNET cases [16]. The final approach involves a molecular biologic examination. In 90–95% of cases of ES/PNET, the chimeric transcript is EWS-FLI-1; the remaining 5–10% are EWS-ERG. Other transcripts, including EWS-ETV1 and EWS-EIAF, have also been reported [16].

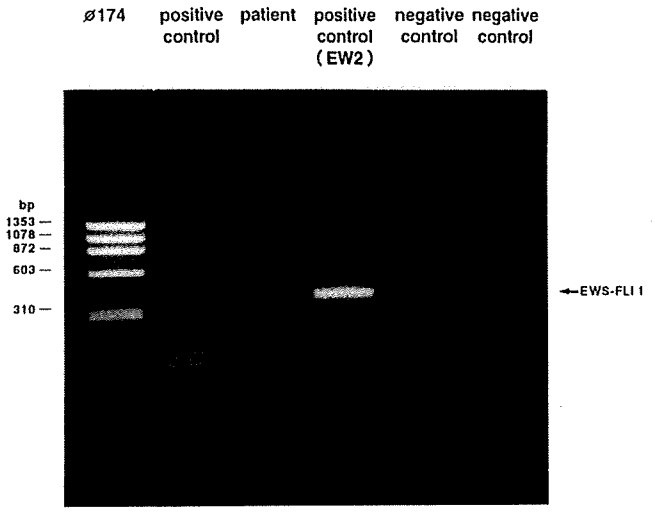

Fig. 2. A single 330 base pair transcript is detected in the patient sample following reserve transcriptase polymerase chain reactor (RT-PCR) performed on RNA extract from tumor tissue.

In terms of prognosis, the 5-year disease-free survival rate of ES/PNET is 45–55% [17], but the prognosis of ES/PNET of the kidney appears worse [1,18]. In pediatric cases (Table I), 5 of 8 patients were alive when the cases were reported; however, 1 patient (no. 6) was alive with disease, 2 patients (no. 3 and no. 5) were followed-up only for 6 and 8 months, and 1 patient was under treatment (no. 9). The follow-up duration was not described in this case. Only 2 patients (no. 8 and our case) were alive after 5 years. For 2 patients, it was not defined whether they were alive or not (Table I). Jimenez et al. [8] described that 3 of 11 patients were alive for 4–64 months, and 5 patients had local recurrence or distance metastasis then died of their disease, and 3 patients were lost to follow-up. Most of the recent therapeutic protocol for children with ES/PNET consists of vincristine, doxorubicin, cyclophsphamide, ifosphamide, and etoposide. Radiation and surgery have been used; some patients have been treated with myeloablative chemoradiotherapy followed by autologous bone marrow rescue. In spite of a lack of radiation therapy and our not using ifosphamide and etoposide for chemotherapy, our patient has survived for a relatively long period with no recurrence. Possible reasons for this good outcome might include the pathologic features of the tumor, the well-encapsulated nature of

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TABLE I. Clinical and Pathological Features of ES/PNET of the Kidney in Pediatric Cases

Case	Ref.	Age	Gender (yr)	Symptoms	Metastasis	Pathology (immunohistochemistries)	Chimeric transcript	Therapy	Outcome (follow-up [Mo])
1	1	4	F	Abdominal pain, fever	RPLN, liver	CD99(+),NSE(+),S-100(+), Ker(+),Act(−),Vim(−),Chro(−)	NS	IFO, CBP, VP-16 radiation	Died (1)
2	1	14	M	Bone pain, weight loss	Lung, bone, bone marrow	CD99(+),NSE(+),Vim(+),Synapto(+) (±)S-100(−),Ker(−),Act(−),Chro(−)	EWS/FLI-1(−) EWS/ERG(−)	CY, VCR, DOX,IFO,VP-16 auto BMT	Alive (under treatment)
3	2	13	NS	Abdominal pain, hematuria	No	MIC2(+),NSE(+),ker(−),Des(−), Act(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	NS
4	3	10	M	Abdominal mass	No	MIC2(+),NSE(+),Leu7(+), S-100(−),Ker(−), Des(−),Vim(−),Chro(−)	EWS/FLI-1(+)	Nephrectomy chemotherapy	Alive (6)
5	4	5	F	NS	IVC, right heart	NS	NS		NS
6	5	15	F	Abdominal pain, abdominal distention	No	MIC2(+),Vim(+),NSE(−), S-100(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (8)
7	6	9	M	Abdominal pain, abdominal mass, weight loss	No	MIC2(+),NSE(−),Vim(−),Ker(−), LCA(−)	NS	Nephrectomy CY, VCR, DOX,IFO,VP-16	Alive (relapse+) (10)
8	7	9	F	Abdominal distention, abdominal mass	No	CD99(+),LCA(−),Ker(−),Act(−), NFM(−)	EWS/FLI-1(+)	Nephrectomy IFO,VP-16,CY,DOX,VCR auto BMT	Died (5)
9	8	11	M	Gross hematuria, abdominal mass	No	CD99(+)	NS	Nephrectomy VCR, DOX, VP-16, CY, DAC	Alive (64)
10	9	14	F	Abdominal pain, abdominal mass	IVC, right heart, liver	NS	NS	Chemotherapy	Died (24)
11	Present case	6	F	Abdominal pain, abdominal mass	No	MIC2(+),Vim(+)NFM(−),Chrom(−)	EWS/FLI-1(+)	Nephrectomy VCR, DAC, CY, DOX,	Alive (90)

RPLN, retroperitoneal lymphonode; IVS, inferior vena cava; NSE, neuron specific enolase; Ker, keratin; Act, actin; Vim, Vimentin; Chro, chromogrn A; MIC2, B microgloblin; Des, desmin; NFM, neurofibrofilament; Synapto, sinaptophilin; IFO, ifomide; CBD, carboplatinum; CY, cyclophosphamide; VCR, vincristine; DOX, doxrubicine; DAC, actinomycin D; BMT, bone marrow transplantation.

the tumor with no involvement beyond the capsule and the accurate diagnosis followed by prompt treatment with chemotherapy. Several approaches including cytogenetical methods are important for early, accurate diagnosis of ES/PNET.

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ランチョンセミナー

小児がん経験者のQOL

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Ⅰ．はじめに

近年小児がんの治療成績は著しく向上し，現在では70～80％が治癒すると考えられている。現在，本邦における15歳以下の１年間あたりの小児がんの発生率は，１万人に約１人といわれている。治癒率を70％と仮定すると日本では若年成人の930人に１人が小児がん経験者であるということになる。またアメリカ合衆国では，現在20～39歳の640人に１人が小児がん経験者であり，そう遠くない将来に約450人に１人になると予想されている[1)]。

しかし，治療が終了した後に小児がんの治療に起因する合併症，あるいは小児がんの疾患自体の侵襲による後遺症を呈する者が少なくない。このことは小児がん経験者のQOLが必ずしも良好でないことを意味する。彼らが直面している問題は，身体的な事項だけでなく，心理的な問題，さらに社会的な問題と多岐にわたる。これらを小児がんにおける晩期合併症（late effects）といっており，この晩期合併症が彼らのQOLに大きく影響しているといってよい。

Ⅱ．小児がん経験者とQOL

小児がん経験者におけるQOLは，図１に示すように，身体機能，心理状態，社会生活機能などと密接に関係する。年齢，性別，家庭環境，経済状態，教育環境などの本人の特性や，病気の発症年齢，原発部位，治療内容によっても大きく左右される。疾患によりQOLが異なると

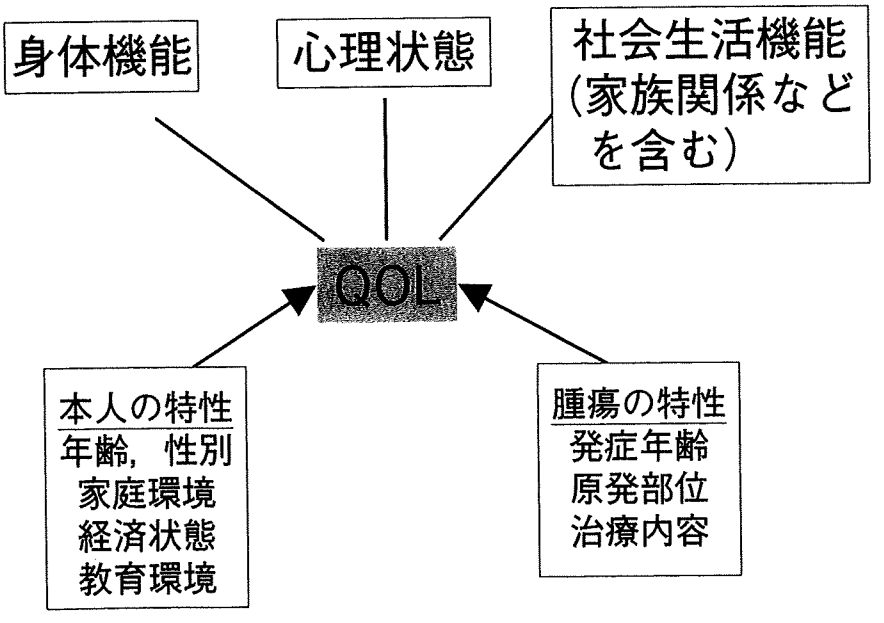

図１　小児がん経験者のQOL

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いう研究もある[2]。

そもそもQOLとは，個人の主観的な満足度を示すものであり，一人ひとりその評価は異なる。以前，小児がんのほとんどが治癒しなかった時代では，小児がんのQOLは，残された時間をいかに本人にとって幸せに過ごすかということから評価されていたが，現在，小児がんのQOLは，小児がんを経験し，それを克服した人たちが，成長，発達し成人になっていく過程，および成人になってからの生活がいかに満足のいくものであるかという観点から，評価されることがほとんどである。

しかし，小児がんのQOLの調査は非常に困難である。対象者が小児の場合，QOL調査に本人が回答できないため，両親が回答することが少なくない。また病名の告知の有無により，回答は大幅に異なる。本人にはそのような調査が行われていることを隠していることさえある。また欧米では小児がんに対するQOL評価表の整備が進んでいる[3~6]が，日本では最近ようやく小児用のQOL評価表ができたところであり，まだ一般的に使用されているわけではない。

Ⅲ．晩期合併症とQOL

以上述べてきたように，現在，小児がん経験者のQOLを規定するもののほとんどが晩期合併症といっても過言ではない。晩期合併症には，治療終了時には認められず，治療終了後年月を経て問題になってくる事項もある。診断5年後では約30%が晩期合併症を抱えているが，20～30年後には約70%になるとの報告もある。最近オランダから報告された研究では，1966～1996年に小児がんの治療を受けた1,362名の約75%に一つ以上の有害事象が発生しており，40%に重度，あるいは生命にかかわる機能障害をともなう有害事象が1つ以上あった。治療との関係では放射線療法のみでは55%，化学療法のみでは15%，外科手術のみでは25%であった。さらに疾患別では骨腫瘍の経験者の64%に高度の有害事象が認められ，白血病およびウイルムス腫瘍の経験者における有害事象は12%と最も頻度が低かったとの結果であった[7]。

表1に小児がんの晩期合併症の項目について示した。

Ⅳ．身体的晩期合併症

晩期合併症は身体のあらゆる部位に起こり，さまざまな身体機能に関係する。疾患の種類や治療法あるいは治療を受けた年齢，性別などによって，起こりやすい症状や身体の部位などが異なる。表2に晩期合併症と治療との因果関係のうち，現在明確にされているものを示した。

頭蓋放射線照射は，脳腫瘍の治療や白血病・リンパ腫の中枢神経浸潤予防のために行われる治療である。照射野の中には，視床下部や下垂体など内分泌と大きくかかわる臓器が含まれるため，成長ホルモンをはじめとするいくつかのホルモンの分泌に障害が出てくることがある。われわれが，東京小児がん研究グループのプロトコールで治療された急性リンパ性白血病（ALL）の経験者287名（全例頭蓋放射線照射を受けている）の最終身長を調べた結果では，男子161名中8名（5.0%），女子126名中6名（4.8%）が－2SD以下の低身長であった。また小児がんの治療後にはさまざまな神経障害の報告があるが，頭蓋放射線照射との関連が強く示唆される障害も少なくない。たとえばわれ

表1　小児がんの晩期合併症

1）成長・発達への影響
低身長，肥満，やせ，骨格・筋・軟部組織の異常，知能低下，認知力低下，心理的，社会的成熟に関する問題，性的成熟の異常

2）生殖能力への影響
妊孕力低下，子孫への影響

3）免疫機能低下

4）臓器機能への影響
心毒性，呼吸器障害，肝機能障害，腎機能障害，消化管障害，骨・筋の異常，内分泌機能異常，視力・視野異常，聴力障害，皮膚障害，神経障害

5）二次性腫瘍
良性腫瘍，
悪性腫瘍（二次性白血病，脳腫瘍など）

表2 晩期合併症と治療との関係

成長ホルモン欠乏	頭蓋放射線照射
肥満	頭蓋放射線照射
神経・認知障害	頭蓋放射線照射，MTX/Ara C 髄注
心毒性・うっ血性心不全	アントラサイクリン
思春期早発	頭蓋放射線照射
甲状腺機能低下	甲状腺・頭蓋・脊椎放射線照射
不妊	アルキル化剤，全身放射線照射，腹部・睾丸放射線照射
骨粗鬆症	副腎皮質ホルモン，性腺放射線照射，頭蓋・脊椎放射線照射，MTX
大腿骨頭壊死	副腎皮質ホルモン
白内障	頭蓋放射線照射，副腎皮質ホルモン
HCV 関連肝障害	1992年2月以前の輸血
歯芽異常	頭蓋放射線照射，幼少時の抗がん剤使用
二次性脳腫瘍	頭蓋放射線照射
二次性白血病	トポイソメラーゼII阻害薬，アルカリ化剤
皮膚癌	放射線照射

われの調査では，ALL 治療後にもやもや病を発症した6例は全例頭蓋放射線照射を受けていた[8]。さらに二次性の脳腫瘍などの発症原因ともなることが指摘されている[9]。

抗がん剤と晩期合併症との関係についてもいくつか明らかになっていることがある。たとえば，アントラサイクリン系の抗がん剤には心毒性があり，とくに慢性蓄積性の心毒性は拡張型心筋症，さらにはうっ血性心不全を起こすことがあり，晩期合併症の中でも重大な問題である[10,11]。また，トポイソメラーゼII阻害剤や代謝拮抗剤による二次性白血病の発症も生命にかかわる重大な晩期合併症である[12]。

近年，小児がんの治療成績向上に大きな役割を果たした造血幹細胞移植（SCT）に関する晩期合併症も，最近多くの報告がある。その内容は移植後の GVHD と関連したもの，全身放射線照射による不妊やさまざまな内分泌学的な問題，二次性腫瘍など多種多様であり，化学療法のみの治療より重大でかつ頻度が高いとされている。しかし最近でも，SCT 治療を選択する際に疾病の治癒が最優先され，治療後の QOL を重要視するという意識は患者側には低いというアンケート結果が報告されている。この論文では QOL について医師が利用できるデータが少ないため，患者への説明が困難なことに原因があり，医師と患者が共有できる QOL についての情報の蓄積が必要であると結論されている[13]。

V．その他の晩期合併症

小児がん経験者の15～30％に心的外傷後ストレス症候群（PTSD：Post Traumatic Stress Disorder），うつ状態，情緒不安定などの心理的な問題があるといわれている。生命の危機，治療にともなう苦痛だけでなく身体的晩期障害である成長障害や不妊，四肢の切断などは PTSD の原因となり，小児がん経験者の約20％が PTSD の診断基準を満たすとの報告がある[14]。また教育（学校），就職，結婚，保険への加入など小児がんに罹患したことがその後の人生に大きなマイナスの影響を及ぼすことがある。これらも広い意味で晩期合併症の範疇となり，QOL と多大な関係があるものである。

VI．小児がん経験者が良好な QOL を保つために

治療が成功した後，小児がんの経験者が良好な QOL を保った健常な生活を一生送れるようにするために，どのような支援をすべきかということを医療者は考えなければならない。その中で，小児がんを患った方たちを長期にわたりきちんとフォローアップし，必要に応じ援助できるような体制を用意すべきではないかという考えが広まりつつあり，最近その準備が始まっている。日本小児白血病リンパ腫研究グループ（JPLSG）長期フォローアップ委員会では，この活動の一環として，本邦での現状を把握し，今後のあり方を提言するためにアンケート調査を行い報告した。その結果，多様な晩期合併症

に対し各施設が限られた体制の中で対処している現状が浮き彫りになった[15]。2006年には厚生労働省がん助成，2007年には厚生労働省科学研究費補助金による研究班が成立し，今後国のレベルで小児がん経験者に対する対策がたてていける可能性が出てきたことは喜ばしいことである。

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Case Report

A CASE SERIES OF CHILDREN WITH HIGH-RISK METASTATIC NEUROBLASTOMA TREATED WITH A NOVEL TREATMENT STRATEGY CONSISTING OF POSTPONED PRIMARY SURGERY UNTIL THE END OF SYSTEMIC CHEMOTHERAPY INCLUDING HIGH-DOSE CHEMOTHERAPY

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□ *The aim of this study was to clarify the feasibility of a novel treatment strategy consisting of postponed primary surgery till the end of systemic chemotherapy including HDC without interruption by local therapy for neuroblastoma patients at a high risk for relapse. After induction chemotherapy, patients received double conditioning HDC consisting of thiotepa and melphalan. Radical surgery was applied to local lesions. Irradiation was not applied to any lesions. Eleven consecutive pediatric neuroblastoma patients were treated according to this strategy. Seven of 11 patients remained in complete remission for 21{171 months. This treatment strategy seems feasible and a further study is warranted.*

Keywords delayed primary surgery, high-dose chemotherapy, high-risk neuroblastoma, melphalan, thiotepa

Advanced neuroblastoma is a systemic disease that spreads to the whole body, including the bone marrow, liver, lymph nodes, and bones. Morphologic or radiologic methods only detect metastases larger than a certain size. This indicates that high-risk neuroblastoma should be considered as a

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systemic disease and that an increase of chemotherapy intensity is a premise for the improvement of treatment outcome. Indeed, the only method that has been proven to significantly improve survival is strengthening of chemotherapy intensity, including high-dose chemotherapy (HDC) with stem cell rescue. Thus, HDC with stem cell salvage following intensive induction chemotherapy has been widely accepted as being required for neuroblastoma treatment in high-risk groups, and treatment results have improved [1–5]. However, the 5-year event-free survival (EFS) rate is 30–40% and remains unsatisfactory despite various intensive efforts [3–5].

Neuroblastoma cells acquire resistance to chemotherapy in the early stages of treatment: it is therefore a premise for attaining a cure to eradicate tumor cells before they acquire chemotherapy resistance. We therefore assumed that interruption of systemic chemotherapy and/or reduction of dose intensity by surgery and radiotherapy might promote acquisition of drug resistance by malignant cells and clonal evolution. We also assumed that intensive chemotherapy combined with potent HDC might enable us to postpone local therapy until after the completion of all systemic chemotherapies. Based on this hypothesis, we postponed local therapy until the completion of all systemic chemotherapies, which made it possible to administer intensive chemotherapy in a shorter period of time and increase chemotherapy intensity without interruption of chemotherapy. As local therapy, surgery for the primary focus and residual metastases was finally performed at completion of treatment and response to chemotherapy was then evaluated pathologically.

With respect to local therapy, no difference has been observed in the EFS rate between gross total resection and partial resection in prospective studies despite a decrease in local recurrence rate with gross total resection [6, 7]. In a similar manner, local radiotherapy has been clearly shown to reduce local recurrence [8], but its contribution to the improvement of EFS has not been proven [9, 10]. Thus, though extensive local therapy reduces the local recurrence rate, it does not significantly contribute to increased survival. Since we assumed the significance of local surgery might increase under sufficient control of systemic disease, gross total resection was attempted in all patients. Radiotherapy was not performed because of the acute adverse effects and late complications following intensive chemotherapy. We report the results of this novel treatment approach in a consecutive series of 11 children (1992–2005) with high-risk abdominal neuroblastoma.

PATIENTS AND METHODS

Patients

Eleven consecutive pediatric patients with abdominal and mediastinum neuroblastoma at high risk for relapse were treated according to the

current treatment strategy. The high-risk category includes International Neuroblastoma Staging System (INSS) stage 4 for patients aged ≥1 year and $MYCN^+$ stage 4 for those aged <1 year. Table 1 summarizes the clinical data for the 11 patients (6 males; 1 aged <1 year; age range 6–64 months (median, 33 months)). Amplification of the MYCN gene was analyzed in primary tumors at first surgery in 8 patients and in bone marrow samples for the other 3. Six patients had MYCN amplification and 5 had no amplification by fluorescence in situ hybridization analysis. Seven of 8 patients who underwent biopsy of primary tumor or metastatic lymph nodes had unfavorable histopathological findings. Eight patients had poorly differentiated neuroblastoma and 1 had undifferentiated neuroblastoma according to the International Neuroblastoma Pathology Classification. Three patients (#6, #8, and #11) did not undergo biopsy at the outset but histological confirmation was performed in patient 6 at final surgery.

Induction Chemotherapy

For induction chemotherapy, we basically employed the new A1 regimen (cyclophosphamide (CPA) 1.2 g/m^2, etoposide (VP-16) 100 mg/m^2 × 5, tetrahydropyraniyl-adriamycin (THP-ADR) 40 mg/m^2, and cisplatin (CDDP) 90 mg/m^2) or the 98A3 regimen (CPA 1.2 g/m^2 × 2, CDDP 90 mg/m^2, THP-ADR 40 mg/m^2, and vincristine (VCR) 1.5 mg/m^2). We administered newA1 or 98A3 regimen every 4 weeks. Three patients received carboplatin (CBDCA) instead of CDDP because of insufficient renal function. Irinotecan was additionally administered to 4 patients [11]. Induction chemotherapy was administered for 3–6 courses, principally until normalization of tumor markers (neuron-specific enolase (NSE), vanillyl-mandelic acid (VMA), and homovanillic acid (HVA)) and disappearance of distant metastases. The disappearance of metastasis was evaluated by computed tomography, technetium-99 bone scan, bilateral bone marrow aspiration, and iodine-123 metaiodobenzyl-guanidine scan.

High-Dose Chemotherapy

After induction chemotherapy, patients received a double-conditioning regimen of 2 cycles of high-dose chemotherapy (HDC) consisting of thiotepa and melphalan [12]. Patients aged ≥2 years received 800–1000 mg/m^2 of thiotepa and 280–300 mg/m^2 of melphalan, and patients aged <2 years at HDC received 32 mg/kg of thiotepa and 6 mg/kg of melphalan. This HDC regimen consisted of 2 cycles of administration of thiotepa and melphalan with a 1-week interval; thiotepa (140–200 mg/m^2/day) and melphalan (50–75 mg/m^2/day) were administered on days –11, –10, -4 and –3. When creatinine clearance (Ccr) was <90 mL/min/1.73m^2 in

TABLE 1 Characteristics of Patients with Stage 4 Neuroblastoma

Patient	Age (mo.)	Gender	Primary site	INSS stage	Metastatic site at diagnosis	MYCN	Histology	
							INPC	Shimada
1	25	F	Adrenal	4	LN, B, BM	no amp	Poorly diff. NB	UH
2	53	M	Adrenal	4	LN, B	no amp	Poorly diff. NB + GN	UH
3	20	M	Adrenal	4	LN, B, BM, Lu	14	Undiff. NB	UH
4	19	M	Adrenal	4	LN, B	>20	Poorly diff. NB	UH
5	6	M	Adrenal	4	LN, BM, L	12	Poorly diff. NB	FH
6	48	F	Adrenal	4	LN, B, BM	20	N.E	N.E
7	29	F	Adrenal	4	LN, B, BM	>10	Poorly diff. NB	UH
8	33	M	Adrenal	4	LN, B, BM	>10	N.E.	N.E.
9	54	M	Retroperitoneum	4	LN, B, BM	no amp	Poorly diff. NB	UH
10	64	F	Retroperitoneum	4	LN (mediastinum)	no amp	Poorly diff. NB	UH
11	49	F	Mediastinum	4	B, BM	no amp	N.E.	N.E.

Note. B, bone; BM, bone marrow; F, female; FH, favorable histology; GN, ganglioneuroblastoma; INPC, International Neuroblastoma Pathology Classification; L, liver; LN, lymph node; Lu, lung; M, male; N.E., not evaluable; Poorly diff. NB, poorly differentiated neuroblastoma; UH, unfavorable histology; Undiff. NB, undifferentiated neuroblastoma.

TABLE 2 Induction Chemotherapy and Preconditioning Regimens

Patient	Conventional protocol	Chemotherapy (no. of courses)	Time to HDC from onset (days)	Time of stem cell harvest (course)	Stem cell source	Conditioning regimen	
						Thiotepa (mg/m^2)	Melphalan (mg/m^2)
1	new A1[a]	3	120	3	Auto-BM	1000	300
2	new A1	5	130	2	Auto-PB	800	280
3	new A1[a]/ CPT-11	6		N.D.	N.D.		
4	new A1[a]	5	167	3	Auto-BM	1000	280
5	98A3 / CPT-11	6	185	N.D	u-CB	26[c]	6[b,c]
6	98A3 / CPT-11	5	165	N.D	u-CB	760[b]	210[b]
7	98A3→98A3/ CPT-11	4	139	2 (PB) and 4 (BM)	Auto-PB, BM	800	280
8	98A3	5	167	5	Auto-BM	800	280
9	98A3	4	167	2	Auto-PB	720[d]	252[d]
10	98A3	4	132	1	Auto-PB	720[d]	252[d]
11	98A3	4	148	3 (PB) and 4 (BM)	Auto-PB, BM	570[d]	200[d]

Note. Auto-BM, autologous bone marrow; Auto-PB, autologous peripheral blood; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan N.D., not done; u-CB, unrelated cord blood.

[a]CBDCA was administered instead of CDDP.

[b]Drug dose was reduced because of transplantation from allogeneic donors.

[c]Drug was administered in terms of body weight (mg/kg).

[d]Drug dose was reduced to 70–90% of the prescribed dose according to renal function.

patients aged ≥2 years, dosage was adjusted according to the following formula: given dose (mg/m^2) = (Ccr/100) × 800 mg/m^2 (thiotepa) or 280 mg/m^2 (melphalan). In the case of allogeneic transplantation, doses of these drugs were reduced, because of severe gastrointestinal toxicity due to these alkylating agents. Peripheral blood stem cells (PBSCs) and bone marrow cells were used as salvage stem cells in 4 and 3 patients, respectively. Because PBSC count was insufficient for stem cell rescue in 2 patients, bone marrow cells were also transfused with PBSCs. Autologous bone marrow was used in the patients in whom PBSCs could not be harvested: this was performed at the end of induction chemotherapy. PBSCs were harvested after the 1st to 4th course of induction chemotherapy, after morphologic disappearance of tumor cells from bone marrow. In the 2 patients in whom disappearance of tumor cells from bone marrow was delayed, unrelated umbilical cord blood was used (Table 2).

Local Therapy

After all courses of chemotherapy including HDC, radical surgery was finally applied to remove tumor tissue in local lesions when bone marrow function was acceptably recovered for surgery. Total resection for primary tumor as well as lymph node metastases was attempted. All lesions where the primary tumor and local lymph node metastases existed in onset of the disease were explored and if any suspected tumor tissue was existed, then resection was performed.

CT scan was performed after surgery to confirm no residual tumor in local lesions in all cases. Irradiation was not applied to any local lesions.

RESULTS

Response to Induction Chemotherapy

In 1 patient (#3), tumors did not respond to induction chemotherapy and he showed progressive disease. He died from progression of pulmonary metastatic tumors 6 months after diagnosis before HDC. After 3–6 courses (median, 5 courses) of induction chemotherapy, 10 patients received HDC. Time from initial diagnosis to HDC was 4–6 months (median, 5 months). With respect to metastases at initial diagnosis in patients who received HDC, these were detected in bone ($n = 8$), bone marrow ($n = 7$), lymph node ($n = 9$), and liver ($n = 1$) and evaluated by computed tomography, technetium-99 bone scan, bilateral bone marrow aspiration, and iodine-123 metaiodobenzyl-guanidine scan. After induction chemotherapy, the bone marrow metastases disappeared in all patients, but liver and bone metastases each remained in 1 patient, respectively. Primary tumors and regional lymph node metastases remained in all patients. Tumor marker levels were

normalized in all patients. At HDC, 7 patients attained PR and 2 VGPR according to International Neuroblastoma Response Criteria.

Response to High-Dose Chemotherapy

Nine patients received HDC at PR or VGPR. The size of one primary tumor did not change. After HDC, residual bone metastases disappeared in 1 patient. Liver metastases persisted in 1 patient. Five primary tumors that decreased to below 50% after conventional chemotherapy decreased to below 10% and the sizes of primary tumors did not change dramatically, but metastatic lymph nodes disappeared in 2 patients. With respect to adverse reactions observed during HDC, fungal osteomyelitis was observed in 1 patient who received allograft. In addition, gastrointestinal tract mucositis with bloody stools was observed in 1 patient and NCI-CTC grade III mucositis was noted in all patients.

Surgery and Pathological Evaluation of Tumors

Radical surgery was performed in each patient, resecting all recognizable lesions, including the primary tumor and affected lymphatic tissues. The timing of surgery was 2 months after the initiation of HDC in most patients who received autologous stem cell transplantation, and it was prolonged to 4 months in the patients who underwent allogeneic transplantation and/or had HDC-related complications (Table 3).

We evaluated the effect of chemotherapy including HDC by comparing tumor specimens resected at outset and second-look surgery in 6 patients, according to the histologic criteria for the effects of anticancer therapy for pediatric solid malignant tumors in Japan (Table 4) [13]. We were not able to evaluate the remaining 4 patients as insufficient amounts of pretreatment specimen were available. Necrotic or fibrous lesions were seen in one-third to two-thirds of the area of tumor tissues (Ef1b) of 1 patient. In the 4 cases, prominent necrosis and loss of tumor cells were observed in more than two-thirds of the tumor area and was associated with fibrosis and calcification (Ef2). On histological examination, the specimens from almost all, except one (#11), resected primary tumors had some degree of residual tumor tissue and in occasional cases viable tumor tissue was recognized in concurrently resected lymph nodes. However, residual tumor tissue consisted of scattered nests of neuroblastic cells in degenerative fibrous tissue, occasionally associated with Schwannian cell proliferation. Neuroblastic cells were more differentiating with abundant neutrophil formation as compared to pretreatment tumors. The preoperative induction chemotherapy and HDC produced remarkable cytotoxic effects and induced differentiation toward ganglionic cells. Examples of the histopathologic changes resulting from treatment are shown in Figures 1 and 2.

TABLE 3 Response to Treatment and Outcome

Patient	Response to induction chemotherapy			Response to induction chemotherapy and HDC			Time to surgery		Post therapy histology classification[a]	Outcome from diagnosis (mo.)
	Response	Residual site	VMA,HVA (mg/mg$_{Cr}$)[c]	Response	Residual site	VMA, HVA (mg/mg$_{Cr}$)[c]	From HDC (days)	From onset (days)		
1	PR	P/LN	≦20, ≦20	PR	P/LN	≦20, ≦20	96	216	N.E.	EFS (171)
2	PR	P/LN	N.E.[d]	VGPR	P	N.E.[d]	79	209	N.E.	EFS (104)
3	PD	–		–	–		––	––	–	PD (3[b])
4	PR	P/LN/B	N.E.[d]	VGPR	P	N.E.[d]	68	235	Ef1b	EFS (159)
5	PR	L/LN	≦20, ≦20	PR	L/LN	≦20, ≦20	106	291	Ef2	EFS (73)
6	PR	P/LN	N.E,[d], ≦20	VGPR	P	N.E.[d] ≦20	99	264	N.A	EFS (57)
7	PR	P/LN	N.E.[d], ≦20	VGPR	P	N.E.[d], ≦20	52	191	Ef2	Relapse in LN (24)
8	VGPR	P	≦20, ≦20	VGPR	P	≦20, ≦20	83	250	N.E.	EFS (38)
9	VGPR	P	≦20, ≦20	VGPR	P	≦20, ≦20	85	252	Ef2	Relapse in multiple sites (20)
10	PR	P	≦20, ≦20	VGPR	P	≦20, ≦20	50	182	Ef2	Relapse in LN (18)
11	PR	P	≦20, ≦20	PR	P	≦20, ≦20	55	203	Ef3	EFS (21)

Note. B, bone; CR, complete response; EFS, event-free survival; HDC, high-dose chemotherapy; L, liver; LN, lymph node; NR, no response; P, primary; PD, progressive disease; PR, partial response; VGPR, very good partial response. HVA, urine homovanillic acid; VMA, urin vanillylmandelic acid.

[a]Pathological classification according to the Committee on Histological Classification of Childhood Tumors, Japanese Society of Pathology (see Table 4).

[b]Decreased.

[c]The level of VMA and HVA are revised by urin creatinin. Normal levels of VMA and HVA are below under 20 mg/mg Cr in our institute for every age.

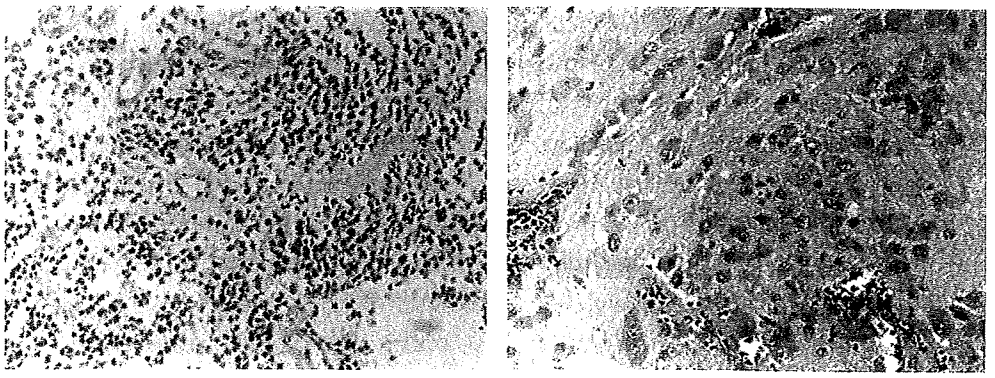
[d]Normal levels of cathecholamine at onset.

TABLE 4 Pathological Classification of Treatment Effect According to the Committee on Histological Classification of Childhood Tumors, Japanese Society of Pathology

Ef0	No effect
Ef1a	Necrosis of tumor cells in less than one-third of tumor area
Ef1b	Necrosis of tumor cells in less than two-thirds and in more than one-third of tumor area
Ef2	Necrosis and disappearance of tumor cells plus calcification and fibrosis in more than two-thirds of tumor area
Ef3	All tumors are affected by obvious necrotic tissue and no tumor cells are seen

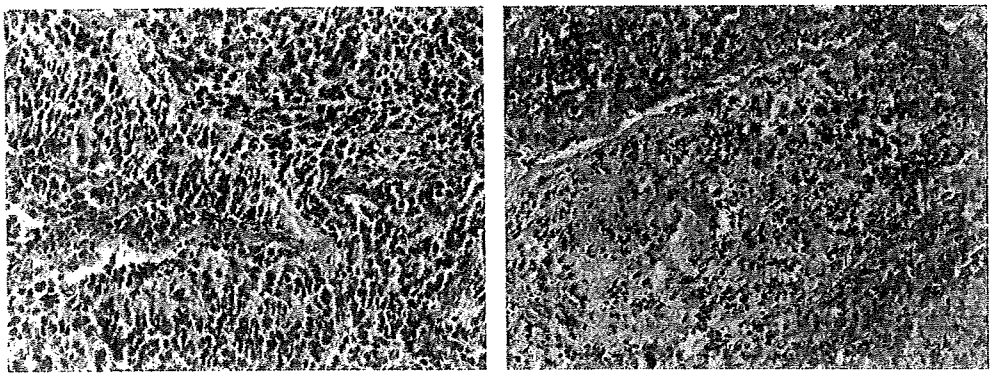
Outcome

Altogether, 10 of 11 patients received HDC and 7 patients have remained in remission for 21–171 months (median, 73 months). In 2 patients (#7 and #10), the tumor relapsed in regional abdominal and thoracic lymph nodes after 24 and 18 months, respectively, from initial diagnosis. In patient #9, relapse was observed in multiple sites including bone, bone marrow, and lymph nodes 20 after from diagnosis. After gross total resection of the tumors, patient #7 received salvage chemotherapy, consisting of irinotecan and topotecan, and local irradiation. Finally, allogeneic stem cell transplantation preconditioned with fludarabine and busulfan was performed. She has been in remission for 21 months after relapse. The other 2 patients are currently undergoing treatment.



(a) (b)

FIGURE 1 Histological findings for primary tumor is from patient 4: (a) before treatment—poorly differentiated subtype with low mitosis karyorrhexis index (MKI); and (b) after HDC—residual tumor nests of differentiating neuroblastic cells.



(a) (b)

FIGURE 2 Histological findings for lymph node metastasis from patient 5: (a) before treatment—poorly differentiated subtype with low mitosis karyorrhexis index (MKI); and (b) after HDC—extensive necrosis with residual differentiating neuroblastic cell nests.

DISCUSSION

Primary surgery is generally and traditionally performed between induction chemotherapy and HDC. It might be possible that tumor cells become more sensitive to chemotherapy after mass reduction, but the rationale of the timing of local therapy is unclear. In this case series, we performed primary surgery after completion of induction chemotherapy and HDC based on the hypothesis that consecutive conventional and high-dose chemotherapies without interruption by local therapy can eradicate systemically spread tumor cells before acquisition of resistance to cytotoxic drugs and clonal evolution of resistant clones. The disadvantage of this treatment strategy is the increased risk for metastasis of tumor cells residing in the local tumors and emergence of resistant clones in these. Among 11 consecutive high-risk patients with stage 4 neuroblastoma, except 1 patient whose tumors were primarily refractory to induction chemotherapy, none displayed progressive disease before local surgery; 7 patients remain in event-free survival; and systemic relapse was observed in only 1 patient.

The disadvantage of performing surgery during chemotherapy appears to be related to the interruption of systemic therapy. Furthermore, when intraoperative/postoperative complications occur, discontinuation of systemic chemotherapy may be prolonged and this may cause systemic relapse. In performing surgery after all courses of chemotherapy, the timing of surgery can be selected under conditions of sufficient tumor control. Surgery was safely performed after recovery of hematopoiesis in this series.

In this treatment strategy, HDC plays a key role, since less potent HDC may allow progression of the local tumor. For HDC, we employed a double-conditioning regimen consisting of thiotepa and melphalan, as previously reported [12]. These agents were chosen for the treatment of neuroblastoma, as they show efficacy as high-dose, single-agent therapy for