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Clinical–patient studies

Ototoxicity of cisplatin plus standard radiation therapy vs. accelerated radiation therapy in glioblastoma patients

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Summary

Purpose: To assess the effect of cisplatin (CDDP) plus concurrent radiation therapy on hearing loss. *Methods*: 451 patients with glioblastoma multiforme (GBM) were randomly assigned after surgery to: Arm A: Carmustine (BCNU) + standard radiation therapy (SRT); Arm B: BCNU + accelerated radiation therapy (ART: 160 cGy twice daily for 15 days); Arm C: CDDP + BCNU + SRT; or Arm D: CDDP + BCNU + ART. Patients on arms C and D received audiograms at baseline, and prior to the start of RT, and prior to cycles 3 and 6. Otologic toxicities were recorded at each visit. *Results*: 56% of patients had hearing loss at baseline. 13% and 50% of patients experienced worsening ototoxicity after 1 year of treatment in arms A and B vs. C and D, respectively, with 13% of those on arms C and D experiencing significant ototoxicity (≥ grade 3) at 6 months. Increasing age was associated with an increased risk of ototoxicity. *Conclusions*: Increased exposure to CDDP increases the risk of ototoxicity over time. Older patients are more susceptible to hearing loss with CDDP. The low proportion of patients with clinically significant ototoxicity suggests that baseline screening is unnecessary in GBM patients.

Introduction

Cisplatin (CDDP) is a chemotherapeutic agent used in the treatment of a variety of malignancies and is a well-known ototoxic agent. Histopathologic evidence suggests that CDDP first destroys outer hair cells in the organ of Corti on the basal turn of the cochlea [1,2]. The outer hair cells are responsible for sensing higher frequencies, and their loss explains the most common otologic toxicity caused by cisplatin – high frequency sensorineural hearing loss [3]. With increased cumulative doses, damage to inner hair cells can occur, resulting in hearing loss at lower frequencies, including conversational speech ranges [1,4], additional damages can include decreased spiral ganglion cells and atrophy of stria vascularis [4,5].

Cranial radiation can contribute to conductive hearing loss by inducing changes to the middle and external ear, [6] primarily by increasing the incidence of serous effusions [5]. The sensorineural aspect of hearing has generally been thought to be fairly resistant to radiation damage, although once damage occurs, it is more likely permanent [6]. One study found that of patients with parotid tumors treated with irradiation, 50% had clinically relevant hearing loss, and in 33%, this loss was permanent and affected quality of life [7]. An increased incidence of hearing loss has been found when CDDP is given following cranial radiation therapy in children, suggesting a synergistic toxic effect [8,9]. This does not appear to hold true when CDDP is given prior to radiotherapy.

One treatment regimen for glioblastoma multiforme (GBM) consists of a combination of surgery, BCNU, and RT. CDDP has been found to have anti-tumor activity against recurrent glioma with intravenous administration [10]. It has also been observed to remain in tissues for extended periods of time following administration [11]. This may account for its action as a radiosensitizer of hypoxic cells and its ability to potentiate post-RT cell kill, [12] thus increasing the effectiveness of the radiation therapy. However, the combination of CDDP and cranial radiation has the potential to cause serious ototoxicity [13]. In a recent clinical trial, this combination was evaluated to determine its effectiveness in prolonging survival of patients with GBM compared to standard treatment [14]. As a component of that study, this trial was designed to assess the ototoxicity of this treatment regimen.

In this study, we set out to examine the frequency and severity of otologic complaints, including hearing loss, tinnitus, and serous otitis media, in patients diagnosed with GBM and undergoing treatment with either standard therapy or chemotherapy including CDDP. Based on the study design, it is also possible to infer the time period during which hearing loss most commonly occurred, either during treatment with CDDP alone, with radiation alone, or with a combination of the two treatment modalities. We used serial

pure tone audiograms to determine the incidence and severity of any hearing impairment in patients treated with CDDP.

Materials and methods

Protocol therapy

Patients with newly diagnosed histologically confirmed glioblastoma multiforme were randomly assigned after surgical biopsy or excision to one of four treatment arms as shown in Figure 1. Treatment began within 4 weeks of surgery. Patients on arms A and B received 200 mg/m^2 intravenous BCNU once every 8 weeks for 6 cycles, and either SRT consisting of 180 cGy once a day for 36 days or ART with 160 cGy twice daily for 15 days. Patients on arms C and D received 50 mg/m^2 intravenous BCNU days 1–3, every 8 weeks for 2 cycles, then 200 mg/m^2 once every 8 weeks for 4 cycles. In addition, they received 30 mg/m^2 intravenous CDDP days 1–3 and 29–31 every 8 weeks for 2 cycles and either SRT or ART. Patients on arms C and D had 8 weeks of chemotherapy prior to initiating RT [14].

Patient evaluation

Serial audiograms were requested of all patients receiving CDDP starting with a baseline audiogram to be scheduled as soon as the treatment arm was assigned. Although testing was preferably prior to the initiation of treatment, commencement of treatment was not to be delayed. Additional audiograms were to be completed prior to the start of RT, prior to cycles 3 and 6 BCNU, and as clinically indicated thereafter.

Assessment of toxicity

At each evaluation, toxicities to be graded included (1) neuro-hearing and (2) acute radiation toxicity to the ear. These were evaluated per National Cancer Institute (NCI) Common Toxicity Criteria grading version 2.0, which defines 'neuro-hearing' toxicity as grade 1: asymptomatic, hearing loss on audiometry only; grade 2: tinnitus; grade 3: hearing loss interfering with function but correctable with hearing aid; grade 4: deafness not correctable; and 'acute radiation toxicity to the ear' as grade 1: mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication with audiogram unchanged from baseline; grade 2: moderate external otitis requiring topical medication/serous otitis medius/hypoacusis on testing only; grade 3: severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus, not drug-related; and grade 4: deafness.

CDDP was to be discontinued if grade 3 neuro-hearing toxicity was recorded, and the patient was to continue on BCNU and RT. Quality control of toxicity monitoring was verified by adhering to NCI guidelines requiring 10% of all cases accrued to be audited. In addition, each case was individually reviewed to insure that all institutions correctly applied the NCI common toxicity grading scale.

Statistical analysis

Categorical variables were summarized by the observed frequency and percent. Comparisons of categorical variables between two groups were performed with a χ^2 test. Continuous variables were summarized using mean ± SD as well as median and range (minimum to maximum values). A rank-sum test was used for comparisons of continuous variables between groups. All time-to-event outcomes were measured from date of study enrollment to date of event or last follow-up. Time-to-event outcomes were estimated via the Kaplan–Meier method [15]. Comparisons of Kaplan–Meier estimated time-to-event experiences between two groups were done with the log-rank test [16]. Univariable Cox proportional hazards models [17] were used to assess the association between baseline patient characteristics (age, gender, performance score, extent of resection, baseline anti-convulsant treatment, baseline corticosteroid treatment, family history of brain tumors), baseline pure tone hearing measures (250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 dB), and treatment arm (C vs. D). No multivariable Cox modeling was performed due to the small number of events. All tests were two-sided and a P-value ≤ 0.05 was considered statistically significant.

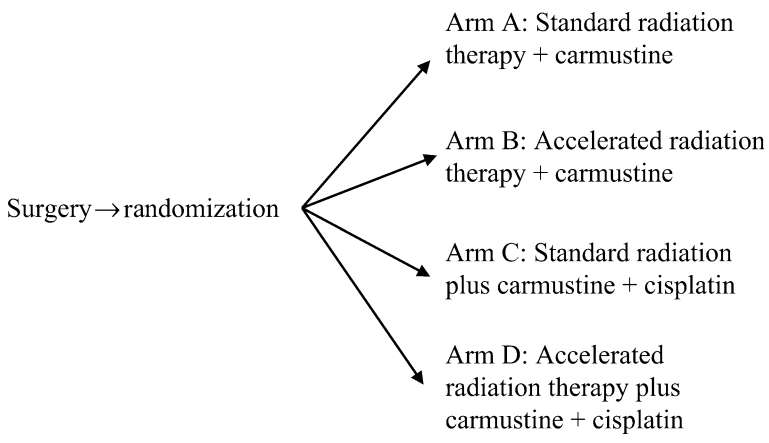

Figure 1. Treatment schedule.

Results

A total of 230 patients were enrolled on arms C and D. Of these, 176 (77%) received a baseline audiogram – 86 (74%) on arm C and 90 (80%) on arm D (see Table 1); these patients comprised the study group. Patients who received baseline audiograms were slightly older than those who did not (56 ± 12 years vs. 53 ± 12 years, respectively), although this difference did not achieve statistical significance (*P*-value = 0.09). In addition, patients who received baseline audiograms tended to have a worse performance score than patients who did not have a baseline audiogram, although this difference also did not quite achieve statistical significance (*P*-value = 0.051). There were no other obvious differences between patients who received a baseline audiogram and those who did not. The study group consisted of 66 (37%) females and 110 (63%) males. Most of these patients had a subtotal (57%) or gross total resection (24%). The majority were being treated with corticosteroids and/or anti-convulsants at baseline.

Table 1. Baseline patient characteristics

Characteristics	Individuals with baseline audiograms $N = 176$	Individuals with no baseline audiogram $N = 54$	*P*-value
Arm, *n*(%)			0.28
C	86 (74)	31 (26)	
D	90 (80)	23 (20)	
Gender, *n*(%)			1.00
Female	66 (37)	20 (37)	
Male	110 (63)	34 (63)	
Age, years			0.090
Mean ± SD	55.8 ± 11.5	52.8 ± 11.8	
Median (min, max)	56.0 (22, 79)	52.8 (29, 78)	
Age groups, *n*(%)			0.075
≤ 40 years	16 (9)	10 (19)	
40+ to 60 years	96 (55)	31 (57)	
>60 years	64 (36)	13 (24)	
PS, *n*(%)			0.051
0	59 (34)	28 (52)	
1	93 (53)	20 (37)	
2, 3 or 4	24 (14)	6 (11)	
Extent of resection, *n*(%)			0.11
Biopsy	33 (19)	13 (24)	
STR	100 (57)	22 (41)	
GTR	43 (24)	19 (35)	
Baseline steroids, *n*(%)			0.45
Yes	141 (81)	41 (76)	
No	34 (19)	13 (24)	
Missing	1	0	
Baseline anti-convulsants, *n*(%)			0.47
Yes	126 (73)	41 (79)	
No	47 (27)	11 (21)	
Missing	3	2	
Family hx of brain tumor, *n*(%)			0.25
Yes	11 (7)	6 (11)	
No	158 (93)	48 (89)	
Missing	7		

Table 2 summarizes the audiograms that were obtained. Of the 176 patients, 161 went on to receive RT, 78 were on arm C and received SRT along with CDDP and BCNU and the remaining 83 were assigned to arm D and received ART along with CDDP and BCNU. Audiograms prior to RT were obtained from 85 (53%) of the 161 patients with baseline audiograms who received RT: 48 (62%) on arm C and 37 (44%) on arm D. Although audiograms were stipulated by the protocol prior to cycle 3 (immediately post-RT) and prior to cycle 6, only 19 audiograms were obtained post-radiotherapy from the 142 patients with baseline audiograms who started cycle 3: 3 (4%) from arm C and 16 (22%) from arm D.

On baseline audiograms, 99 (56%) of patients had some degree of hearing loss, defined as any abnormality on an audiogram. Of these 99 patients, 84 had loss in both ears, 7 had loss only in the left ear, and 8 had loss only in the right ear. The majority of patients with hearing loss (70%) had losses in frequencies above 3000 dB. After 8 weeks of treatment with CDDP and BCNU and prior to the initiation of RT treatment, 54 (61%) of the patients who had an audiogram prior to radiotherapy had some degree of hearing loss. Of the19 patients who had an audiogram post-radiotherapy, 12 (63%) had some degree of hearing loss. There was no evidence of a difference in hearing loss between arms C and D.

Auditory/hearing adverse events, defined as hearing loss, otitis, tinnitus, and RT-ear, of grade 1 or higher were more frequent in patients on arms C or D compared to patients on arms A or B. There was no evidence of a difference in hearing adverse events between arms C and D. Forty-one of the 117 (36%) patients on arms C and 43 of the 113 patients on arm D (38%) reported at least one hearing related adverse event of grade 1 or higher. By comparison, 13 of the 111 (12%) of patients on arm A and 13 of the 110 (12%) on arm B reported at least one hearing related adverse event of grade 1 or higher. At 6 months, 15% (95% CI: 9–21) of patients on arms A or B experienced a hearing related adverse event of grade 1 or higher compared to 45% (95% CI: 36–52) of patients on arms C or D (Figure 2). This difference was statistically significant (*P*-value < 0.001). The most commonly reported hearing related adverse events on arms C and D were hearing loss followed by tinnitus. Defining serious hearing related adverse events as grade 3 or higher, there was no apparent difference in the occurrence of serious hearing related adverse events between arms A/B and arms C/D (*P*-value = 0.19).

Table 2. Summary of audiograms

Characteristics	Arm C	Arm D
Number enrolled	117	113
No. (%) with baseline audiograms	86 (74)	90 (80)
Number with baseline audiogram who received RT	78	83
No. (%) with audiogram prior to RT	50 (64)	38 (46)
Number who started cycle 3 with baseline audiogram	67	73
No. (%) with audiograms post-RT	3 (4)	16 (22)

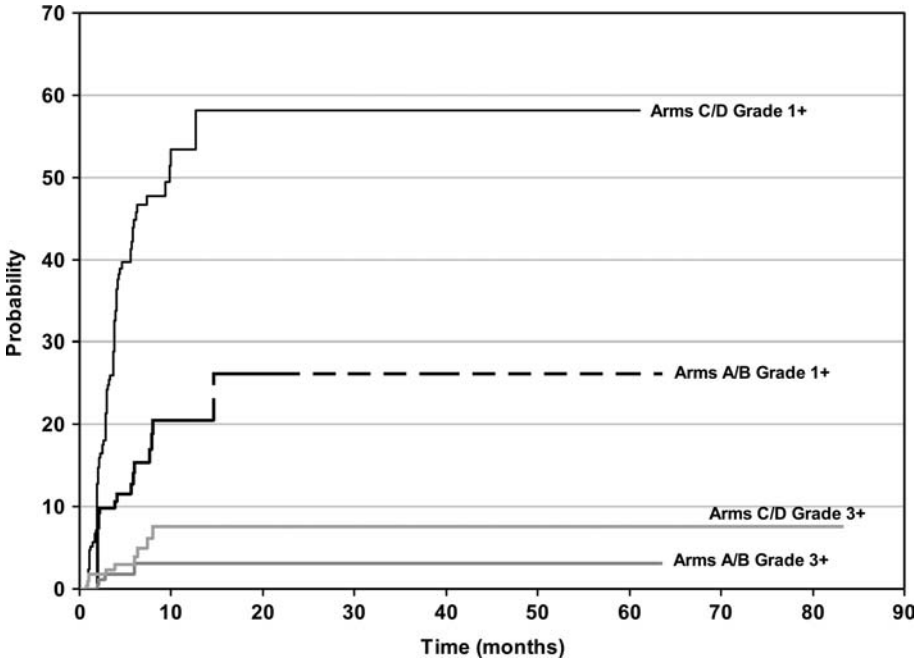

Figure 2. Hearing-related adverse events by treatment arm and severity.

Specifically, 3% (95% CI: 0–6) of the patients on arms A or B experienced a serious adverse event by 6 months compared to 4% (95% CI: 1–7) of patients on arms C or D (Figure 2).

Conductive hearing loss was much less frequent than sensorineural hearing loss at baseline. Only 3 (2%) patients had documented conductive hearing loss at baseline compared to 51 (29%) patients with sensorineural loss. These percentages increased after CDDP + BCNU therapy to 6 of 88 (7%) with conductive hearing loss and 32 of 88 (36%) with sensorineural hearing loss. Although the number of patients with a post-RT audiogram was small, it does not appear as though these percentages increased post-RT: 0 of 19 (0%) conductive hearing loss and 6 of 19 (32%) sensorineural.

Figure 3 summarizes the rate of different definitions of hearing loss for patients on arms C and D. The three measures are (a) a loss documented by an audiogram in any pure tone range, (b) a clinically significant hearing loss – a documented loss on audiogram of greater than 20 dB at any frequency less than 3000 dB, and (c) a clinically significant hearing loss and/or a hearing related adverse event of grade 3 or higher. These measures are not meant to be compared to each other,

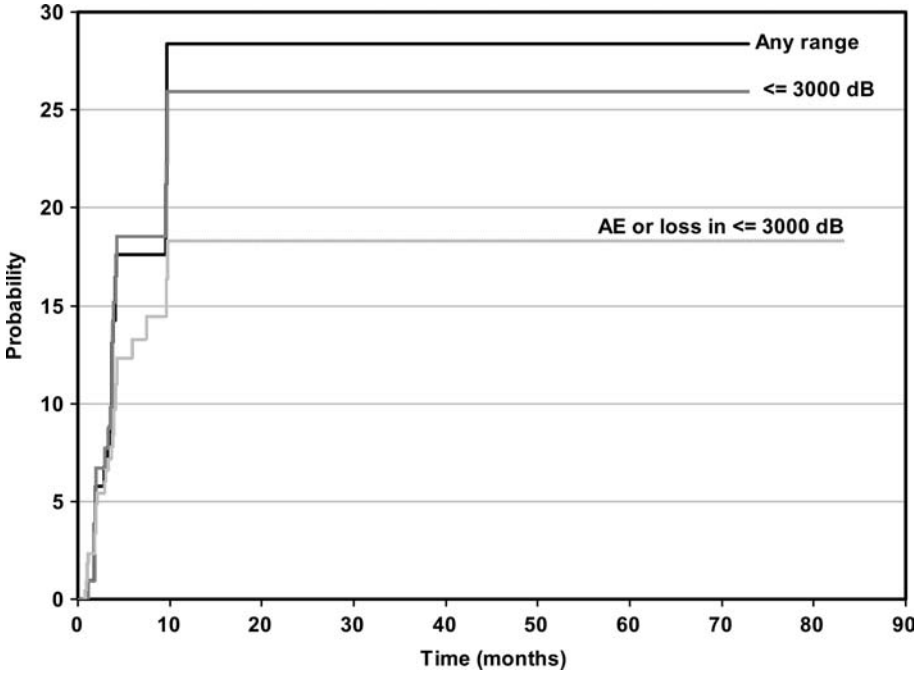

Figure 3. Audiogram findings in patients receiving radiation therapy + carmustine + cisplatin.

because they encompass different patient groups and because the timing of the events differ for the different definitions, but rather are to be examined for changes over time. The patient group for the first two definitions are individuals who had a baseline audiogram, whereas the patient group for the last definition are all individuals on arms C and D. At 60 days from study enrollment, 6% (95% CI: 2–10) had a loss in at least one pure tone, 7% (95% CI: 2–11) had a clinically significant loss, and 5% (95% CI: 2–8) had a clinically significant hearing loss and/or a hearing related adverse event of grade 3 or higher. At 6 months, these numbers increased to 18% (95% CI: 10–25), 19% (95% CI: 10–26), and 13% (8–18), respectively. Five patients were taken off-study due to ototoxicity.

Univariable Cox proportional hazards models identified age as being significantly associated with a clinically significant treatment-related hearing loss (hazards ratio: 1.06, 95% CI: 1.01–1.11, *P*-value = 0.015). No other baseline variable, including the baseline audiogram frequency values, were found to be associated with a clinically significant hearing loss as determined by audiogram. Age was not found to be significantly associated with the event of a clinically significant hearing loss and/or hearing related adverse event of grade 3 or higher (HR = 1.03, 95% CI: 0.99–1.07, *P*-value = 0.11).

Discussion

This study found a high degree of baseline hearing loss, with 56% of patients showing at least some degree of decreased hearing. Although the majority of these hearing losses were at high frequencies, as would be expected, this prevalence of decreased hearing is greater than would be expected for patients in this age range. This raises the question of additional mechanisms of hearing loss in this patient population.

Conductive hearing loss was much less prevalent than sensorineural hearing loss. Our very limited data would seem to support that cranial radiation in GBM patients does not pose a greatly increased risk of conductive hearing toxicity. However, institutions had a much poorer compliance with reporting conductive hearing loss, which could mask significant toxicity. There were no statistically or clinically significant differences in hearing loss or ototoxicity between patients on arms C and D, which suggests that accelerated radiation therapy does not increase ear damage.

Controversy remains as to the proper method to monitor cisplatin ototoxicity. Baseline screening using audiometry has frequently been recommended [18,19]. Other studies have recommended screening only patients with pre-determined risk factors, although these factors vary widely. It is as yet undetermined whether pre-treatment hearing loss does [20,21] or does not [22] contribute to additional loss. Our study found no evidence that underlying hearing loss contributed to additional loss. The only risk factor in our study shown to be statistically significant in predicting treatment damage was patient age above 58. Our data showing 56% of patients having underlying hearing loss supports the importance of baseline screening to prevent incorrect attribution of post-treatment damage. However, the relative infrequency of clinically significant hearing loss in this patient population, despite concurrent RT with CDDP, leads us to conclude that screening is most likely unnecessary and the majority of patients do not need audiograms unless they are symptomatic. Patients with clinically apparent hearing loss should receive CDDP only if there is not an appropriate alternative agent.

Conclusion

Although a large percentage of patients may show audiogram evidence of hearing loss following this treatment regimen, the percentage of patients with clinically significant ototoxicity was minimal, suggesting that screening is likely not necessary in this patient population. This study found no evidence that accelerated radiation therapy had a greater risk of ototoxicity in combination with CDDP compared to SRT, although the number of patients with follow-up audiograms precludes definitive comparisons. Increasing age is a risk factor for treatment-related hearing loss.

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