Multiagent Chemotherapy for Children with Advanced Neuroblastoma

A Comparison of High-Dose Cyclophosphamide, Vincristine and Adriamycin Therapy with James' Therapy plus Adriamycin

YASUHIKO HIYOSHI, HIROMICHI YANO*, TETSURO TANAKA,
AKIHIKO NOGUCHI*, TAMAKI HORIKOSHI AND YASUSHI IRIE**

Departments of Pediatrics, Pediatric Surgery and Pathology**,
Kurume University School of Medicine, Kurume, 830 Japan*

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Summary: Sixteen children with Stage III and IV neuroblastoma were treated using two different chemotherapy protocols; six with a James' therapy plus adriamycin, and ten with a regimen consisting of high-dose cyclophosphamide, vincristine and adriamycin in a nonrandomized fashion. The high-dose cyclophosphamide with vincristine and adriamycin appeared to improve the duration of survival; that is, in the patients treated by this protocol, the median survival duration was 25 months, the one-year survival rate was 75% and the three-year survival rate was 50%. On the other hand, none of the patients treated by James' therapy plus adriamycin survived for more than one year. Their median survival was only four months.

Key words: neuroblastoma — multiagent chemotherapy — survival rate — high-dose cyclophosphamide — vincristine — adriamycin

Introduction

Neuroblastoma is one of the commonest malignant solid tumors observed in childhood. Although significant progress in the control of other malignancies, such as Wilms' tumor, osteosarcoma and rhabdomyosarcoma, is being made with multimodal treatment, an effective therapy for advanced neuroblastoma has not been found (Sutow, 1981).

Multimodal therapy is defined as the preplanned, coordinated, purposeful use of more than one mode of treatment, either simultaneously or sequentially, to achieve optimum therapeutic results. It consists of surgery, radiotherapy and/or chemotherapy. The chemotherapy is a major component of the multimodal treatment of childhood cancer and is generally

given in multidrug combinations. The principal of treatment of neuroblastoma, established in our institute in 1974, has been surgical excision, if possible, and irradiation with chemotherapy utilizing vincristine (VCR), cyclophosphamide (CYD) and adriamycin (ADR) in sequence.

This report describes a comparative study of survival rates in patients with advanced neuroblastoma who were treated with two different chemotherapy protocols, to evaluate the impact of a high-dose CYD therapy on the survival rate and median survival duration.

Materials and Methods

Between January 1974 and May 1982, 16 children with advanced neuroblastoma

(Stages III and IV) who were admitted to the Departments of Pediatrics and Pediatric Surgery, Kurume University Hospital, were involved in this study. The patients' characteristics are described in Table 1. There were 9 boys and 7 girls, ranging in age from 8 months to 7 years and 8 months (median age was 1 year and 11 months). Clinicopathological staging was determined after a laparotomy which included tumor resections or biopsy. According to Evans' criteria (Evans et al. 1971) there were 5 cases of Stage III and 11 cases of Stage IV neuroblastoma. In this series, patients with Stage III neuroblastoma frequently had incomplete removal or incomplete simple biopsy due to the nonresectable nature of the tumor. In almost all the patients with Stage IV neuroblastoma the surgery consisted of metastatic lymph node biopsy.

The 16 patients with advanced neuroblastoma were treated with one of two

different chemotherapy protocols in a non-randomized fashion. The outline of the two protocols are shown in Table 2. The patients constituted two groups. Group A, consisting of 6 cases was treated with the James' therapy (James et al. 1965) plus ADR, and Group B, consisting of ten cases, was treated with the "high-dose CYD" regimen. Group A patients received VCR at a dosage of 1.5 mg/m² on five days (days 8, 22, 36, 50 and 64), CYD at 300 mg/m² on six days (1, 8, 15, 29, 43 and 57) and ADR at 1 mg/kg on days 73 and 74 changing to 0.5 mg/kg on days 87 and 88. Group B patients were treated with VCR at a dosage of 1.5 mg/m² on days 1 and 8, ADR, 20 mg/m² on day 4, and CYD, 10-30 mg/kg on days 1, 2 and 3. This alternation of VCR, ADR and CYD was continued for at least two years, in a three week cycle.

The total dose of ADR for Group B patients did not exceed 450 mg/m². Ra-

TABLE 1
Patients' Characteristics in Advanced Neuroblastoma

	high-dose cyclophosphamide +adriamycin	James' therapy +adriamycin
Number	10	6
Male/female	5/5	4/2
Age in years:		
range	0.8-7.8	1.1-3.0
median	2.5	1.8
Stage:		
III	5	0
IV	5	6
Primary site:		
abdomen	6	5
thorax	3	1
spinal	1	
Catecholamine metabolites		
elevated/non-elevated	7/3	5/1
Histological typing:		
rossete forming type	5	3
round cell type	3	1
ganglioneuroblastoma	1	1
unknown	1	

TABLE 2
Chemotherapeutic regimens of advanced Neuroblastoma

Group A: James' + Adriamycin	
#1. Vincristine	1.5 mg/m ² Day 8, 22, 36, 50, 64
#2. Cyclophosphamide.....	300 mg/m ² Day 1, 8, 15, 29, 43, 57
#3. Adriamycin	1 mg/kg Day 73, 74 0.5 mg/kg Day 87, 88
Group B: High-dose Cyclophosphamide + Adriamycin	
#1. Vincristine	1.5 mg/m ² Day 1, 8
#2. Cyclophosphamide.....	10-30 mg/kg. day×3 Day 1, 2, 3
#3. Adriamycin	20 mg/m ² Day 4
#1, #2, #3	every 3 weeks

diotherapy was also administered to the bulk disease as necessary, but in almost all cases, a residual tumor was present outside the limits of the radiation field.

A review of the patients' characteristics demonstrated that the patients in the two groups were similar in terms of the location of the primary tumor and in the number of patients with elevated urinary catecholamine metabolites. Group B, however, had more females, a higher median age and a higher ratio of patients with Stage III neuroblastomas.

All patients were examined at least at monthly intervals. This examination included a complete physical, blood counts, blood chemistries and urinary catecholamine analyses.

Statistical analyses of survival curves were done using the Kaplan-Meier's method and the Generalized Wilcoxon's test.

Results

The overall survival data, analyzed by the Kaplan-Meier's method, are shown in Fig. 1. Median survival time for the pa-

tients treated with a James' therapy plus ADR was 4 months. In group A, no patients survived more than one year. This is in contrast to Group B which had a median survival of 25 months. The high dose CYD in addition to VCR and ADR seemed more beneficial in increasing the duration of survival. The one-year survival rate was 75 % and the three-year survival rate was 50 %. Using the Generalized Wilcoxon test, there was statistically significant difference between the two groups ($Z_0 = 3.526$).

The median survival period was 4 months in Stage IV patients in Group A, whereas it was 22.5 months in Stage IV patients in Group B. There was a statistically significant difference in the survival period between the two groups in Stage IV patients, when analyzed by the Generalized Wilcoxon test ($Z_0 = 2.5675$).

Of the ten Group B patients treated with high dose CYD plus ADR and VCR, two died of pneumocystitis carinii pneumonia. Four have survived and have been monitored for 27+, 40+, 44+ and 48+ months. One of these shows non-continuous remission.

Fig. 1. Survival curves showing correlation between James'+adriamycin and high-dose cyclophosphamide+adriamycin (Kaplan-Meier method).

Discussion

Multimodal therapy has significantly improved the survival rate of patients with some cancers, such as Wilms' tumor, osteosarcoma and rhabdomyosarcoma. Similar results have not been attained in neuroblastoma, particularly in advanced cases. The current treatment regimens for childhood cancer usually include all known modes of treatment that have individually demonstrated anti-tumor capabilities. These consist of surgery, radiotherapy, chemotherapy and to some extent immunotherapy, as reported by Necheles and associates (Necheles et al. 1978). Above all, chemotherapy is a major component of multimodal treatment of cancer in children. Currently, the major chemotherapy regimens include simultaneous or sequential use of two or more drugs in combinations which may be additive or possibly synergistic for antitumor activity. The three-drug combination of VCR, actinomycin D (AMD) and CYD, designed VAC,

was established in 1965 at M. D. Anderson Hospital (Sutow, 1969) for the management for rhabdomyosarcoma. The original VAC regimen has been subsequently modified to give CYD at higher dosages rather than on a daily low dosage schedule (Finklestein et al. 1969; Haddy et al. 1967). Now the original and modified VAC therapies receive much support because the clinical effectiveness of the combination is significantly better than the effectiveness of any one of the drugs used alone.

With respect to the multiagent chemotherapy for neuroblastoma, a combination of VCR and CYD was suggested by James and co-workers in 1965. This produces more extensive and more frequent regressions of the tumor than either agent alone (James et al. 1965). Since then, there have been many reports on adjuvant chemotherapy for advanced neuroblastoma. In 1972, Helson and coworkers reported that in patients with disseminated neuroblastoma, the administration of three drugs in sequence (VCR, CYD and AMD) re-

sulted in a median survival of 18 months, but unfortunately did not affect the cure rate (Helson et al. 1972). In the following year, they described the use of four drugs, VCR, CYD, AMD and ADR. This produced minimal additional benefit when compared to the three drug regimen. They concluded that to improve the cure rate in children with disseminated neuroblastoma, more effective agents or alternative drug regimens must be developed (Helson and Denoix, 1973). Gasparini and others reported a median survival time of 17.5 months in 11 responders among 19 patients with Stage IV neuroblastoma and a median survival time of 5 months in the 8 nonresponders in this group. The overall median survival time was 13.2 months (Gasparini et al. 1974). In 1979, a report on multi-agent chemotherapy for children with metastatic neuroblastoma by the Childrens Cancer Study Group (CCSG) between 1971 and 1975, was done by Finklestein and others. One hundred and four patients with metastatic neuroblastoma were evaluated for tumor responses. The three-drug regimen of CYD, ADM, VCR and imidazole carboxamide, and also a similar regimen plus ADR, did not significantly alter the median survival time in these children, although long-term survival was significantly increased compared with previous CCSG studies (Finklestein et al. 1979). Helson (1979) also reported that some Stage IV patients finally succumbed to the disease. The median survival time was six months with a range of 24 months. The 45 patients with disseminated neuroblastoma were treated by multi-drug regimens. At the present time, the overall survival rate of children with advanced neuroblastoma is disappointing, and unchanged from previous results. It is clear that aggressive chemotherapy should be given to children with neuroblastoma. There is no data which indicates that a consistent and significant improvement in the survival rate occurs with chemotherapy.

Temporary responses have occurred in advanced neuroblastoma after administration of a number of drugs. Among these drugs, the most effective agents which have been and are being used in various chemotherapeutic regimens, are CYD, VCR and ADR (Carlsen et al. 1981). Additionally, ADR and cisplatin (DDP) have been shown to be effective as single agents for neuroblastoma resistant to conventional therapy, and the specific combination of these two drugs has resulted in some complete remissions and some partial remissions (Nitschke et al. 1979, 1981). The high-dose CYD therapy has received much attention after a report by the Memorial Sloan Kettering Cancer Center Group (Helson, 1979). Recently, Uchino's group reported that high dose CYD therapy was effective for the primary tumor of neuroblastoma, but ineffective for the control of bone, lymph nodes, and liver metastasis, in a clinicopathological study of 14 autopsied children with advanced neuroblastoma. By comparison with the results of James' therapy, they concluded that a more effective therapy for controlling metastasis is necessary to improve the results of the treatment of the advanced neuroblastoma (Sasaki et al. 1983).

Our study revealed that the high-dose CYD with VCR and ADR produces significant improvement in the duration of survival. The one-year survival rate was 75 %, the three-year survival rate was 50 %, and three patients have been in total remission. On the other hand, the James' therapy gave poor results. No patients survived more than one year.

The survival period was longer in group B patients than in group A patients. This better therapeutic result in group B patients may be attributable to the inclusion of 5 stage III patients in this group. However, the comparison of therapeutic results in group A patients with those in stage IV patients in group B, revealed that the results are better for the stage IV patients.

This demonstrates that the newly devised therapeutic protocol is more potent in the management of the stage IV disease.

Our results provide strong evidence supporting other recent reports on multidrug chemotherapy for advanced neuroblastoma. In conclusion unsatisfactory cure rates with Stage IV neuroblastoma were observed. With Stage IV patients a significant advantage is obtained by the use of high-dose CYD methods as opposed to the James' therapy method.

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