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Hearing Loss in Children With Brain Tumors Treated With Cisplatin and Carboplatin-Based High-Dose Chemotherapy With Autologous Bone Marrow Rescue

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Carboplatin is less ototoxic than cisplatin, but ototoxicity may occur with carboplatin at higher doses. We evaluated hearing in children with brain tumors treated with conventional dose cisplatin followed by high-dose carboplatin. Children under 6 years of age, newly diagnosed with brain tumors, were treated after surgery with cisplatin, Etoposide, cyclophosphamide, and vincristine, followed by consolidation with carboplatin, ThioTEPA, Etoposide, and autologous bone marrow rescue. Hearing was assessed before and after consolidation, utilizing standard audiometric techniques. Seven of the 11 evaluable patients developed high-frequency sensorineural hearing loss after induction therapy. Hearing deteriorated after consolidation in five patients, with pure tone threshold shifts of up to 65 dB between 2,000 and 8,000 Hz. Of these five patients, audiological abnormalities were documented in four prior to consolidation, one received cranial irradiation after consolidation, and all five received aminoglycoside antibiotics for at least 2 weeks, with toxic drug levels in four. Three patients have subsequently required hearing aids. Significant ototoxicity is common in these patients. Ototoxicity related to consolidation therapy is likely due to the high dose of carboplatin used, prior cisplatin therapy, aminoglycosides, and, in one patient, cranial irradiation. Audiological assessment is essential in children treated with dose-intensive chemotherapy regimens containing cisplatin and carboplatin for identification and rehabilitation of ototoxicity.

Key words: brain tumors, platinum drugs, ototoxicity

INTRODUCTION

The prognosis is poor for very young children with malignant brain tumors [1]. Strategies employing irradiation and adjuvant chemotherapy have demonstrated some benefit in prolonging survival, but toxicity due to treatment may lead to significant morbidity in those who do survive. The effect of irradiation on the developing brain has been well documented; deleterious effects include intellectual impairment, learning disabilities, impaired skeletal growth, and endocrine abnormalities [2]. The incidence and severity of these complications appear to be inversely proportional to the age at which the child receives irradiation [3]. The "Head Start" protocol was developed to increase the survival of children with malignant brain tumors by using intensive chemotherapy and to improve the quality of that survival by either delaying or obviating the need for radiation therapy [4].

Head Start incorporates dose-intensive induction chemotherapy (including cisplatin), followed by consolidation with myelo-ablative chemotherapy (including carboplatin) and autologous bone marrow rescue. The differences in toxicity profiles between carboplatin and cisplatin have led to their combination in regimens for a variety of malignancies [5,6]. The principle toxicity of carboplatin is myelosuppression [7], whereas the major side effects of cisplatin are nephrotoxicity, peripheral neuropathy, and ototoxicity [8]. Cisplatin produces high-frequency sensorineural hearing loss and tinnitus. The tinnitus commonly subsides, but hearing loss is almost always permanent [9]. Cisplatin ototoxicity is primarily due to injury to the hair cells of the organ of Corti [10]; damage to the stria vascularis also has been described

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[11]. The reported incidence of cisplatin ototoxicity ranges from 11–100% [9]. Several factors are associated with a higher incidence of cisplatin ototoxicity. These include prior or concomitant cranial irradiation [12–14], pre-existing hearing loss [9], decreased renal function [9], the concomitant use of other ototoxic drugs such as aminoglycoside antibiotics [9], faster infusion rate (particularly bolus administration) and higher peak plasma concentration [15–17], very young age [9,18,19], older age [20], larger doses [9,15,21], and higher cumulative dose [15,18,19,21,22]. In children, ototoxicity occurs at a cumulative dose of 301–400 mg/m^2 or greater [18,19,22]. Individual susceptibility also plays a role [23].

Ototoxicity is less common with carboplatin than with cisplatin. Guinea pig studies show high-frequency hearing loss but either minor or no loss of hair cells [24,25]. Early single-agent studies demonstrated subclinical ototoxicity in 15% and clinical ototoxicity in 1% of patients [7]. Most other studies have demonstrated a similar low incidence of ototoxicity, ranging from 0–19%, which is usually not clinically significant [26–29]. Ototoxicity may be a greater problem with carboplatin at higher doses [30] and in those patients treated either previously or concomitantly with cisplatin [5,30].

Given the potentially ototoxic nature of Head Start, we have prospectively studied hearing in children treated with this protocol.

MATERIALS AND METHODS

Children less than six years of age with newly diagnosed high-grade malignant brain tumors were eligible for enrollment on the Head Start protocol. Patients received four to six 21–28-day cycles of induction therapy, consisting of cisplatin 3.5 mg/kg and vincristine 0.05 mg/kg on day 0 (vincristine in first three cycles only), and cyclophosphamide 65 mg/kg/day and Etoposide 4 mg/kg/day on days 1 and 2. The consolidation phase consisted of carboplatin 500 mg/m^2/day given via 4-hour infusion on days −8, −7, and −6—dose derived from a radio-labelled glomerular filtration rate or creatinine clearance and calculated according to the Calvert formula [31], using an area under the curve of 7 mg/ml × min, on 3 consecutive days—ThioTEPA 300 mg/m^2/day and Etoposide 250 mg/m^2/day on days −5, −4, and −3, and re-infusion of autologous bone marrow on day 0. Patients with localized residual disease following induction therapy were considered for second-look surgery and re-resection. Patients with residual tumor at the completion of the induction phase were irradiated following recovery from consolidation therapy (except those patients who had >50% reduction in tumor size after induction and who were then converted to a complete response at second-look surgery).

Audiological evaluations were performed before and after consolidation therapy. Standard audiometric techniques, behavioral and play audiometry under earphones or in the sound field were utilized to assess responses to pure tone, warble tone, narrow band, or speech stimuli, depending on the child's age. Testing was conducted in a double-walled audiometric test suite (IAC 1400 series). Air and bone conduction thresholds (250–8,000 Hz) were obtained using a Grason-Stradler (model GSI 10 or model GSI 16) clinical audiometer or a Play Tone audiometer with TDH 50 or TDH 49 earphones. Speech audiometry (speech reception threshold and speech discrimination) scores were obtained depending on the age of the child. There is a close relationship between the pure tone average at 500 Hz, 1,000 Hz, and 2,000 Hz and the speech reception threshold, enabling frequency specific information to be derived from this testing. The hearing of five patients was evaluated at outside facilities employing standard audiometric techniques. All findings were reviewed by a single audiologist and were judged to be reliable and consistent with standard audiometric practice.

RESULTS

Fourteen patients were enrolled on the protocol in our institution between October 1991 and February 1993. Two patients were excluded from evaluation because of significant changes in their induction therapy regimen, and complete audiometry was not obtained in one patient. Patient characteristics are shown in Table I. The median age at diagnosis of the 11 evaluable children (1 boy, 10 girls) was 43 months (range 17–63 months). There were three patients with supratentorial primitive neuroectodermal tumor, two with pineoblastoma, two with anaplastic ependymoma, two with medulloblastoma, one with a brainstem tumor that was not biopsied but presumed to be a high-grade glioma, and one with a high-grade spindle cell sarcoma. Eight children received five courses of induction therapy, while two received four courses and two received six courses. The total dose of carboplatin received was 537–1,306 mg (mean 786 mg, median 793 mg). Seven children received radiation therapy following consolidation chemotherapy.

Air and bone conduction testing was conducted on 8 of the 11 evaluable children; the other three were evaluated by soundfield testing only due to age or developmental limitations. Tympanometry or evaluation by an otolaryngologist was performed in nine patients. Seven of the 11 patients had high-frequency sensorineural hearing loss at the completion of induction therapy (Table I). Five of these seven patients had serial audiometry performed

TABLE I. Patient Characteristics and Audiologic Results After Induction Therapy

Patient	Age (mo)	Diagnosis	Cycles CDDP[a]	Hearing loss after induction therapy[b] <3,000 Hz	Hearing loss after induction therapy[b] ≥3,000 Hz
1	29	ependymoma	4	moderate	moderate
2	42	pineoblastoma	4	mild	moderate
3	16	medulloblastoma	5	moderate	severe
4	26	ependymoma	5	mild	severe
5	59	PNET	5	mild	moderate
6	53	brainstem glioma	6	normal	normal
7	16	medulloblastoma	5	normal	normal[c]
8	31	PNET	5	normal	normal[c]
9	53	spindle cell tumor	5	normal	severe
10	60	PNET	5	normal	normal
11	63	pineoblastoma	6	mild[d]	not tested

[a]Dose of CDDP (cisplatin) was 3.5 mg/kg/cycle.
[b]Legend: normal, 0–25 dB hearing threshold; mild, 26–45 dB; moderate, 46–60 dB; severe, 61–90 dB.
[c]Not tested >4,000 Hz.
[d]Hearing assessed using speech reception threshold.

TABLE II. Results of Audiometry Before and After Consolidation Therapy in Four of the Five Patients in Whom Hearing Deteriorated After Consolidation*

Patient		500 Hz Pre	500 Hz Post	1,000 Hz Pre	1,000 Hz Post	2,000 Hz Pre	2,000 Hz Post	3,000 Hz Pre	3,000 Hz Post	4,000 Hz Pre	4,000 Hz Post	6,000 Hz Pre	6,000 Hz Post	8,000 Hz Pre	8,000 Hz Post
2	L	5	25C	0	20C	30	60	30	70	50	70	60	70	65	80
	R	5	5	5	20C	5	65	25	65	40	60	70	55	60	60
4	L	10	30	10	15	5	70	45	95	65	100	60	ND	65	90
	R	10	20	10	35	10	55	45	85	65	90	65	ND	65	100
5	L	15	30	15	20	45	60	55	80	50	80	50	95	55	100
	R	15	25	10	20	15	60	55	70	55	70	60	70	65	65
8	L	10	10	10	15	0	40	ND	ND	0	35	ND	ND	ND	ND
	R	10	15	10	15	5	20	ND	ND	0	40	ND	ND	ND	ND

*In the other patient, pure tone audiometry could not be performed; in this child, hearing loss was determined by deterioration in speech reception threshold. Thresholds represent sensorineural loss unless designated otherwise. Legend: Pre = preconsolidation therapy; Post = postconsolidation therapy; L = left ear; R = right ear; C = conductive hearing loss; ND = not done.

prior to the completion of induction therapy: deterioration in hearing was documented in two, but results were inconclusive in three due to poor patient cooperation (related to both the underlying disease as well as factors such as the age and behavior of the patients). Hearing loss at the completion of induction therapy was more marked at higher frequencies (3,000 Hz and above) than at lower frequencies that encompass the speech range (500–2,000 Hz). The severity of the hearing loss was unrelated to the total dose/kg of cisplatin that the children received.

Hearing remained unchanged in 6/11, and deteriorated in 5/11 after consolidation therapy (Table II, Fig. 1). In four patients (patients 2, 4, 5, and 8), there were pure tone threshold shifts of up to 65 dB between 2,000 and 8,000 Hz. Pure tone audiometry could not be performed in the other patient (patient 11), but assessment using a closed set of spondee picture cards revealed a deterioration of speech reception threshold from 25 dB prior to consolidation to 50–55 dB after consolidation. There was no evidence of conductive hearing loss contributing significantly to hearing loss. Three patients have subsequently required hearing aids. Only one of these five patients had a normal audiological evaluation prior to consolidation therapy; however, frequencies above 4,000 Hz were not tested in this patient. Deterioration in hearing following consolidation therapy was unrelated to the total dose/kg of cisplatin received during induction therapy. One patient received cranial irradiation after consolidation (and before postconsolidation audiometry). All received aminoglycoside antibiotics for at least 2 weeks; drug levels were in the toxic range on at least one occasion in four patients. Renal function was normal in all five children. There was no evidence of tumor progression in any of these children to suggest a role for central auditory processing in the deterioration of hearing. Three of the 11 evaluable patients in this study have been referred for speech therapy because of their hearing loss.

Seven of the 11 patients are currently alive with no

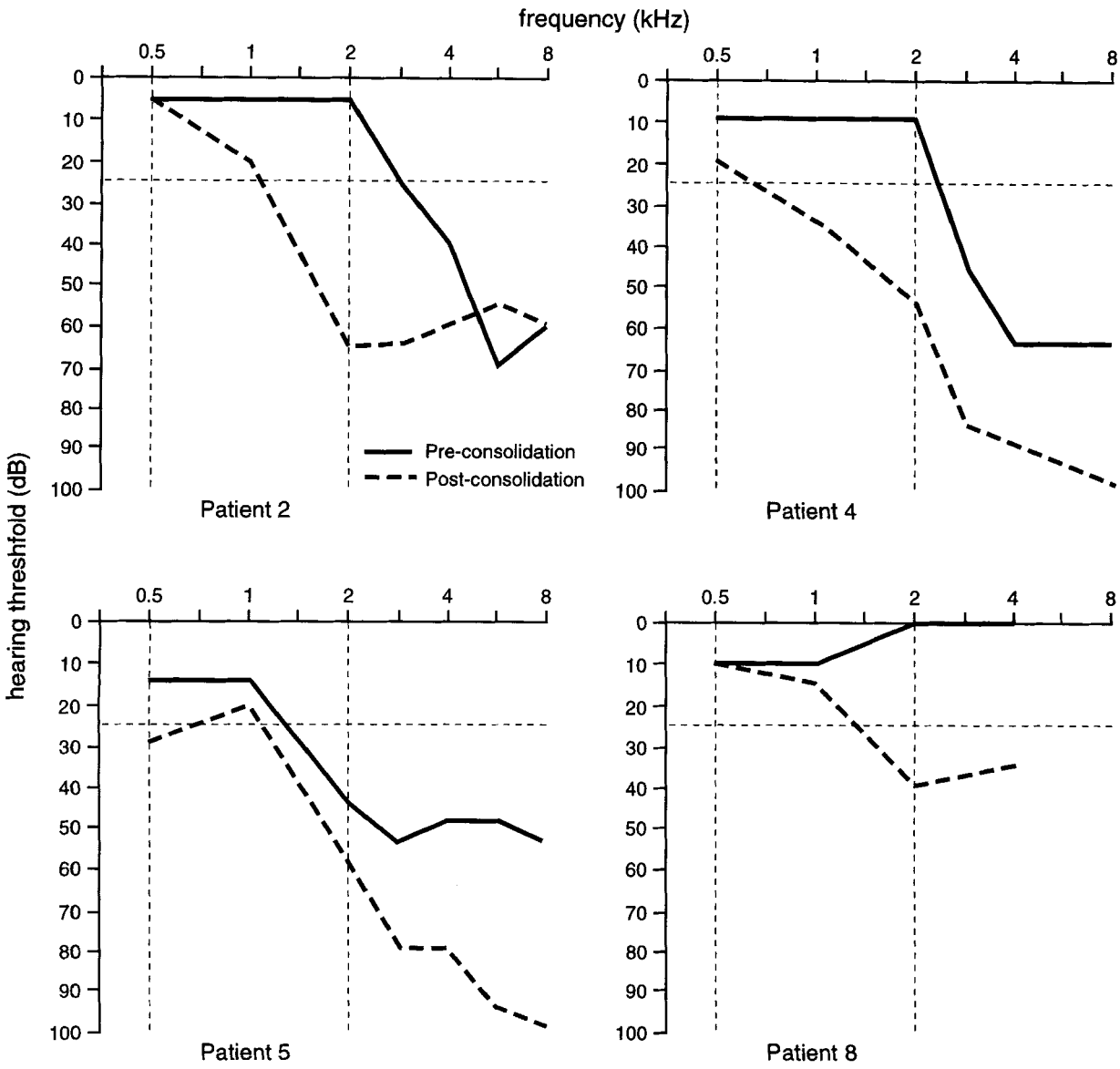

Fig. 1. Graphical representation of the audiograms of the four children detailed in Table I who developed hearing loss after consolidation therapy. Results from the most affected ear of each patient are shown. Solid and dashed lines represent testing pre- and postconsolidation, respectively. The upper limit of normal hearing (25 dB) and the speech range (500–2,000 Hz) are marked with dotted lines. Note that in patient 2, there is an air-bone gap at 1000 Hz in the postconsolidation audiogram (not drawn on the graph), indicating conductive hearing loss at this frequency only.

evidence of disease; four of these seven patients have received radiation therapy. Three patients are alive but with progressive disease, and one patient has died of the disease. The survivors have been followed for 2–3 years after bone marrow transplantation.

DISCUSSION

The wide range of reported ototoxicity due to drugs such as cisplatin reflects not only the presence or absence of associated factors that influence the severity of that ototoxicity, but also differences in the way ototoxicity is defined and tested. These definitions of ototoxicity include a shift of auditory threshold of 30 dB at any frequency [27], a shift of 15 dB of the mean value of hearing thresholds at several frequencies [5], grading systems characterized by hearing thresholds of $\geq$40 dB at particular frequencies [18], and qualitative scales such as the National Cancer Institute (NCI) Common Toxicity Criteria. Furthermore, different frequencies are used to determine the presence of ototoxicity; hearing loss at 8,000 Hz and greater is common [16,32] but is not as clinically

significant as hearing loss in the speech range [500–2,000 Hz], although high frequency hearing loss is a prognostic factor for further damage by other ototoxic drugs. Documenting hearing thresholds at a wide range of frequencies, and presenting them in both tabular and graphical form allows more precise interpretation of audiometry, provides a better understanding of the degree of ototoxicity and can be used in a standardized fashion to allow comparisons between different studies.

Seven out of 11 patients in this study had some degree of hearing loss at the completion of induction therapy, and this relatively high rate is likely due to the young age of the patients and the dose per cycle and cumulative dose of cisplatin received. The dose of 3.5 mg/kg of cisplatin used in this study is approximately equivalent to 105 mg/m^2; patients therefore received a cumulative dose of 420–630 mg (depending on the number of cycles given). A further factor is that most patients also received aminoglycoside antibiotics during induction therapy.

Hearing deteriorated in a high proportion of patients (5/11) after they received carboplatin-containing consolidation therapy, with significant loss occurring in the speech range. In three patients, hearing loss was severe enough to lead to the requirement of a hearing aid. Soundfield testing, which represents the hearing of the better ear (providing a difference between the ears exists), was the only form of audiological evaluation performed in three children. The use of this technique may have led to an underestimation of the degree of hearing loss in two children in whom no change in hearing was demonstrated following consolidation therapy.

There are several possible reasons for the high rate of ototoxicity in these patients. The first factor is the use of high dose carboplatin. Studies in adults have suggested increased ototoxicity at doses of 2,000 mg/m^2 or greater [30], but not at lower doses [30,33–35]. Doses of 1,500 mg/m^2 (as used in the current study) have not been associated with increased ototoxicity; however, most of these studies infused carboplatin at a slower rate or gave it over >3 days. The rate of infusion and peak plasma concentration of cisplatin may influence the development of cisplatin ototoxicity [15–17], and by analogy the rate of infusion of carboplatin may be an important contributing factor in the pathogenesis of carboplatin ototoxicity. Furthermore, it is possible that carboplatin, as with cisplatin, is more ototoxic in children than adults, so a dose of 1,500 mg/m^2 may be more toxic in a younger age group. In a phase I study in children, carboplatin was given in doses of up to 1,875 mg/m^2 with no ototoxicity [28]. However, the drug was given over a longer period of time (continuous infusion over 5 days), and the age range of 2–16 years was greater than our study group.

The second factor is the prior use of cisplatin in these patients. The concomitant use of cisplatin and carboplatin produces ototoxicity in up to 100% of patients; the incidence and severity of this ototoxicity may be related to the dose of cisplatin (occurring particularly at doses of 100 mg/m^2 or greater) and the rate of cisplatin infusion [5,6,36]. Prior cisplatin therapy has not been shown to significantly increase carboplatin ototoxicity in all cases [26,30], but it may play a role when higher doses of carboplatin are used [30]. Pre-existing hearing loss has not been shown to increase carboplatin ototoxicity [27].

The third factor that likely contributed to the ototoxicity related to consolidation therapy is the concomitant use of ototoxic antibiotics. By its very nature, myelo-ablative chemotherapy inevitably leads to fever, neutropenia, infection, and treatment that commonly includes aminoglycosides and vancomycin. Although levels of aminoglycosides or vancomycin were not toxic in all patients, ototoxicity may occur without such levels, particularly in patients treated for prolonged periods of time. All patients in this study received ototoxic antibiotics for at least 2 weeks.

Finally, cranial irradiation given after consolidation therapy is likely to have contributed to ototoxicity in one child. Apart from this one patient, there are no other factors evident to indicate why some but not all patients developed ototoxicity following consolidation therapy. It is likely that individual susceptibility is an important factor in the development of ototoxicity in these patients.

CONCLUSIONS

Significant hearing loss involving the speech range was common in young children with primary malignant brain tumors who received the Head Start protocol. Part of the rationale for combining cisplatin and carboplatin in treatment protocols is to take advantage of their different toxicity profiles and therefore minimize complications such as ototoxicity. For the reasons outlined above, however, hearing deteriorated in association with the carboplatin-containing consolidation phase of therapy in almost half of our patients. As the aim of protocols such as Head Start is to prolong survival in otherwise devastating and invariably fatal diseases, consideration of morbidity in survivors gains increasing importance. Audiologic assessment is essential in all patients, but particularly in children, treated with dose-intensive chemotherapy containing platinum-based compounds. Hearing loss in the young child likely will impact significantly on acquisition of speech, and so close monitoring of speech and language development with the intervention of aural rehabilitation and speech therapy in affected children is essential.

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