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Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose

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Abstract

The aim of this study was to determine the risk factors for high-frequency hearing loss in children treated with cisplatin. We scored off-treatment pure-tone audiograms from 153 children (age 6 months to 18 years) who had completed cisplatin therapy (40–200 mg/m^2/cycle) for germ cell tumours, hepatoblastoma, neuroblastoma or osteosarcoma. The risk of developing bilateral moderate to severe high-frequency hearing loss was significantly related to the age at treatment ($P < 0.001$), and individual and cumulative cisplatin dosages (both $P < 0.005$). Logistic regression showed that children younger than 5 years were at a greater risk of sustaining cisplatin ototoxicity than children older than 15 years, controlling for individual and cumulative doses of cisplatin (Odds Ratio (OR) = 21.17, 95% Confidence Interval (CI): 2.48–180.94). Age at treatment and the cumulative dose of cisplatin were the two most important risk factors in predicting moderate to severe high-frequency hearing loss in children treated with cisplatin.

Keywords: Cisplatin; Ototoxicity; Risk modeling; High-frequency hearing loss

1. Introduction

Cisplatin is known to cause high-frequency hearing loss in adults and in children [1–10]. The ototoxicity is non-reversible, appears soon after therapy, and may worsen after repeated doses [3,5,8–10]. As cisplatin is an important chemotherapy agent for childhood cancer, and as less ototoxic alternative (e.g., carboplatin) treatments are sometimes inappropriate or unavailable, there is a continuing need to achieve a fuller understanding of the risk of cisplatin ototoxicity related to patient characteristics and treatment regimens.

Several important risk factors have been identified. The prevalence of hearing loss after paediatric cisplatin therapy ranges widely. This is in part due to the difficulty in monitoring hearing loss in hepatoblastoma and neuroblastoma patients, who have a median age at diagnosis of less than 18 months [11]. Pure-tone audiometry has low reliability at this young age. Other measures such as oto-acoustic emissions may not detect the changes in the inner hair cells due to carboplatin in a multi-agent therapy [12,13].

Brock's [1] grade 2+ hearing losses have been observed in 18% of infants who received cisplatin (median age at diagnosis 8 months; range 1–11.5 median cumulative dose at 400 mg/m^2; range 105–1000) [11]. Other studies reported a risk of 48% (median age 2 years 2 months; range 1 month–13.5 years; median cumulative dose 540 mg/m^2; range 120–1860) [1], 34% [14], and 41% (mean age 13 years; range 7–19; median cumulative dose 542 mg/m^2; range 312–1072) [15]. More recently, a risk of 21% was found in an international collaboration (20 with grade 2+ per 96 for whom audiometric data were available; median age 16.5 months; range new born –155 months; highest cumulative dose 480 mg/m^2) [16].

Larger individual and cumulative doses are the leading risk factors [1–4,6,8,15,17–19]. Age is important and

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hearing loss is more prevalent in younger children [2,5,20,21]. The findings derived from these risk factors tend to be repetitive and analyse the same factors in different diagnoses. Other risk factors have been examined. It has been found that rapid chemotherapy administration (e.g., bolus administration) causes more severe ototoxicity in adults [4]. The European trend for the last decade has been to administer cisplatin to children in a 24-h infusion instead of 6 h or less [15,16], although there has been no definitive proof of its superiority. Other risk factors are also significant, including potential genetic causes [22] and prior cranial irradiation [21,23].

Advances have been made in understanding how children may develop hearing loss after cisplatin chemotherapy, although to date many important questions remain unanswered. The potential interactions between patients' characteristics and treatment regimens – which can be very important in the patients' clinical management – are not well understood.

This article aims to build a predictive model that estimates a child's risk in sustaining what Brock considers 'moderate to severe' losses as a function of patient risk factors. The focus is on developing a practical procedure in constructing a risk model: several common risk factors are analysed individually, followed by a logistic regression model that simultaneously considers risk factors that show statistical significance. In particular, we examined the extent to which younger age and higher cumulative dose of cisplatin increase the risks of developing hearing loss.

2. Patients and methods

The study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia. The data came from two sources. One was the records of audiometric findings from 80 paediatric patients who participated in two Intergroup clinical trials for treating germ cell tumours (Children's Cancer Group (CCG) protocols 8882 and 8891). We obtained single off-treatment audiograms for 80 patients who had completed the protocols. Approximately half the patients were assigned to a regimen of bleomycin, etoposide and conventional dose cisplatin (100 mg/m^2/cycle, administered over 5 days as 1-hour infusions of 20 mg/m^2 each day; $n = 38$), while the other half received the same regimen with high-dose cisplatin (200 mg/m^2/cycle, administered over 5 days as 1-hour infusions of 40 mg/m^2 each day; $n = 42$) [24]. The protocols entailed no modifications for ototoxicity. The audiograms were scored according to Brock's criteria, and additional data included the child's gender, age at treatment, ethnicity, individual cisplatin dose, cumulative cisplatin dose, and the amount of time between the completion of cisplatin therapy and the audiometric assessment.

The CCG audiometric data only contained the patients' level of hearing loss evaluated by Brock's grading system, without the detailed hearing threshold data. In order to better understand the changes in the profiles of audiograms after repeated cisplatin doses, we extracted charts of another 73 patients who had completed comparable cisplatin therapy at The Children's Hospital of Philadelphia (CHOP) and whose hearing was tested by pure-tone audiometry at the end of their cisplatin therapy. The earliest record dated back to 1988. To be consistent with the contents of the CCG archive, we collected data on the patient's gender, age at treatment, race, time off treatment, and the findings in the first off-treatment audiogram. We excluded patients who had received cranial irradiation. We did not exclude patients who subsequently died. Among the 73 patients, 13 were diagnosed with hepatoblastoma, 40 with neuroblastoma, and 20 with osteosarcoma. The Children's Hospital's protocol for administering cisplatin uses (henceforth the CHOP group) 6-h infusions ranging from an individual dose of 40 to 200 mg/m^2/cycle.

2.1. Audiometry

Generally, patients were assessed by pure-tone audiometry on both ears to quantify the changes in hearing threshold at different frequencies: 125, 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz. Eight CHOP patients were also tested at an additional frequency of 1500 Hz. The bilateral audiometric findings were further categorised into five discrete levels of hearing loss ranging from minimally affected to severely affected.

2.2. Brock's classification of high-frequency hearing loss in children

Brock's method categorises the pure-tone thresholds into five levels of hearing loss, ranging from 0 (considered 'minimally affected') to 4 ('severely affected'). At grade zero, the child is able to hear all tested frequencies at thresholds less than 40 dB. Grade 1 entails a threshold at 40 dB or greater at 8000 Hz. At grade 2, the child is unable to hear frequencies higher than 4000 Hz at the same 40 dB loudness. Grade 2 is considered 'moderate loss' and translates to a loss of speech phonemes 's', 'f' and 'th' at the conversation level. In this study, we used grade 2 and worse to represent functionally significant hearing losses because such losses may lead to delays in cognition [1], speech perception [3], and a lower quality of life [25]. At grades 3 and 4, the loss further advances to 40 dB loss in 2000 Hz and above and 1000 Hz and above, respectively.

The classification criteria were applied to both ears. If hearing was not symmetrical, the grade for the 'better' ear was taken to be the child's overall un-aided hearing [2].

2.3. Statistical analysis

A predictive risk model was built in three sequential steps. We first tested the appropriateness of aggregating data from the two sources. We tested whether or not the CHOP patients differed significantly in their distribution of hearing losses; and the data sets were merged because no statistically significant differences were found. Using the aggregated data, the risk factors were analysed. We selected risk factors most commonly studied in the literature, including patients' characteristics (gender, age at treatment, ethnicity and the elapsed time since the end of chemotherapy) and treatment regimens (the individual and cumulative doses of cisplatin). Comparisons were tested by Chi-square and Fisher's exact test whenever appropriate.

Factors that showed statistically significant associations were next entered into a logistic regression model for a multivariate analysis. Adequate numbers of independent variables were chosen so that they satisfy the minimum 10 Events Per Variable (EPV) rule [26]. The dependent variable was a dichotomised outcome, coded 1 if the child developed Brock's 'moderate to severe' losses (grades 2–4) and 0 if the child developed grade 0 or 1 losses. The logistic regression analysed the probability of developing Brock's 2+ hearing loss as a function of the child's age at treatment and the individual and cumulative doses of cisplatin.

The quality of the model was evaluated by (1) the model's discriminatory power using the area under the receiver operating characteristic (ROC) (c-statistic) [27,28] and by (2) the Hosmer–Lemeshow statistic for model calibration [27].

3. Results

3.1. Patient's characteristics

Table 1 summarises the patients' characteristics. The CHOP and CCG patients developed similar levels of hearing losses (Fisher's test, $P = 0.47$). Overall, 72 patients (47%) developed grade 0 hearing loss, 26 (17%) developed grade 1 loss, and 54 (35%) developed grade 2 or worse hearing losses. Approximately half of the patients were male. Fifty percent of them were younger than 5 years at the time of their treatment. The median time of the first off-treatment audiogram was measured at 8 months posttreatment. The median individual dose was 100 mg/m^2/cycle, with the minimum dose at 40 mg/m^2/cycle and the maximum dose at 200 mg/m^2/cycle. The median cumulative dose was at 397 mg/m^2, with the minimum cumulative dose at 120 mg/m^2 and the maximum dose at 1213 mg/m^2.

Table 2 summarises how important each risk factor was. It shows the extent to which patients' characteristics and the doses of cisplatin were statistically significant in distinguishing children who developed 'minimal to mild' losses from those who developed 'moderate to severe' hearing losses. Age at the time of treatment had a significant impact on the risk of developing moderate to severe hearing losses. Patients younger than 5 years were especially susceptible to cisplatin ototoxicity. Among patients who developed moderate to severe losses, 69% were younger than 5 years, while 28% were 5–14-year-olds and only 4% were children older than 15 years at the time of treatment. However, among children who developed minimal to mild losses, 40% were younger

Table 1
Patients' characteristics[a]

Characteristic		CCG ($n = 80$)	CHOP ($n = 73$)	Combined ($n = 153$)
Extent of Brock's hearing loss	N (%)[b]			
Grade				
0		38 (48)	34 (47)	72 (47)
1		11 (14)	15 (21)	26 (17)
2		19 (24)	17 (23)	36 (24)
3		7 (9)	5 (7)	12 (8)
4		5 (6)	1 (1)	6 (4)
Gender	N male (%)	25 (31)	44 (60)	69 (45)
Age at treatment (years)	N (%)			
younger than 5		33 (41)	44 (60)	77 (50)
5–14		33 (41)	21 (29)	54 (35)
15–20		14 (18)	7 (10)	21 (14)
Race	N white (%)	53 (66)	60 (82)	113 (74)
Months since end of treatment	Median (S.D.)	9 (11)	7 (5)	8 (9)
Individual dose of cisplatin	Median mg/m^2/cycle (S.D.)	200 (50.3) (range 100–200)	90 (29.9) (range 40–120)	100 (54.9)
Cumulative dose of cisplatin	Median mg/m^2 (S.D.)	520 (196.2) (range 277–1213)	360 (342.4) (range 120–700)	397 (196.26)

CCG, Children's Cancer Group; CHOP,The Children's Hospitcal of Philadelphia Group; SD, standard deviation.
[a] Data are given as number (percentage) unless otherwise indicated.
[b] Audiogram was not available for 1 patient.

Table 2
Risk factors of high frequency hearing loss related to cisplatin therapy

Characteristic		Minimal to mild losses (grades 0–1) ($N=98$)[a]	Moderate to severe losses (grades 2–4) ($N=54$)	P value
Age at treatment (years)	<5	40 (40)	37 (69)	$P=0.001$
	5–14	39 (40)	15 (28)	
	15–20	19 (20)	2 (4)	
Male		48 (49)	21 (39)	$P=0.24$
White		74 (76)	39 (72)	$P=0.54$
Time since end of therapy	<8 months	51 (52)	28 (52)	$P=1.00$
	⩾8 months	47 (48)	26 (48)	
Individual dose of cisplatin[b] (mg/m^2/cycle)	<100	31 (32)	18 (33)	$P<0.0001$
	=100	39 (40)	4 (7)	
	=120	12 (12)	5 (9)	
	=200	15 (15)	27 (50)	
Cumulative dose (mg/m^2)[c]	100–300	22 (22)	7 (13)	$P<0.005$
	301–500	49 (50)	18 (33)	z
	501–700	8 (8)	9 (17)	
	701–1300	7 (7)	13 (24)	

Values are number (percentage) unless otherwise indicated.
[a] Audiogram was not available for 1 patient in the CHOP group, thus the patient's extent of hearing loss was not determined.
[b] Individual dose information not available for 1 patient who had grade 0–1 hearing loss.
[c] Cumulative cisplatin dose information was not available for 12 patients who had grade 0–1 hearing loss and 7 patients who had grade 2–4 hearing loss.

than 5 years, 40% were 5–14-years-olds and 20% were children older than 15 years of age. The overall difference was statistically significant ($P=0.001$).

The individual dose of cisplatin strongly affected the extent of hearing loss ($P<0.001$). Among the 54 patients who developed moderate to severe losses, 27 (50%) had received the largest individual dose (200 mg/m^2/cycle) and 33% had received less than 100 mg/m^2/cycle. The remaining 17% were patients who had received 100 and 120 mg/m^2/cycle.

A higher cumulative dose of cisplatin was also associated with an increased risk of hearing loss. Among the 29 children who received 100–300 mg/m^2, only 7 (13%) developed grade 2 and worse losses. This risk increased almost 3-fold, to 22% at cumulative doses of 701–1300 mg/m^2 ($P<0.005$).

Factors showing statistical significance were next entered into a logistic regression model, including the child's age at treatment, and individual and cumulative doses of cisplatin. Factors not statistically significant in Table 2 were excluded, including the child's gender and ethnicity, and the elapsed time since the end of treatment.

The model contained four independent variables, including two dummy variables for age. One dummy variable coded for patients younger than 5 years and the other for 5–14 years. Thus, the two age dummy variables contrasted the differential risks between the youngest (less than 5 years of age) and the intermediate (5–14 year olds) compared with the reference group, 15–20-year-olds, respectively. The cisplatin doses were dichotomised (above versus below the median, 100 mg/m^2/cycle) and the cumulative dose (above versus below the median, 400 mg/m^2).

Table 3 shows increased risks for moderate to severe losses for younger children and for cumulative cisplatin doses greater than or equal to 400 mg/m^2. After controlling for age and the effect of higher cumulative doses, higher individual doses appeared to entail no significantly increased risk of moderate to severe losses. Age at treatment was highly significant in predicting the risk of hearing loss. Patients younger than 5 years of age were

Table 3
Results of logistic regression analysis

Risk factor	Odds ratio	95% CI for the odds ratio
Age at treatment (years)		
younger than 5 versus 15–20 years of age	21.17	(2.48–180.94)
5–14 versus 15–20	10.09	(1.18–86.08)
Individual cisplatin dose (above versus below 100 mg/m^2/cycle)	0.93	(0.35–2.50)
Cumulative cisplatin dose (above versus below 400 mg/m^2)	3.35	(1.39–8.04)

95% CI, 95% Confidence Interval.

around 21 times more likely to develop moderate to severe high-frequency hearing loss than 15–20-year olds (95% CI: 2.48–180.94). Patients between 5 and 14 years of age were about 10 times more likely to develop such losses (95% CI: 1.18–86.08).

Overall, the Hosmer–Lemeshow test showed that the model's predictions had good calibration ($F_{(df=5)} = 2.28$, $P < 0.81$) and good discrimination (c-statistic = 0.72).

Fig. 1 shows the model's prediction of the probability of developing moderate to severe losses as a function of the cisplatin cumulative dose and age. The predicted risk profiles for the three age groups are plotted in separate curves. The CIs of the predictions at the median cumulative dose of 400 mg/m^2 are also identified for the youngest and oldest age groups. At a median dose of 400 mg/m^2, patients younger than 5 years have an estimated 40% chance of developing moderate to severe losses (95% CI: 0.307–0.550), as compared with the estimated 5% chance for patients between the ages of 15 and 20 years (95% CI: 0.006–0.256). At 1200 mg/m^2, the estimated risk for children younger than 5 years increases to nearly 90%, while for 15–20-year-olds the risk was 38%.

The CIs suggest a large individual variability in the predicted risk of hearing loss. To better visualise this large individual variability, Fig. 2 plots audiometric measurements for CHOP patients, grouped roughly evenly according to three- levels of cumulative cisplatin doses. The curves are smoothed by local regression applied to neighbouring points [29]. Dotted lines are plotted to indicate Brock's level-2 hearing loss. The bottom left-hand section of each panel (i.e. to the left and also below the dotted lines) represents grade 2 loss.

The smoothed curves show that higher cumulative cisplatin is associated with progressively worse hearing

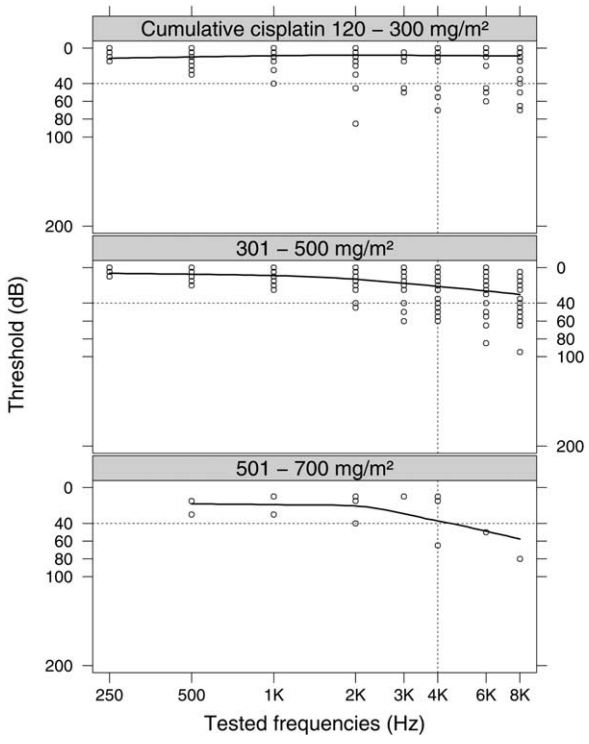

Fig. 2. Varying effects of total cisplatin dose on high-frequency hearing thresholds for the 73 (CHOP) patients. The three panels represent the profiles of hearing thresholds for patients who had received cumulative doses from 120–300 mg/m^2 (top panel), 301–500 mg/m^2 (middle), to 501–700 mg/m^2 (bottom). The circles represent the hearing thresholds for each tested frequency for the child's 'better' ear. The smoothed lines show the profiles of hearing thresholds for a typical patient at a given dosage level. Brock's grade-2 loss is identified by the dotted lines, showing a threshold at 40 dB for 4000 Hz. The bottom left-hand section of each panel (i.e. to the left and also below the dotted lines) represents grade 2 loss. The smoothed audiogram gradually approaches grade 2 loss as higher cumulative doses of cisplatin are administered.

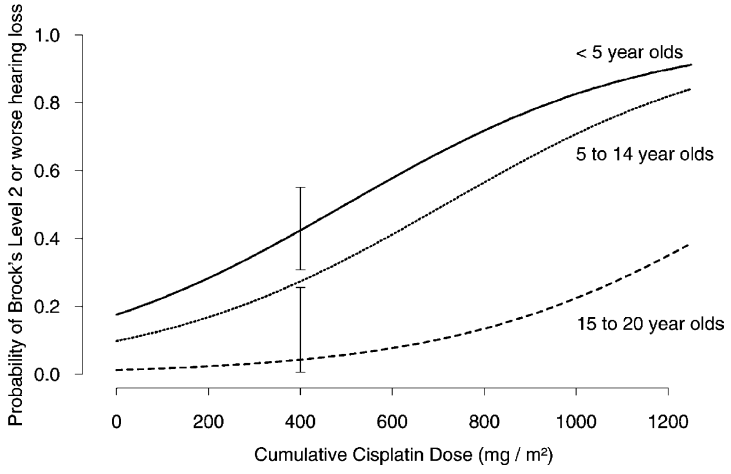

Fig. 1. Predicted probability of developing 'moderate to severe' losses as a function of the child's age at treatment and the total cumulative dosage of cisplatin. The 95% confidence intervals (CIs) for the predicted risk probability at the overall median dose, 400 mg/m^2, are also identified. At 400 mg/m^2, the youngest group would have a significantly higher risk than the oldest group in developing moderate to severe loss.

losses in frequencies higher than 4000 Hz. At a cumulative dose of 120–300 mg/m^2, an average patient (the smoothed curve) shows no discernable loss, although some patients exhibit signs of moderate loss. The smoothed curve shows that hearing loss worsens at larger doses of cisplatin. At 301–500 mg/m^2, many more patients show losses worse than the level-2 criterion. At even higher doses (501–700 mg/m^2), an average patient develops hearing loss near level-2.

4. Discussion

Cisplatin ototoxicity in children is highly dependent on age and the cumulative cisplatin dose. The increased risk due to larger individual doses was not statistically significant after adjusting for the cumulative dose.

Previous studies evaluated how cisplatin ototoxicity disproportionately affected younger children, but they were limited in their sample size: a recent review of 11 published studies showed that 10 of them included less than 60 children [3,20]. Conflicting results have also been reported. In a study of 34 children between 2 and 19 years of age, Cohen and colleagues [23] did not find a significant correlation between the age of the patient and hearing loss and, more recently, Berg and colleagues [3] found no significant increased risk due to a higher cumulative dose.

Brock's criteria is perhaps the most useful tool to date in classifying high-frequency hearing loss due to cisplatin therapy. Conventional severity classification systems, including the National Cancer Institute Common Toxicity Criteria version 2.0, are not appropriate because they do not specifically consider high-frequency losses [1]. Graphical methods have been used to illustrate the deterioration of hearing after repeated doses [2,30,31]. They too can be impractical because the profiles of audiometric findings need to be interpreted subjectively. Brock's system is sensitive to the typical pattern of hearing loss in children treated with cisplatin. Each severity grade entails the partial or complete loss to important speech phonemes, making the classification more meaningful for a developing child.

In our study, children younger than 5 years of age are the most susceptible to cisplatin ototoxicity. The model predicts that approximately 40% of the children younger than 5 years would develop moderate to severe losses when they receive a cumulative dose of 400 mg/m^2, compared with the 5% risk among children between 15 and 20 years of age. This translates into an average of an 8-fold relative risk. At a higher dose of 1200 mg/m^2, the relative risk decreases to approximately 2-fold (approximately 90%/38% = 2.4). At such a high dose, even the more resilient teenage patients start to show signs of hearing loss. As higher doses are administered, the gap between the differential risks narrowers.

The model's predictions may be helpful in finding a balance between cisplatin treatment efficacy and ototoxicity. Higher doses of cisplatin are, in general, more effective, but they also entail an increased risk of ototoxicity. Our findings suggest that a higher dose may entail a superior risk/benefit ratio for teenage patients than for patients younger than 5 years of age. Cushing and colleagues recently reported that raising the cumulative cisplatin dose from approximately 100 to 200 mg/m^2/cycle increased the median 2-year event-free survival rate among children with high-risk malignant germ-cell tumours from 75–87% [24]. This 75 to 87% boost in disease-free survival may be reassuring for a 15- to 20-year-old patient, whose predicted risk of sustaining moderate to severe losses is relatively low. For a child younger than 5 years, the same overall increase in survival rate may entail substantially higher risks of moderate to severe hearing loss. This risk/benefit trade-off becomes less clear the higher the cumulative dose of cisplatin.

Evaluating the trade-off between survival and toxicity in younger children is plagued by a lack of critical information. No existing data describe how cisplatin-induced childhood hearing loss affects children's functional states when they become adolescents and when they enter early adulthood. Literature on language development as well as on sensorineural hearing loss provide some guidance, but they do not address comorbidities associated with surviving cancer; they also lack long-term follow-up [32–34]. A formal analysis of this trade-off, particularly in the form of a decision tree [35], is bound to be problematic unless there is better understanding of the functional consequences and their associated probability distributions. The predictive model reported herein should be helpful in establishing a formal decision analytical method.

Our data highlight the importance of audiology monitoring during cisplatin treatment, especially for children younger than 5 years of age. In this age range, the impact of hearing loss is most profound because it compromises language development. Children older than 15 years of age appear to be more tolerant of cisplatin ototoxicity.

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