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ORIGINAL ARTICLE

Neuroblastoma: treatment outcome after incomplete resection of primary tumors

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Abstract
Purpose For International Neuroblastoma Staging System (INSS) stages III or IV neuroblastoma (intermediate or high risk), complete excision of the primary tumor is not always feasible. Most current studies on the treatment outcome of these patients have reported on the complete excision status. The aim of this study is to review the treatment outcome after the incomplete resection.
Methods The medical records of 37 patients that underwent incomplete resection between January 1986 and December 2005 were reviewed retrospectively. Incomplete resection was assessed by review of the operative notes and postoperative computerized tomography. Age, gender, tumor location, INSS stage, N-*myc* gene copy number, pre- and postoperative therapy, and treatment outcome were reviewed. The treatment outcome was evaluated according to the postoperative treatment protocol in the high-risk group.
Results Intermediate-risk patients were treated with conventional chemotherapy, isotretinoin (ITT) and interleukin-2 (IL-2). High-risk patients were treated with peripheral blood stem cell transplantation (PBSCT), ITT, and IL-2 ($N = 11$). Before the introduction of PBSCT, the high-risk patients were also treated with the conventional chemotherapy ($N = 19$). Intermediate-risk patients ($N = 5$) currently have no evidence of disease (NED). For the high-risk patients ($N = 32$), 19 patients were treated with chemotherapy alone; 15 patients died of their disease while four patients currently have an NED status. Eight of 11 patients that underwent PBSCT are currently alive.
Conclusions For intermediate risk, conventional chemotherapy appears to be acceptable treatment. However, for high-risk patients, every effort should be made to control residual disease including the use of myeloablative chemotherapy, differentiating agents and immune-modulating agents.

Keywords Neuroblastoma · Incomplete excision · Stem-cell transplantation · Retinoic acid · Interleukin-2

Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children. Its clinical behavior varies from spontaneous regression to rapid and potentially fatal progression. Therefore, treatment plans must vary from close clinical observation to multimodal interventions, including surgery, chemotherapy, and radiotherapy. Complete surgical removal of the primary tumor remains to be an essential component of treatment for the majority of patients with NB [1]. Studies have shown the positive outcome of primary tumor resection in patients with NB [2, 3]. For low risk, International Neuroblastoma Staging System (INSS) stages I and II tumors, complete surgical excision alone can provide adequate treatment for a cure [4, 5]. However, in patients with INSS stages III or IV tumors (intermediate or high risk), complete excision is not always feasible, and can occasionally cause serious complications [5]. Most NB treatment results have been

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reported on the basis of a complete excision status; there are few studies that have evaluated the treatment outcome after an incomplete resection. Here, we report the treatment outcome of patients with NB without complete excision.

Methods

Of the 191 patients who were treated between January 1986 and December 2005 at the Department of Pediatric Surgery and Department of Pediatrics, 47 patients (24.6%) underwent incomplete surgical resection and 10 patients were excluded because of loss during follow-up ($N = 5$) or lack of N-*myc* gene copy number testing ($N = 5$). Incomplete resection of NB was defined in patients where a gross total resection could not be achieved, even after a second-look operation. It was determined by the review of the surgeon's operative report in conjunction with postoperative computerized tomography. The medical records of 37 patients were reviewed retrospectively. The information collected was as follows: gender, age at diagnosis, tumor location, INSS stage, N-*myc* gene copy number, preoperative and postoperative therapy, and treatment outcome. Neuroblastoma risk group was defined according to the Children's Oncology Group protocols [1], and INSS stage, age, and N-*myc* gene copy number were considered to define the patients' risk group. The disease-free survival (DFS) and overall survival (OS) were estimated using a Kaplan–Meier curve and compared with log-rank test. Statistical significance was accepted at a $P < 0.05$. Institutional review board review and approval was obtained for this study (IRB No. H-0701-045-196).

Results

Patient characteristics

Twenty-seven patients were male and ten were female. The mean age at diagnosis was 3.2 years (range 5 months–7.6 years), and four patients (11%) were under 1 year of age. The median follow-up duration after the diagnosis was 5.0 years (range 6 months–17.6 years). The adrenal glands (10 right, 8 left) were the most common primary site. Thirty-two patients were considered high risk (2 stage III, 30 stage IV) and five patients intermediate risk (4 stage III, 1 stage IV). Four patients who were under 1 year of age had intermediate-risk disease. There were no low-risk patients. The patient characteristics are summarized in Table 1.

Table 1 Patients characteristics (N = 37)

Age at diagnosis (years)	
<1	4
>1	33
Sex	
Male	27
Female	10
Primary site	
Adrenal	18 (10 right, 8 left)
Extra adrenal	19 (12 retroperitoneum, 4 mediastinum, 2 pelvic, 1 primary site not identified)
N-*myc* gene copy number	
Single	23
Amplification	14
Risk group	
Intermediate	5 (4 stage III, 1 stage IV)
High	32 (2 stage III, 30 stage IV)

Preoperative therapy

Twenty-nine patients received four or five cycles of chemotherapy before surgery. The CCG-321-P2 chemotherapy regimen was used, which consisted of cisplatin, VP-16, doxorubicin, and cyclophosphamide [6]. Eight patients underwent surgery without preoperative chemotherapy.

Postoperative therapy

All patients received local radiation therapy after surgery up to 24 Gy. Total body irradiation was not performed for NB at our institute. Intermediate-risk patients ($N = 5$) were treated with conventional chemotherapy, and 13-*cis* retinoic acid [isotretinoin (ITT)], interleukin-2 (IL-2) therapy were offered after chemotherapy. Myeloablative chemotherapy with stem-cell transplantation was not performed for intermediate-risk patients.

High-risk patients were treated with peripheral blood stem-cell transplantation (PBSCT) after myeloablative chemotherapy ($N = 11$). Two kinds of conditioning regimen were used; MEC regimen (melphalan, etoposide, carboplatin) for nine patients and TopoThioCarbo regimen (topotecan, thiotepa, carboplatin) for two patients. Before the introduction of PBSCT, patients were treated with conventional chemotherapy alone postoperatively ($N = 19$). Patients whose parents refused PBSCT ($N = 2$) were treated with conventional chemotherapy.

Post-transplantation therapy

All patients received ITT and IL-2 therapy after PBSCT. Patients that received conventional chemotherapy instead of PBSCT (due to parental refusal) also received ITT and IL-2 therapy after chemotherapy. Patients were started on ITT 28 days after the PBSCT (dose 100 mg/m^2 per day for 1 year). A single subcutaneous injection of recombinant

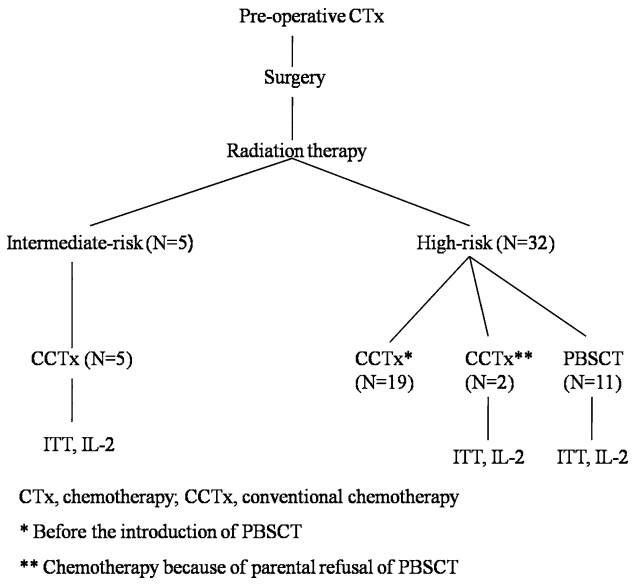

Fig. 1 Flow chart showing the treatment plan after the incomplete resection of primary tumors

IL-2 (dose 3×10^6 IU/m^2) was provided daily for five consecutive days every other week for 11 weeks (total 30 doses), starting when the absolute neutrophil count and platelet counts increased to more than 1,000 per μL and 50,000 per μL, respectively. Treatment flow is summarized in Fig. 1.

Treatment outcome

Treatment outcome was classified into three groups: no evidence of disease (NED), alive with disease (AWD), and died of disease (DOD). All patients with intermediate risk ($N = 5$) currently have an NED status. The mean follow-up duration after diagnosis, for these patients was, 5.7 years (range 21 months–10.8 years). For the high-risk patients ($N = 32$), 18 patients were DOD, 2 AWD, and 12 NED. Most of the NED patients (8/12) underwent PBSCT and ITT, IL-2 were given as post-transplantation therapy. Most of the DOD patients (15/18) underwent conventional chemotherapy alone. Four patients were NED with conventional chemotherapy alone and three DOD despite the combined PBSCT, ITT, and IL-2 therapy. Two AWD patients underwent ITT and IL-2 without PBSCT therapy because of parental refusal. They showed distant relapse and are currently on chemotherapy, waiting for PBSCT. Detailed treatment outcomes are shown in Table 2 according to the postoperative treatment protocol. In high-risk patients, the DFS and OS among all patients were 31.6 and 41.8%, respectively (Fig. 2a). The DFS was compared according to the use of PBSCT, and survival was found to have significantly improved in the patients that underwent PBSCT ($P = 0.015$; Fig. 2b).

Discussion

The role of primary tumor resection in high-risk NB patients continues to be debated. Kiely compared the survival of patients with stages III and IV disease undergoing a complete versus incomplete resection and showed no differences associated with surgery [7]. In contrast, La Quaglia et al. concluded that gross total resection should be a part of the management of high-risk NB. They also found more positive outcomes reported in the medical literature [5]. However, gross total resection is a serious and often life-threatening operation, and complete resection cannot be achieved in some cases despite the repeated surgery. Therefore, in this study, we focused on the outcome of incompletely resected NB, and our findings show the importance of postoperative management in such cases.

Isotretinoin can induce the arrest of cell growth and morphological differentiation of human NB cell lines [8]. Patients that were treated with ITT, as post-intensive chemotherapy, showed significantly higher rates of survival in prior studies [9, 10]. To control the minimal residual disease, targeted immunotherapy has been studied in NB patients with a poor prognosis [11, 12]. IL-2 given after intensive chemotherapy proved to be a significant prognostic factor in previously published papers [13]. In this study, intermediate-risk patients were treated with chemotherapy, ITT, IL-2 and showed good results. As the

Table 2 Detailed description of the treatment outcome according to the postoperative management protocol in high-risk patients ($N = 32$)

Treatment protocol	INSS stage	N-*myc* gene copy number	Current status
Chemotherapy only ($N = 19$)	Stage III ($N = 2$)	Amplification ($N = 2$)	2 DOD
	Stage IV ($N = 17$)	Single ($N = 10$)	4 NED, 6 DOD
		Amplification ($N = 7$)	7 DOD
Chemotherapy + ITT + IL-2 ($N = 2$)	Stage IV ($N = 2$)	Single ($N = 1$)	2 AWD
		Amplification ($N = 1$)	
PBSCT + ITT + IL-2 ($N = 11$)	Stage IV ($N = 11$)	Single ($N = 7$)	6 NED, 1 DOD
		Amplification ($N = 4$)	2 NED, 2 DOD

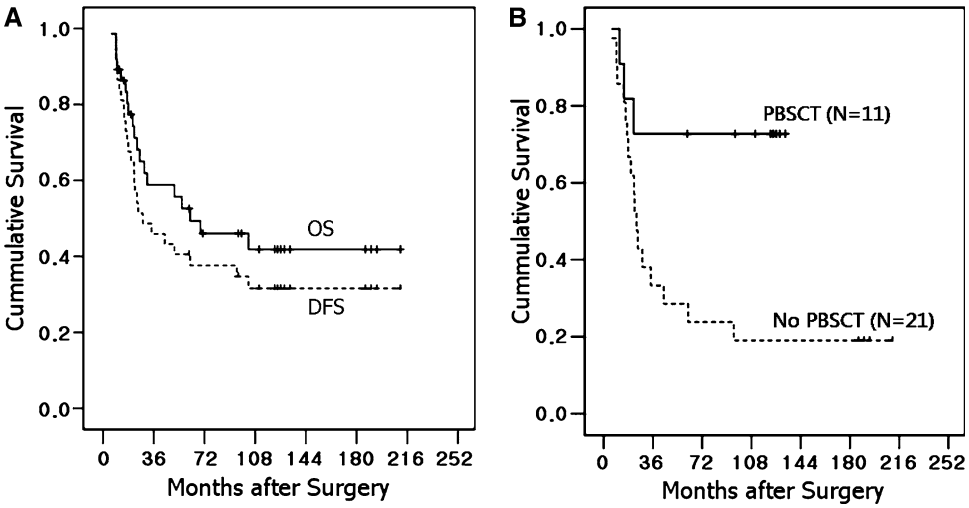

Fig. 2 **a** Kaplan–Meier probabilities of DFS and OS for high-risk NB patients and **b** improved DFS after PBSCT

positive benefit of ITT was not evident in patients with histologically proven residual disease [9], we speculate that the majority of tumor cells were killed by chemotherapy, and minimal residual disease was controlled by ITT and IL-2.

Myeloablative chemotherapy has become the standard treatment for high-risk patients since the report by the Children's Cancer Group was published [9], and its long-term benefit has also been published recently [14, 15]. At our institute, PBSCT was first introduced at 1997 along with ITT and IL-2 therapy. Most of the high-risk patients that survived in this study underwent PBSCT. Moreover, distant relapse occurred in two high-risk patients that refused PBSCT. These findings support the role of myeloablative chemotherapy in eradicating residual viable tumor cells following the incomplete resection of high-risk NB. In high-risk patients, the four patients that were treated before the introduction of PBSCT, survived without myeloablative chemotherapy. Three of them showed morphological differentiation of tumor cells following the surgical resection; these findings illustrate the evolution of NB that eventually leads to the development of a ganglioneuroma. Another patient showed complete resolution of paraspinal NB and bone marrow metastasis with preoperative chemotherapy alone, which is difficult to explain. Our speculation is that this might reflect the spontaneous regression of the tumors, which is one of the enigmatic features of neuroblastoma.

Two patients died due to disease relapse after PBSCT, and one hypothetical explanation is that the infused stem cells were contaminated by NB cells. Studies have shown that up to 50% of bone marrow and PBSC harvests from patients with bone marrow remission contain tumor cells [16, 17]. The most widely adopted tumor purging method, which is currently practiced at our institute, is $CD34^+$ selective stem cell collection. CD34 is the surface antigen of hematopoietic stem cells. Although Hafer et al. showed that some NB cell lines express CD34 antigen, and there is no evidence to support a survival benefit of $CD34^+$ selective transplantation [18], every effort should be made to reduce tumor cell contamination to prevent disease relapse by tumor-contaminated stem-cell transplantation.

This study has the following limitation. As a retrospective study, we could not evaluate the exact extent of the resection. Castel et al. analyzed the outcome of stage IV patients according to the extent of the resection and used a four group classification from biopsy only to complete resection [19]. In this study, the relationship between the amount of residual tumor and the patient survival could be further evaluated if the extent of the resection had been further classified, although the study of Castel et al. failed to show a survival benefit for the patients with more extensive resections. In summary, when complete resection for NB is not possible, intermediate-risk patients can be treated with conventional chemotherapy along with ITT and IL-2. For high-risk patients, however, every effort should be made to control the residual disease with treatments, including myeloablative chemotherapy, ITT, and IL-2. Stem-cell treatment should proceed cautiously to minimize tumor cell contamination.

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