Platinum compounds in children with cancer: toxicity and clinical management

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Platinum compounds are widely used in the treatment of pediatric tumors such as neuroblastoma, germ-cell tumors, osteosarcoma, retinoblastoma, hepatoblastoma, brain tumors (low-grade gliomas and medulloblastoma/PNET), and relapsed and refractory lymphomas. The three major platinum compounds (cisplatin, carboplatin, and oxaliplatin) have a similar pharmacokinetics profile and mechanism of action, but the differences in their chemical structure are responsible for their different antitumor activity and toxicity. In this review, we have described the main characteristics of cisplatin, carboplatin, and oxaliplatin, focusing on their toxic effects and possible strategies to prevent them to improve the clinical outcomes in pediatric cancer patients. The underlying mechanism of each platinum-related toxicity is shown together with the clinical manifestations. Furthermore, possible preventive strategies are suggested to reduce the negative impact of platinum compounds on the quality of life of children with cancer. Cisplatin seems to be mostly ototoxic and nephrotoxic, carboplatin mainly produces myelosuppression, whereas oxaliplatin induces predominantly peripheral sensory neurotoxicity. In contrast, nausea and vomiting can be linked to all platinum compounds, although cisplatin exerts the strongest emetic effect. A correct knowledge of pharmacokinetics and toxicological profile of platinum compounds may aid physicians prevent their toxicity on auditory, nervous, renal, and bone marrow function, improving the quality of life of pediatric cancer patients. *Anti-Cancer Drugs* 00:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The use of the platinum compounds (cisplatin, carboplatin, and oxaliplatin) in the chemotreatment of pediatric malignancies has extended long-term survival of pediatric patients [1]. Unfortunately, platinum drug agents have numerous toxicities including ototoxicity, neurotoxicity, nephrotoxicity, myelotoxicity, and emesis [2]. This can have a negative impact on the quality of the treatment and the life of children with cancer.

Several authors have developed strategies to ensure controlled systemic exposure to the drug to reduce toxicity [3]. The aim of this study was to review the main characteristics of cisplatin, carboplatin, and oxaliplatin, focusing on their toxic effects and possible strategies to prevent them, to improve clinical outcomes in pediatric cancer patients.

Platinum compounds

Cisplatin

Cisplatin was discovered in 1965 by Rosenberg and colleagues during an experiment on the effect of electric fields on the cell division of bacteria. It was the first platinum compound introduced in clinical practice in the early 1970s, and since then, it has continued to be a basic drug in modern chemotherapy [4,5].

Cisplatin chemotherapy is used in the treatment of several pediatric cancers, such as neuroblastoma, germ-cell tumors, osteosarcoma, relapsed, and refractory lymphomas [6].

Cisplatin (*cis*-diamminedichloroplatinum II) (Fig. 1) contains a platinum atom surrounded by two ammonia groups and two chloride leaving groups in the *cis* position. Cisplatin undergoes an activation by a replacement reaction in which water molecules replace the chloride ligands of cisplatin, thus forming platinum cations that covalently bind with purine DNA bases and create intrastrand and interstrand cross-links [7].

The cytotoxic effect of cisplatin depends on the formation of cisplatin–DNA adducts [N-7 adducts at d(GpC) and d(ApG)] that block DNA, RNA, and protein synthesis, thus halting the proliferation of cancer cells [5,8].

Pharmacokinetics

Cisplatin has a high binding capacity with the plasma protein, and after an intravenous infusion, almost 90% of the drug actually binds with the plasma protein (Table 1).

The drug penetrates more rapidly and in greater quantity into the liver, kidneys, testicles, colon, and small bowel,

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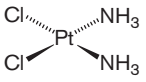
Fig. 1



Chemical structure of cisplatin.

Table 1 Pharmacokinetic features of platinum analogs

Pharmacokinetic features	Cisplatin	Carboplatin	Oxaliplatin
Binding protein (%)	>90	24–50	85
Terminal half-life of total platinum (h)	24–127	8.2–40	38–47
Urinary excretion (%)	23–50	54–82	>50

although it does not reach the central nervous system (CNS) [2]. Both the ultrafiltrable platinum, which is represented by intact drug not bound to protein and metabolites, and the total platinum, which consists of all platinum species, bound and unbound, may be measurable in serum, although only the ultrafiltrable platinum is related to the antitumor and toxic effects of the drug. Approximately 90% of the drug is eliminated by the kidney, combining glomerular filtration with tubular secretion, whereas 10% is eliminated by biliary excretion.

Generally, about 25% of the cisplatin dose is excreted from the body during the first 24 h [2,4,9], although platinum adducts can be found in tissue for over a decade after exposure [5–7].

The main adverse effects associated with cisplatin, which limit the maximum dosing of the drug, are nephrotoxicity, neurotoxicity, and ototoxicity [8].

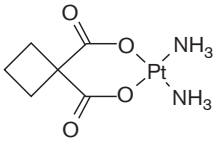
Carboplatin

Carboplatin is an analog of cisplatin developed to reduce the dose-limiting toxicity of cisplatin. It is commonly used in the treatment of pediatric tumors such as neuroblastoma, retinoblastoma, hepatoblastoma, brain tumors, and germ-cell tumors.

Veal and colleagues report that approximately one-third of children with solid tumors are exposed to carboplatin during the therapy [10,11]. Carboplatin has greater chemical stability compared with cisplatin, and is therefore less reactive with DNA but also less toxic than cisplatin [2].

Previous studies [12,13] have shown that carboplatin is 8–45 times less potent than cisplatin and to achieve comparable antitumor effects, it is necessary to administer carboplatin in higher doses. Probably, this is because of its weaker DNA-damaging effect: carboplatin actually produces a DNA adduct more slowly than cisplatin. On the basis of an analysis of the literature, Lokich *et al.* [4] have pointed out that carboplatin requires a therapeutic dose of carboplatin four times higher than the cisplatin dose (400–500 vs. 100 mg/m^2) to be equivalent to cisplatin.

Fig. 2



Chemical structure of carboplatin.

In terms of its structure, *cis*-diammine (1,1-cyclobutanedicarboxylato) (Fig. 2) platinum has a cyclobutanedicarboxylato leaving group that facilitates a slow reaction with antioxidant molecules, such as glutathione and metallotheonines. For this reason, the drug, after cell internalization, has a higher nuclear concentration than cisplatin [8].

The mechanism of action of carboplatin is similar to that of cisplatin: the drug binds covalently to DNA, causing chain alkylation; however, carboplatin is found to be weaker in causing DNA damage because it produces DNA adducts more slowly [3,12,14]. Inside the cell, a slow conversion of carboplatin into reactive species occurs, which then form interstrand and intrastand cross-linking of DNA molecules inhibiting DNA synthesis [14].

Pavelka *et al.* [15] have shown how the hydrolysis reaction of carboplatin occurs through a biphasic mechanism with an initial ring-opening, followed by the loss of the malonato ligand.

Pharmacokinetics

Because of its chemical structure, carboplatin is less reactive to plasma protein. In terms of elimination of the drug, about 90% is excreted intact by the kidneys within 24 h (Table 1). Indeed, the renal elimination of carboplatin is achieved almost exclusively by glomerular filtration. Therefore, the drug clearance is closely related to the glomerular filtration rate (GFR) and the latter is linked to the area under the carboplatin concentration–time curve (AUC), which describes the systemic exposure to the drug and correlates with its clinical efficacy and toxicity, mainly myelosuppression and emesis [2,11]. On the basis of these data, Calvert *et al.* [16] suggested a formula to calculate the dose of carboplatin to obtain a specific, protocol-dependent AUC. 'Calvert formula': dose (mg) = target AUC (mg/ml × min) × [GFR (ml/min) + 25] [16].

The most popular and economical method for measurement of the GFR is creatinine clearance, although a preferable method is to use an isotopic tracer such as ^{51}Cr-EDTA [16–18].

Oxaliplatin

Oxaliplatin (*trans*-L-diaminocyclohexane oxalate platinum II) (Fig. 3) is a third-generation platinum compound approved initially in the European Union (1999) and then in the USA (2002) [19].

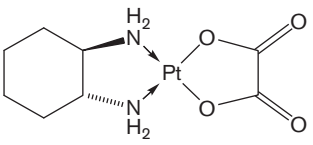
As reported in several studies [20,21], the drug has a wide-spectrum antitumor activity against neuroblastoma, ovarian melanoma, non-small-cell lung, colon, and bladder carcinoma, and breast and gastric cell lines. The structure of oxaliplatin includes a central platinum atom surrounded by a 1,2-diaminocyclohexane (DACH) group and a bidentate oxalate ligand. The cytotoxic effect of the drug is related to the production of platinum–DNA adducts that interrupt DNA synthesis and transcription [19,22].

The prodrug activation occurs by slow hydrolysis and displacement of the oxalate group. This reaction leads to the formation of monochloro, dichloro, and diaquo intermediate compounds that react specifically with sulfur and amino groups in proteins, RNA, and DNA [19].

According to the literature, oxaliplatin creates fewer DNA adducts than cisplatin because the DACH carrier ligand converts the monoadduct into a diadduct more slowly. Despite this, it causes apoptosis more effectively, and indeed, DACH–platinum adducts are highly cytotoxic and the DACH carrier ligand impairs the mechanisms that allow cells to withstand unrepaired platinum [23].

In addition, oxaliplatin has no cross-resistance with either cisplatin or carboplatin because of two mechanisms. The first one is related to the drug structure; the large DACH ring sterically prevents the mismatch-repair enzyme complex from binding to oxaliplatin adducts [24] and second mechanism consists of the lack of the replicative bypass present in the cells resistant to cisplatin [25].

Fig. 3



Chemical structure of oxaliplatin.

Unlike other platinum compounds, its toxicity profile is acceptable, with an incidence of ototoxicity of less than 1%, renal toxicity of less than 3%, and the presence of a neurotoxicity specifically with respect to peripheral sensory nerves [19].

Pharmacokinetics

The pharmacokinetics profile of oxaliplatin is similar to that of carboplatin and cisplatin. After an intravenous infusion, initially, about 70% of the drug is bound to plasma protein, especially albumin; ultimately, this reaches 95% (Table 1).

The bound drug loses a part of its antitumor activity. In addition, oxaliplatin compounds are present in various tissues, although a part of the drug constituted of platinum associated with erythrocyte exists; this association is because the drug is blocked inside the cells with small molecules and it remains in red blood cells for longer than in plasma. On this basis, O'Dwyer and colleagues have reported that the red cells may probably represent a reservoir of drug [2,19].

The free platinum is eliminated from the body mainly through the kidneys and only 2% in the feces. Renal excretion occurs principally by glomerular filtration, but there is no correlation between renal function and platinum exposure (AUC).

Unlike other platinum compounds, oxaliplatin does not accumulate after multiple courses of treatment; thus, oxaliplatin-related neurotoxicity is rapidly reversible [19].

Toxicity

In the literature, many papers describe the adverse effects of platinum agents. Table 2 shows the toxic profile of cisplatin, carboplatin, and oxaliplatin.

Ototoxicity

Cisplatin

Cisplatin is more ototoxic than other platinum drugs: 60% of pediatric patients (range 26–90%) exposed to cisplatin-based chemotherapy develop irreversible bilateral hearing loss [1,26–29].

The ototoxicity of cisplatin requires a high dose of drug administered intraperitoneally or intravenously; nevertheless, a single low dose might be ototoxic if infused retrograde into the common carotid artery, probably for the first pass into the vertebral artery that provides blood to the cochlea [29,30].

Table 2 Toxic profile of platinum compounds

Platinum compounds	Ototoxicity	Myelosuppression	Nephrotoxicity	Neurotoxicity	Nausea/vomiting
Cisplatin	+		+	+	+
Carboplatin		+			+
Oxaliplatin				+	+

Sensory cells of the inner ear are located inside a blood–labyrinth barrier that is very similar to the blood–brain barrier. However, platinum can be found in the tissues of the cochlea with an intact blood–labyrinth barrier; the passing mechanism is not completely clear [29,31]. The blood–labyrinth barrier could be bypassed by introducing cisplatin directly into the cochlea. Another approach involves using loop diuretics to temporarily open the blood–labyrinth barrier [32,33]; the third method involves administration of cisplatin in combination with noise [34]. Noise exposure can damage the stria vascularis and disrupt the blood–labyrinth barrier [35]; it also makes the cochlea more vulnerable because it induces oxidative stress and decreases antioxidant enzyme levels [32,34].

Cochlear hair cells die first at the base of the cochlea and gradually toward the apex with increasing exposure to the drug [29,36]. In the mitochondria of cochlear cells, cisplatin alkylation induces the production of proapoptotic factors and high levels of reactive oxygen species (ROS), which can activate caspases, thus triggering cell death. Moreover, toxic levels of ROS damage proteins and lipids and exhaust the cell's antioxidant agents, amplifying damage [37].

Laurell and colleagues pointed out that cisplatin also induces degeneration of stria vascularis, progressively reducing spiral ganglion cells [32,38,39]. Several studies emphasize the role of p53 in the initial stages of the hair cell death mechanism induced by cisplatin [40,41].

Devarajan *et al.* [42] suggested that 3 h post-treatment with cisplatin in a cochlear cell causes upregulation of p53 and subsequently the upregulation of Bax, cytochrome-c, and caspase 8–9, followed by apoptotic cell death.

Carboplatin

A considerable body of literature suggests that carboplatin is less ototoxic than cisplatin [2,4,17,43,44]. As reported in numerous studies, the use of nonmyeloablative doses of carboplatin typically does not cause ototoxicity [43,45–47]. However, Jehanne *et al.* [48] described ototoxicity in 4.5% of children treated with nonmyeloablative doses of carboplatin for conservative management of unilateral or bilateral retinoblastoma. Subsequently, Qaddoumi *et al.* [49] also reported that children younger than 6 months of age treated with carboplatin were 21 times more likely to have sustained hearing loss than patients who were older than 6 months of age.

When carboplatin is administered at a myeloablative dose in alternating cycles with cisplatin, after cisplatin chemotherapy, or in combination with osmotic agents (such as mannitol) by opening the blood–brain barrier, it may cause significant ototoxicity [45,50,51].

A large number of studies [52–54] have pointed to the high toxicity of carboplatin to inner hair cells (IHC). Indeed, only after the destruction of all IHC do large doses of carboplatin damage the outer hair cells (OHC). The lesions of the IHC occur to the same degree along the entire length of the cochlea as carboplatin destroys every second, third, or fourth internal cell along the length of the cochlea; conversely, OHC lesions tend to shrink, proceeding from the base to the apex [54].

In terms of the carboplatin–p53 relation, Zhang and colleagues and numerous other authors have shown that p53 contributes toward the carboplatin-induced IHC lesions [32,55,56].

Oxaliplatin

According to Hellberg *et al.* [57], oxaliplatin appears to be less ototoxic than cisplatin probably because of its minor uptake by the cochlear cells compared with cisplatin.

This could be linked to the presence of different drug transporters such as organic cation transporter 1–2 and the multidrug and toxic extrusion pump [58]. However, Malhotra *et al.* [59] noted that oxaliplatin can cause significant hearing loss. Treating the cochlear cells with 10 μmol/l of oxaliplatin, Ding and colleagues observed a significant damage of the nerve fibers, whereas cochlear cells appeared normal. This confirmed that oxaliplatin is primarily neurotoxic and responsible for a peripheral neuropathy.

Increasing the dose of the drug to 50, 100 μmol/l also induced damage of hair cells and stereocilia; ironically, increasing the dose to 500 or 1000 μmol/l induced less hair cell and nerve fiber damage [32].

Clinical features

According to previous studies [1,29,60], platinum ototoxicity generally occurs in the form of permanent sensorineural bilateral hearing loss that initially affects high frequencies and then, with continuous administration and increasing cumulative dose, also lower frequencies. Also, the severity of hearing loss becomes worse with increasing cycles of cisplatin chemotherapy; this typically becomes clinically evident after more than one cycle of a platinum drug [61].

As several reviews have observed [1,62], platinum hearing loss is permanent after the end of treatment, although Bertolini *et al.* [46] have described a worsening up to 11 years after the end of therapy.

Ototoxicity and hearing loss in pediatric oncology patients have been defined by several different ototoxicity criteria over the years. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) was typically used in cancer treatment studies but it did not address pediatric patients because it requires a measurement to be made before starting therapy and periodic evaluations during the treatment. In fact, obtaining baseline evaluations and

true auditory thresholds can be complicated and inaccurate in children. In addition, the NCI-CTCAE does not indicate test frequencies [63,64].

The American Speech-Language Hearing Association (ASHA) ototoxicity criteria were introduced into clinical practice to assess the effects of ototoxic therapy; they can be used for extended high frequencies (> 8000 Hz) and allow the auditory threshold to be monitored during treatment. Also, these criteria require a complete baseline assessment, which is difficult to obtain in children; moreover, the major limitation of the ASHA criteria is the lack of a grading scale to evaluate the severity of hearing loss [65].

The Brock criteria, in particular, allow hearing loss induced by platinum agents in pediatric patients to be evaluated and so there is no basic measurement. Typically, the auditory threshold at which hearing loss occurs is higher than 40 dB and so this frequency is considered the cutoff level. The possible presence of a mild hearing impairment level (25–35 dB) after cisplatin therapy cannot be detected and this is the main limitation of the Brock criteria [60]. Chang and Chinosornvatana's grading system assesses the hearing loss related to ototoxicity, highlighting the impact on speech and language and the need for assistive hearing devices. In addition, it is more sensitive than the traditional CTCAE criteria and specifies the severity of hearing loss more accurately [66].

The New International Society of Pediatric Oncology (SIOP) Boston Ototoxicity Grading Scale (Table 3) is based on sensorineural hearing thresholds, but is simpler and virtually superior to the previous ones. It was developed by consensus in the autumn of 2010 at a working group meeting with the aim of finding a practical measurement that allows the results of different clinical studies to be compared [29,64].

Otoprotection

Children are more susceptible to ototoxicity from platinum agents than adults. In young children, especially if they are prelingual or in the early stages of language development or if they have other functional deficits, such as cognitive or visual dysfunction, the ototoxic damage may exert a negative effect on speech, language, and social development.

Table 3 New International Society of Pediatric Oncology Ototoxicity Scale [60]

Hearing loss (HL), sensorineural hearing loss (SNHL) thresholds	Grade
≤ 20 dB for all frequencies	0
>20 dB HL, SNHL above 4000 Hz	1
>20 dB HL, SNHL at 4000 Hz and above	2
>20 dB HL, SNHL at 2000 Hz or 3000 Hz and above	3
>40 dB HL, SNHL at 2000 Hz and above	4

According to current practice, in pediatric patients treated with platinum drugs, the detection of clinically significant ototoxicity during audiologic monitoring justifies the reduction of the dose or the discontinuation of the drug. However, this does not allow the irreversible damage caused by ototoxic drug to be repaired but rather reduces the effectiveness of cancer treatments and the probability of survival. The development of otoprotectants is aimed to prevent the ototoxic damage induced by the platinum compounds without reducing their potent antitumor activity [29]. Several different otoprotective agents are used in clinical and preclinical studies. The reactive species of platinum preferably bind the antioxidant molecules such as glutathione and metallothioneins, altering the antioxidant system of the OHC and increasing their susceptibility to oxidative damage [17,37,67].

For this reason, many agents that reduce oxidative stress of cochlear cells have been tested as otoprotectants: *N*-acetyl-cysteine, α-tocopherol, lipoic acid, sodium thiosulfate salicylate, ebselen, D-methionine, and amifostine [68–74]. At present, the efficacy of the otoprotection agents is uncertain. Marina *et al*. [75] reported that amifostine does not protect against the ototoxicity of high-dose cisplatin combined with etoposide and bleomycin in pediatric germ-cell tumors. In contrast, Fouladi *et al.* [76] emphasized the role of amifostine against cisplatin-induced ototoxicity when administered at an intensive dosage.

Katzenstein *et al.* [77] observed that it does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma when it is used at the standard dosage. Sodium thiosulfate is currently being tested by the Children's Oncology Group and SIOPEL (International Pediatric Oncology Epithelial Liver Tumor Strategy Group) in a randomized-controlled trial of pediatric patients treated with cisplatin. According to preclinical data, it may confer otoprotection without reducing the cytotoxicity of cisplatin [29,61]. Vitamin E and D-methionine have been found to exert promising otoprotective effects in preclinical studies [78,79].

Nonetheless, the Food and Drug Administration has not yet approved any agents to prevent the ototoxic damage induced by platinum drugs. In addition, another approach to achieve otoprotection is anatomic or compartmental therapy, which consists of delivering D-methionine to the round window before systemic treatment with platinum-based chemotherapy [29,80].

Risk factors

Numerous risk factors increase the likelihood of hearing loss associated with the use of platinum compounds, the main ones being higher cumulative dose of chemotherapy, younger age, CNS tumors, and CNS radiation [61]. In terms of the cumulative dose of chemotherapy for cisplatin, the cutoff level to prevent irreversible hearing loss related

to the speech frequencies is 400 mg/m^2 in pediatric patients and 600 mg/m^2 in adult patients [1,62,81].

Cushing *et al.* [82] have compared children with germ cell tumors exposed to high doses of cisplatin (800 mg/m^2) with those exposed to low doses of the drug (400 mg/m^2). They noted that the incidence of significant hearing loss was 14 and 0%, respectively [82]. Li *et al.* [83] subsequently reviewed the audiograms from this study and showed a higher incidence of ototoxicity of 67 and 10%, respectively. Moreover, the high-dose cisplatin ranged from 800 to 1200 mg/m^2 and the standard dose ranged from 400 to 600 mg/m^2 [83].

The ototoxicity threshold for carboplatin is 400 mg/m^2 and the dose of carboplatin prescribed in transplant protocols for neuroblastoma is four times higher than this limit dosage [45,84]. Children with neuroblastoma constitute a large risk group for hearing loss because they may receive both cisplatin chemotherapy and high-dose carboplatin-containing myeloablative regimens for stem-cell transplantation [85].

In their study, Yancey *et al.* [86] reported that the age at the time of exposure to cisplatin therapy is inversely related to the severity of ototoxicity. As reported by Qaddoumi *et al.* [49], age at the start of treatment with carboplatin was found to be a statistically significant risk factor for hearing loss.

In accordance with previous studies, another high-risk group for ototoxicity consists of young children with CNS tumors, such as medulloblastoma, because these patients have often been treated with cranial radiation and platinum-based chemotherapy.

Warrier and colleagues have observed a high incidence of hearing loss in children with brain tumors exposed to cisplatin and cranial radiation with initial impairment in the high frequencies progressively involving the lower frequencies down to the speech range (4000 Hz) [87–90]. Cranial radiotherapy is a main risk factor for ototoxicity. The cochlea, especially the part codifying for high frequencies, is highly sensitive to the effects of radiation [91]. Therefore, during the treatment for brain tumors, infratemporal and nasopharyngeal tumors, cochlear irradiation can occur.

Hua and colleagues have indicated a cumulative cochlear dose of less than 35 Gy to avoid an ototoxic effect [92,93]. Several studies [90,91,93,94] have examined the relation between cranial irradiation and cisplatin chemotherapy in children with cancer.

Shell *et al.* [88] reported that the probability of developing hearing loss is greater in patients receiving both treatments rather than only chemotherapy, although the cumulative dose of cisplatin is the same. Moreover, many authors have stressed that the ototoxicity of cisplatin is enhanced especially when the drug is administered after irradiation [94–96].

Warrier *et al.* [87], although not reporting this timing relation, suggest that cranial radiation probably enhances drug penetration and makes the cells more susceptible to hypoxic damage and to the effects of cisplatin.

To minimize ototoxic risk, particularly in patients also receiving platinum-based chemotherapy, radiation therapy has been administered using the well-known conformal techniques with the aim to reduce the dose to the cochlea and eighth cranial nerve [97].

Recently, Merchant *et al.* [98] treated children with brain tumors with proton-beam irradiation to evaluate the dose to the cochlea with this technique without the scattering effects. Their data suggest that the dose distributed to the cochlea is less than the threshold dose for ototoxic damage [94].

Ototoxicity related to platinum agents can also be influenced by other factors such as aminoglycoside antibiotics and loop diuretics used in supportive therapy [33,99], compromised renal function that reduces the elimination of ototoxic platinum agents, and ear pathologies that impair the auditory function, such as chronic otitis and middle-ear effusions [61].

Ultimately, Ross *et al.* [100] have observed that genetic factors may also contribute toward platinum toxicity. Indeed, about 20% of children do not develop any toxicity. In particular, in this study, the authors have identified two genes, thiopurine-*S*-methyltransferase (*TPMT*) and catechol-*O*-methyltransferase (*COMT*), both strongly associated with cisplatin-induced ototoxicity in children [100]. Therefore, the analysis of *TPMT* and *COMT* genotypes could be used as a clinical test to identify patients at a high risk of ototoxicity and to adapt the treatment on the basis of risks for each child and each tumor type [33].

Screening

The pediatric cancer survivors exposed to potential ototoxic treatment should undergo a long-term follow-up with a complete audiological evaluation consisting of speech audiometry, tympanometry, air conduction, and bone conduction.

The auditory brainstem response measurement might be necessary for young children who are difficult to test [101].

In addition, Warrier *et al.* [87] recommend a serial monitoring of the patients exposed to cranial irradiation and platinum-based chemotherapy for the early identification of audiological damage. Nevertheless, further follow-up studies are required; the detection of auditory changes after ototoxic therapy seems to be necessary to evaluate the measures adopted before treatment and the first audiological assessment [61,102].

Myelosuppression

Carboplatin

Myelosuppression is the dose-limiting toxicity of carboplatin [2]. Go and Adjei [17] report that severe thrombocytopenia is detected in 25% of patients exposed to the drug, whereas severe neutropenia occurs in 18% of cases. Despite this, infectious and bleeding complications are rare. Anemia is observed more frequently with increased carboplatin exposure [103].

O'Dwyer *et al.* [2] report that the platelet counts reach a nadir 17–21 days after a single dose of carboplatin.

Several studies [12,15,103] have shown that myelotoxicity of carboplatin is strongly associated with the AUC and the clearance of drug is directly proportional to the GFR. For this reason, Calvert *et al.* [16] introduced a formula to guide carboplatin dosage and prevent its myelotoxicity. However, for those patients with poor performance status, who are elderly, pretreated, Calvert's formula is not sufficient to reduce carboplatin toxicity because they constitute a high-risk group [1].

Cisplatin

Myelotoxicity induced by cisplatin is dose related and reversible. Clinically, it is generally mild and involves all three hematopoietic lines.

The literature suggests that cisplatin has a cumulative toxicity for CFU-S and CFU-C in mice [104]. Go and Adjei [7] report serious leukopenia or thrombocytopenia in 5–6% of cases. Previous studies have treated the anemia induced by cisplatin and the authors concluded that in some cases it was secondary to hemolysis and in other cases to erythropoietic alteration [105,106].

In general, cisplatin appeared to be well tolerated.

Oxaliplatin

Myelosuppression is rare and mild if oxaliplatin is used as a single agent rather than in combination regimes with other drugs. However, the drug is most toxic to the platelet precursors, with an incidence of thrombocytopenia of 26%; neutropenia occurs in 16% of cases and leukopenia in 12% of patients.

In 2006, Fouladi and colleagues confirmed that dose reduction is primarily because of myelosuppression, transaminitis (7%), or sensory neuropathy (4.7%) [2,107].

Risk factors

Risk factors for myelosuppression related to platinum compounds include previous cytotoxic therapy (especially cisplatin), poor performance status, old age, impaired renal function, and concurrent myelosuppressive therapy [15].

Nephrotoxicity

Cisplatin

Among platinum compounds, it is mainly cisplatin that produces nephrotoxicity with considerable individual differences in severity [108]. Several studies have investigated the molecular mechanism of cisplatin nephrotoxicity, suggesting that its accumulation in renal tubular cells causes direct inflammation, oxidative damage, apoptosis with possible tubular injury, and dysfunction [109].

Alterations are mainly produced in the epithelial cells localized in the S3 segment of the proximal tubule, likely because in this renal site, the cisplatin concentration is about five times the serum concentration. The organic cation transporter (OCT2) is crucial for the active uptake into tubular renal cells and it seems to play a role in cisplatin nephrotoxicity; indeed, cimetidine is an OCT2 substrate that reduces cisplatin uptake and nephrotoxicity. Moreover, in 2009 Filipski and colleagues found that the presence of a nonsynonymous single-nucleotide polymorphism in the OCT2 gene *SLC22A2* (rs316019) reduces cisplatin-induced nephrotoxicity in patients [110,111].

Other molecular researches have proposed that the nephrotoxicity of cisplatin is dependent on the cleavage of a cisplatin–glutathione conjugate by γ-glutamyl transpeptidase (GGT) localized on the luminal surface of the renal proximal tubules. GGT catalyzes the initial step in the metabolism of glutathione-conjugated drugs to mercapturic acids, some of which are severely nephrotoxic. Hanigan *et al.* [112] administered a bolus of glutathione 30 min before cisplatin, which is a physiological substrate for GGT, finding an inhibited cisplatin-induced nephrotoxicity.

Inside tubular cells, cisplatin damages nuclear and especially mitochondrial DNA, activating both mitochondrial and nonmitochondrial pathways of apoptosis and necrosis. Mitochondria are highly susceptible to injury, because of the loss of any efficient DNA repair mechanism; their fullness in the proximal tubule may explain the particular tendency of this renal site to cisplatin damage [113].

Both the intrinsic mitochondrial pathway and the endoplasmic reticulum stress pathway and extrinsic activation of tumor necrosis factor (TNF) or Fas receptors are implicated in cisplatin-induced renal cell death, although significant interactions exist among these pathways.

Lieberthal *et al.* [114] reported that the mechanism of cell death induced by cisplatin is concentration dependent; indeed, high concentrations of cisplatin induce necrosis, whereas lower concentrations produce apoptosis, through the activation of caspases 1, 3, 8, and 9.

Furthermore, cisplatin enhances renal expression of TNF-α, which seems to induce apoptosis, to produce ROS, to activate proinflammatory cytokines and chemokines, playing a central role in the pathogenesis of cisplatin renal injury.

Ramesh *et al.* [115] reported that TNF-α-deficient mice were resistant to cisplatin nephrotoxicity; in addition, TNF-α inhibitors seem to reduce cisplatin-induced structural damage.

The production of proinflammatory cytokines induces an inflammatory response, with the infiltration of macrophages and lymphocytes, which in turn induce significant interstitial fibrosis [116].

Understanding the multiple mechanism of cisplatin-induced toxicity has allowed various potentially protective agents to be proposed. For example, amifostine, melatonin, vitamin C and vitamin E, allopurinol, ebselen, and erdosteine may play a role in preventing oxidative stress injury; erythropoietin and amifostine may be used as cytoprotective and antiapoptotic agents. Besides, salicylates have been shown to reduce renal inflammation in cisplatin toxicity models and fibrates seem to prevent cisplatin nephrotoxicity in an animal study. Nevertheless, only a few of these agents have been tested in human studies [108,117].

Cisplatin-induced acute renal failure is produced by degeneration, necrosis, desquamation of epithelial cells of the proximal, distal tubules, and collecting ducts, without obvious morphologic changes in the glomerulus. Besides, after long-term treatment with cisplatin, patients with chronic nephrotoxicity develop tubular necrosis, with cystic dilated tubules and interstitial fibrosis [118]. The tubule injury precedes acute renal insufficiency and hemodynamic dysfunction. The reduction in mitochondrial and ATPase activity and the decreased expression of solute transporters, cotransporters, and water channel aquaporin lead to a reduction in sodium and water tubular reabsorption, increasing the excretion of water and sodium. Between 24 and 48 h after cisplatin infusion, patients may develop polyuria and decreased urine osmolarity, while maintaining a stable GFR. Later, the GFR may decrease and patients excrete sodium, potassium, magnesium, calcium, glucose, and small amounts of proteins in the urine, with possible orthostatic hypotension. Renal function is usually reinstated 2–4 or more weeks after the treatment [119].

Cisplatin-induced nephrotoxicity mainly consists of acute renal injury, but may also manifest itself in isolated hypomagnesemia (especially after repeated doses of the drug), Fanconi-like syndrome, distal tubular acidosis, hypocalcemia, renal salt wasting, and renal concentrating defect, hyperuricemia, transient proteinuria, erythropoietin deficiency, and thrombotic microangiopathy [120].

Children treated with cisplatin develop nephrotoxicity, with nephron toxicity, GFR decline, hypomagnesemia, hypokalemia, and hypocalcemia. Nevertheless, data on the long-term outcomes of cisplatin nephrotoxicity in children are not sufficient, perhaps because chronic renal damage becomes evident in adult life [121,122].

Skinner *et al.* [121] reported that cisplatin nephrotoxicity was higher in children of older age (> 10 years old); moreover, the decrease in GFR was less severe in children who received a lower dose rate of cisplatin (not exceeding a 40 mg/m^2/dose).

Erdlenbruch *et al.* [123] verified data on the rate of cisplatin infusion and the severity of renal damage in children, proposing that long-term infusions of cisplatin are less nephrotoxic than repetitive and intermittent bolus administrations.

Appropriate hydration with an isotonic saline solution is the most reasonable strategy to reduce the incidence of cisplatin-induced nephrotoxicity. Recent clinical guidelines have established that the addition of diuretics, such as mannitol and furosemide, is no more nephroprotective than the use of hydration alone [120,124].

Magnesium deficiency itself may enhance cisplatin nephrotoxicity; thus, continuous magnesium supplementation (both endovenous supplements during treatment and oral supplements between courses) should be a routine part of the treatment regime [125].

In addition, Jones *et al.* [126] underline that during cisplatin courses, other nephrotoxic agents (such as ifosfamide, nephrotoxic antibiotics, intravenous radiographic contrast) may increase renal injury and must thus be avoided.

Carboplatin

The absence of any interactions between carboplatin and human OCT2 reduces its uptake into tubular cells and carboplatin-induced nephrotoxicity, which seems to be cumulatively dose dependent [109].

In adults, carboplatin nephrotoxicity develops with single doses higher than 800 mg/m^2.

English *et al.* [127] examined renal function in children treated with carboplatin, observing that after the treatment, the predominant changes in renal function were hypomagnesemia and reduction of GFR. The cumulative dose of carboplatin was inversely related to mean serum magnesemia at the end of the treatment; besides, a high cumulative dose of carboplatin may produce renal damage qualitatively similar to but less severe than that induced by cisplatin.

Therefore, nephrotoxicity of carboplatin is more common with previous or concomitant nephrotoxic therapy or when high doses of carboplatin are associated with melphalan, vincristine, and etoposide for autologous bone marrow rescue [127,128].

Oxaliplatin

Previous studies identified no significant oxaliplatin-induced nephrotoxicity. Patients may present with increased urinary excretion of oxalate, calcium, magnesium, sodium, and potassium. Moreover, acute tubular

acidosis caused by urinary bicarbonate wasting has been reported [129].

Neurotoxicity

The clinical application of platinum drugs can be compromised by cumulative damage to the peripheral nervous system [127].

Brain and central structures of the spinal cord are protected from platinum accumulation, because platinum compounds penetrate poorly through the blood–brain barrier. Besides, they have a preference for entering the peripheral nervous system, especially the dorsal root ganglia (DRG), which represent the neural structure most exposed to cisplatin neurotoxicity [130,131].

Aquation reactions transform platinum compounds into a positively charged molecule, which cross-links to DNA, forming the DNA–platinum adducts, which interfere with DNA replication and lead to neuronal apoptosis [132,133].

Neurotoxicity is directly related to the concentration of platinum intermediary aquation products. Cisplatin produces more DNA–platinum adducts than oxaliplatin; thus, the degree of cisplatin neurotoxicity is greater than that of oxaliplatin.

Conversely, neurological dysfunctions are rarely associated with carboplatin and are described only in a few older patients and after treatment with high doses of carboplatin or multidrug therapy [134,135].

Cisplatin

Cisplatin-induced neuropathy is cumulatively dose dependent and develops in about 50% of patients treated with cumulative doses higher than 300 or 600 mg/m^2 [136].

Clinical features range from moderate to severe, with signs and symptoms of peripheral injury, such as numbness, loss of vibration and position sense, tingling and painful paresthesias, loss of taste, tremor, and ataxia. Symptoms may improve gradually after cisplatin discontinuation and the neuropathy seldom becomes permanent [137].

Researchers suggest that thiol compounds (such as amifostine, glutathione, and melanocortin) can play a protective role against cisplatin neurotoxicity [136]. Even if further studies on safety are required, glutathione seems to reduce the neurotoxicity of cisplatin without altering its antineoplastic effect [138].

The concentration of cisplatin in DRG depletes vitamin E reserves, with an increased susceptibility to oxidative stress; thus, Pace *et al.* [139] reported the neuroprotective effect of supplementation of vitamin E before and after cisplatin treatment.

Granowettwer *et al.* [140] described the onset of severe neurologic deterioration after the infusion of cisplatin for the treatment of eight children with recurrent brain tumors previously also treated with one or more courses of cranial irradiation. In these patients, acute neurological symptoms consist of coma, multiple cranial nerve palsies, quadriparesis, and seizures. There was an interaction between radiotherapy and neurological deterioration. Furthermore, the large fluid volume used to administer cisplatin could trigger the neurological symptoms, and so the authors suggested that starting a treatment with cisplatin in children with brain tumors has to be carefully considered, in view of the risk of a significant hearing loss and acute neurological deterioration afterwards [140].

Carboplatin

A thorough analysis of the literature provided no information on carboplatin-related neurotoxicity.

Oxaliplatin

Oxaliplatin treatment is usually discontinued after the onset of peripheral sensory neurotoxicity, which may manifest itself in two different patterns: acute and chronic oxaliplatin-induced neurotoxicity (OXIN) [138,141]. Acute OXIN is characterized by a peripheral nerve hyperexcitability, because of an impairment of voltage-gated sodium channels. It begins during the first infusion or within hours of completion; it may be exacerbated by exposure to cold and it is dose related, usually autolimited, and reversible. Symptoms include paresthesias, dysesthesias, and pain in the upper and the lower extremities and the perioral region. Chronic OXIN results from a gradual dose-dependent accumulation of the drug in the DRG cells, causing a symmetrical axonal neuropathy similar to that induced by cisplatin. Patients develop severe paresthesias and dysesthesias, loss of motor coordination, and more rarely 'Lhermitte's sign' and urinary retention; symptoms usually resolve about 6–8 months after the discontinuation of oxaliplatin [137,142].

Because of the reversibility of symptoms after discontinuation of the drug, an intermittent and non-continuous 'stop-and-go' strategy should be adopted in managing the OXIN [143].

Nevertheless, several neuromodulatory agents such as calcium–magnesium infusions, amifostine, α-lipoic acid, glutathione, and antiepileptic drugs such as carbamazepine or gabapentin, have been proposed for the prophylaxis and the treatment of OXIN, although no evidence-based recommendation can be given for their use [144].

In addition, Durand *et al.* [145], in the EFFOX (a randomized, double-blind, placebo-controlled, phase III trial), have defined as appropriate the use of venlafaxine for the treatment of oxaliplatin-induced acute neurosensory toxicity.

Nausea and vomiting

Cisplatin

Nausea and vomiting are the most common adverse effects of cisplatin. Chemotherapy-induced emesis can be immediate ($\leq$ 24 h after treatment) or delayed ($>$ 24 h after treatment). The development of 5-hydroxytryptamine (5-HT3) receptor antagonists has reduced cisplatin-related acute emesis significantly [17].

Carboplatin and oxaliplatin

Nausea and vomiting related to carboplatin and oxaliplatin are much less frequent and severe than emesis associated with cisplatin and easily controlled with standard antiemetics (dexamethasone, lorazepam) [2,17,30].

Conclusion

Platinum compounds, mainly cisplatin, carboplatin, and oxaliplatin, play an important role in pediatric oncology and have contributed toward improving the prognosis quod vitam of children with cancer. However, they also have several toxic effects that can negatively impact on the auditory and nervous system, as well as on the renal and bone marrow function.

Knowledge of their pharmacokinetics properties and toxicological profile is quite crucial to controlling systemic exposure to the drug, preventing its toxicity, and improving the quality of life of pediatric cancer patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. *J Clin Oncol* 2005; **23**:8588–8596.
2 O'Dwyer PJ, Stevenson JP, Johnson SW. Clinical pharmacokinetics and administration of established platinum drugs. *Drugs* 2000; **59 (Suppl)**:19–27.
3 Mercier C, Ciccolini J, Pourroy B, Fanciullino R, Duffaud F. Dose individualization of carboplatin after a 120-hour infusion schedule: higher dose intensity but fewer toxicities. *Ther Drug Monit* 2006; **28**:212–218.
4 Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. *Ann Oncol* 1998; **9**:13–21.
5 Boulikas T, Pantos A, Bellis E, Petros C. Designing platinum compounds in cancer: structures and mechanisms. *Cancer Ther* 2007; **5**:537–583.
6 Peng B, English MW, Boddy AV, Price L, Wyllie R, Pearson ADJ, *et al*. Cisplatin pharmacokinetics in children with cancer. *Eur J Cancer* 1997; **33**:1823–1828.
7 Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; **17**:409–422.
8 Drug name: Cisplatin. BCCA Cancer Drug Manual, October 2008.
9 Van den Berg H, van den Anker JN, Beijnen JH. Cytostatic drugs in infants: a review on pharmacokinetic data in infants. *Cancer Treat Rev* 2012; **18**:3–26.
17 Gietema JA, Meinardi MT, Messerschmidt J, Gelevert T, Alt F, Uges DR, Sleijfer DT. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet* 2000; **355**:1075–1076.
11 Gerl A, Schierl R. Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. *Acta Oncol* 2000; **39**:519–522.
12 Sprauten M, Darrah T, Petersonm D, Campbell ME, Hannigan R, Cvancarova M. Impact of long-term serum platinum concentrations on neuro- and oto-toxicity in cisplatin-treated survivors of testicular cancer. *J Clin Oncol* 2012; **3**:300–303.
10 Veal GJ, Errington J, Tilby MJ, Pearson AD, Foot AB, McDowell H, *et al*. Adaptive dosing and platinum–DNA adduct formation in children receiving high-dose carboplatin for the treatment of solid tumours. *Br J Cancer* 2007; **96**:725–731.
11 Lebwohl D, Canetta R. Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. *Eur J Cancer* 1998; **34**:1522–1534.
12 Knox RJ, Friedlos F, Lydall DA, Roberts JJ. Mechanism of cytotoxicity of anticancer platinum drugs: evidence that cis-diamminedi-chloroplatinum (II) and cis-diammine (1,1-cyclobutane-diacarbo-xylate) platinum (II) differ only in kinetics of their interaction with DNA. *Cancer Res* 1986; **46**:1972–1979.
13 Micetich KC, Barnes D, Erickson LC. A comparative study of the cytotoxicity and DNA-damaging effects of cis-(diammino) (1,1-cyclobutanedicarboxylato)-platinum (II) and cis-diamminedichloroplatinum (II) on L1210 cells. *Cancer Res* 1985; **45**:4043–4047.
14 Drug name: Carboplatin. BCCA Cancer Drug Manual, October 2008.
15 Pavelka M, Lucas MF, Russo N. On the hydrolysis mechanism of the second-generation anticancer drug carboplatin. *Chemistry* 2007; **13**:10108–10116.
16 Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7**:1748–1756.
18 Thomas H, Boddy AV, English MW, Hobson R, Imeson J, Lewis I, *et al*. Prospective validation of renal function-based carboplatin dosing in children with cancer: a United Kingdom children's cancer study group trial. *J Clin Oncol* 2000; **18**:3614–3621.
19 Kweekel DM, Gelderblom H, Guchelaar HJ. Pharmacology of oxaliplatin and the use of pharmacogenomics to individualize therapy. *Cancer Treat Rev* 2005; **31**:90–105.
20 Raymond E, Lawrence R, Izbicka E, Faivre S, Von Hoff DD. Activity of oxaliplatin against human tumor colony forming units. *Clin Cancer Res* 1998; **4**:1021–1029.
21 Riccardi A, Ferlini C, Meco D, Mastrangelo R, Scambia G, Riccardi R. Antitumor activity of oxaliplatin in neuroblastoma cell lines. *Eur J Cancer* 1999; **35**:86–90.
22 Spunt SL, Freeman BB III, Billups CA, McPherson V, Khan RB, Pratt CB, *et al*. Phase I clinical trial of oxaliplatin in children and adolescents with refractory solid tumors. *J Clin Oncol* 2007; **25**:2274–2280.
23 Page JD, Husain I, Sancar A, Chaney SG. Effect of the diaminocyclohexane carrier ligand on platinum adduct formation, repair, and lethality. *Biochemistry* 1990; **29**:1016–1024.
24 Fink D, Nebel S, Aebi S, Zheng H, Cenni B, Nehme A, *et al*. The role of DNA mismatch repair in platinum drug resistance. *Cancer Res* 1996; **56**:4881–4886.
25 Vaisman A, Varchenko M, Umar A, Kunkel TA, Risinger JI, Barrett JC, *et al*. The role of hMLH1, hMSH3, and hMSH6 defects in cisplatin and oxaliplatin resistance: correlation with replicative bypass of platinum–DNA adducts. *Cancer Res* 1998; **58**:3579–3585.
26 Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high frequency audiometry and evoked distortion product otoacoustic emissions. *J Clin Oncol* 2007; **25**:1190–1195.
27 Blakely BW, Myers SF. Patterns of hearing loss resulting from cisplatinum therapy. *Otolaryngol Head Neck Surg* 1993; **109**:385–391.
28 Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. *Br J Cancer* 1990; **61**:927–931.
29 Brock PR, Knight KR, Freyer DR, Campbell KCM, Steyger PS, Blakley BW, *et al*. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston Ototoxicity Scale. *J Clin Oncol* 2012; **30**:2408–2417.
30 Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced ototoxicity by *N*-acetylcysteine in a rat model. *Hear Res* 2004; **193**:25–30.
31 Van Ruijven MW, de Groot JC, Hendriksen F, Smoorenburg GF. Immunohistochemical detection of platinated DNA in the cochlea of cisplatin-treated guinea pigs. *Hear Res* 2005; **203**:112–121.
32 Ding D, Allman BL, Salvi R. Ototoxic characteristics of platinum antitumor drugs. *Anat Rec* 2012; **295**:1851–1867.
33 He J, Yin S, Wang J, Ding D, Jiang H. Effectiveness of different approaches for establishing cisplatin-induced cochlear lesions in mice. *Acta Otolaryngol* 2009; **129**:1359–1367.
34 Gratton MA, Salvi RJ, Kamen BA, Saunders SS. Interaction of cisplatin and noise on the peripheral auditory system. *Hear Res* 1990; **50**:211–223.

35 Shi X, Nuttall AL. Upregulated iNOS and oxidative damage to the cochlear stria vascularis due to noise stress. *Brain Res* 2003; **967**:1–10.
36 Laurell G, Bagger-Sjoback D. Dose-dependent inner ear changes after i.v. administration of cisplatin. *J Otolaryngol* 1991; **20**:158–167.
37 Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2007; **226**: 157–167.
38 Laurell G, Ekborn A, Viberg A, Canlon B. Effects of a single high dose of cisplatin on the melanocytes of the stria vascularis in the guinea pig. *Audiol Neurootol* 2007; **12**:170–178.
39 Sergi B, Ferraresi A, Troiani D, Paludetti G, Fetoni AR. Cisplatin ototoxicity in the guinea pig: vestibular and cochlear damage. *Hear Res* 2003; **182**:56–64.
40 Boulikas T, Vougiouka M. Cisplatin and platinum drugs at the molecular level. *Oncol Rep* 2003; **10**:1663–1682.
41 Park CM, Park MJ, Kwak HJ, Moon SI, Yoo DH, Lee HC, *et al*. Induction of p53-mediated apoptosis and recovery of chemosensitivity through p53 transduction in human glioblastoma cells by cisplatin. *Int J Oncol* 2006; **28**:119–125.
42 Devarajan P, Savoca M, Castaneda MP, Park MS, Esteban-Cruciani N, Kalinec G, *et al*. Cisplatin-induced apoptosis in auditory cells: role of death receptor and mitochondrial pathways. *Hear Res* 2002; **174**:45–54.
43 Lambert MP, Shields C, Meadows AT. A retrospective review of hearing in children with retinoblastoma treated with carboplatin-based chemotherapy. *Pediatr Blood Cancer* 2008; **50**:223–226.
44 Alberts DS. Carboplatin versus cisplatin in ovarian cancer. *Semin Oncol* 1995; **22**:88–90.
45 Parsons SK, Neault MW, Lehmann LE, Brennan LL, Eickhoff CE, Kretschmar CS, *et al*. Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant* 1998; **22**:669–674.
46 Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, *et al*. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. *J Pediatr Hematol Oncol* 2004; **26**:649–655.
47 Dean JB, Hayashi SS, Albert CM, King AA, Karzon R, Hayashi RJ. Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens. *J Pediatr Hematol Oncol* 2008; **30**:130–134.
48 Jehanne M, Lumbroso-Le Rouic L, Savignoni A, Aerts I, Mercier G, Bours D, *et al*. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer* 2009; **52**:637–643.
49 Qaddoumi I, Bass JK, Wu J, Billups CA, Wozniak AW, Merchant TE, *et al*. Carboplatin-associated ototoxicity in children with retinoblastoma. *J Clin Oncol* 2012; **30**:1034–1041.
50 Punnett A, Bliss B, Dupuis LL, Abdolell M, Doyle J, Sung L. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. *Pediatr Blood Cancer* 2004; **42**:598–603.
51 Doolittle ND, Muldoon LL, Brummett RE, Tyson RM, Lacy C, Bubalo JS, *et al*. Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001; **7**:493–500.
52 Wake M, Takeno S, Ibrahim D, Harrison R, Mount R. Carboplatin ototoxicity: an animal model. *J Laryngol Otol* 1993; **107**:585–589.
53 Takeno S, Harrison RV, Mount RJ, Wake M, Harada Y. Induction of selective inner hair cell damage by carboplatin. *Scanning Microsc* 1994; **8**:97–106.
54 Hofstetter P, Ding D, Salvi R. Magnitude and pattern of inner and outer hair cell loss in chinchilla as a function of carboplatin dose. *Audiology* 1997; **36**:301–311.
55 Zhang M, Liu W, Ding D, Salvi R. Pifithrin-alpha suppresses p53 and protects cochlear and vestibular hair cells from cisplatin-induced apoptosis. *J Neurosci Res* 2003; **120**:191–205.
56 Ding D, Wang J, Yu Z, Jiang H, Wang P, Salvi R. Spontaneous proliferation in organotypic cultures of mouse cochlea. *J Otol* 2008; **3**:76–83.
57 Hellberg V, Wallin I, Eriksson S, Hernlund E, Jerremalm E, Berndtsson M, *et al*. Cisplatin and oxaliplatin toxicity: importance of cochlear kinetics as a determinant for ototoxicity. *J Natl Cancer Inst* 2009; **101**:37–47.
58 Zhang S, Lovejoy KS, Shima JE, Lagpacan LL, Shu Y, Lapuk A, *et al*. Organic cation transporters are determinants of oxaliplatin cytotoxicity. *Cancer Res* 2006; **66**:8847–8857.
59 Malhotra NK, Aslam R, Lipman SP, Bilski VJ. Acute ototoxicity from a single infusion of oxaliplatin. *Ear Nose Throat J* 2010; **89**:258–261.
60 Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: a practical grading system. *Med Pediatr Oncol* 1991; **19**:295–300.
61 Grewal S, Merchant T, Reymond R, McInerney M, Hodge C, Shearer P. Auditory late effects of childhood cancer therapy: a report from the children's oncology group. *Pediatrics* 2010; **125**:938–950.
62 Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. *Cancer* 2006; **107**:417–422.
63 Neuwelt EA, Brock P. Critical need for international consensus on ototoxicity assessment criteria [editorial]. *J Clin Oncol* 2010; **28**:1630–1632.
64 Gurney JG, Bass JK. New International Society of Pediatric Oncology Boston ototoxicity grading scale for pediatric oncology: still room for improvement [editorial]. *J Clin Oncol* 2012; **30**:2303–2306.
65 American Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA* 1994; **36**:11–19.
66 Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. *J Clin Oncol* 2010; **28**:1788–1795.
67 Minami SB, Sha SH, Schacht J. Antioxidant protection in a new animal model of cisplatin-induced ototoxicity. *Hear Res* 2004; **198**:137–143.
68 Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by *N*-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. *J Pharmacol Exp Ther* 2005; **314**:1052–1058.
69 Dickey DT, Muldoon LL, Doolittle ND, Peterson DR, Kraemer DF, Neuwelt EA. Effect of *N*-acetylcysteine route of administration on chemoprotection against cisplatin-induced toxicity in rat models. *Cancer Chemother Pharmacol* 2008; **62**:235–241.
70 Hyppolito MA, de Oliveira JA, Rossato M. Cisplatin ototoxicity and otoprotection with sodium salicylate. *Eur Arch Otorhinolaryngol* 2006; **263**:798–803.
71 Neuwelt EA, Gilmer-Knight K, Lacy C, Nicholson HS, Kraemer DF, Doolittle ND, *et al*. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood–brain-barrier disruption. *Pediatr Blood Cancer* 2006; **47**:174–182.
72 Rybak LP, Whitworth C, Somani S. Application of antioxidants and other agents to prevent cisplatin ototoxicity. *Laryngoscope* 1999; **109**:1740–1744.
73 Hussain AE, Blakley BW, Nicolas M, Balderston J. Assessment of the protective effects of amifostine against cisplatin-induced toxicity. *J Otolaryngol* 2003; **32**:294–297.
74 Campbell KC, Meech RP, Klemens JJ, Gerberi MT, Dyrstad SS, Larsen DL, *et al*. Prevention of noise- and drug-induced hearing loss with D-methionine. *Hear Res* 2007; **226**:92–103.
75 Marina N, Chang KW, Malogolowkin M, London WB, Frazier AL, Womer RB, *et al*. Amifostine does not protect against the ototoxicity of high-dose cisplatin combined with etoposide and bleomycin in pediatric germ-cell tumors: a Children's Oncology Group study. *Cancer* 2005; **104**:841–847.
76 Fouladi M, Chintagumpala M, Ashley D, Kellie S, Gururangan S, Hassall T, *et al*. Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *J Clin Oncol* 2008; **26**:3749–3755.
77 Katzenstein HM, Chang KW, Krailo M, Chen Z, Finegold MJ, Rowland J, *et al*. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. *Cancer* 2009; **115**:5828–5835.
78 Kalkanis JG, Whitworth C, Rybak LP. Vitamin E reduces cisplatin ototoxicity. *Laryngoscope* 2004; **114**:538–542.
79 Korver KD, Rybak LP, Whitworth C, Campbell KM. Round window application of D-methionine provides complete cisplatin otoprotection. *Otolaryngol Head Neck Surg* 2002; **126**:683–689.
80 Wimmer C, Mees K, Stumpf P, Welsch U, Reichel O, Suckfüll M. Round window application of D-methionine, sodium thiosulfate, brain-derived neurotrophic factor, and fibroblast growth factor-2 in cisplatin-induced ototoxicity. *Otol Neurotol* 2004; **25**:33–40.
81 Bokemeyer C, Berger CC, Hartmann JT, Kollmannsberger C, Schmoll HJ, Kuczyk MA, *et al*. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. *Br J Cancer* 1998; **77**:1355–1362.
82 Cushing B, Giller R, Cullen JW, Marina NM, Lauer SJ, Olson TA, *et al*. Randomized comparison of combination chemo-therapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study – Pediatric Oncology Group 9049 and Children's Cancer Group 8882. *J Clin Oncol* 2004; **22**:2691–2700.
83 Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. *Eur J Cancer* 2004; **40**:2445–2451.

84 Kushner BH, Kramer K, Modak S, Kernan NA, Reich LM, Danis K, *et al*. Topotecan, thiotepa, and carboplatin for neuroblastoma: failure to prevent relapse in the central nervous system. *Bone Marrow Transplant* 2006; **37**:271–276.

85 Laverdiere C, Cheung NK, Kushner BH, Kramer K, Modak S LaQuaglia MP, *et al*. Long-term complications in survivors of advanced stage neuroblastoma. *Pediatr Blood Cancer* 2005; **45**:324–332.

86 Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. *Pediatr Blood Cancer* 2012; **59**:144–148.

87 Warrier R, Chauhan A, Davluri M, Tedesco SL, Nadell J, Craver R. Cisplatin and cranial irradiation-related hearing loss in children. *Ochsner J* 2012; **12**:191–196.

88 Schell MJ, McHaney VA, Green AA, Kun LE, Hayes FA, Horowitz M, *et al*. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. *J Clin Oncol* 1989; **7**:754–760.

89 Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, *et al*. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. *J Neurosurg* 1994; **81**:690–698.

90 Cohen BH, Zweidler P, Goldwein JW, Molloy J, Packer RJ. Ototoxic effect of cisplatin in children with brain tumours. *Pediatr Neurosurg* 1990–1991; **16**:292–296.

91 Bohne BA, Marks JE, Glasgow GP. Delayed effects of ionizing radiation on the ear. *Laryngoscope* 1985; **95**:818–828.

92 Merchant TE, Gould CJ, Xiong X, Robbins N, Zhu J, Pritchard DL, *et al*. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. *Int J Radiat Oncol Biol Phys* 2004; **58**:1194–1207.

93 Hua C, Bass JK, Khan R, Kun LE, Merchant TE. Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. *Int J Radiat Oncol Biol Phys* 2008; **72**:892–899.

94 Miettinen S, Laurikainen E, Johansson R, Minn H, Laurell G, Salmi TT. Radiotherapy enhanced ototoxicity of cisplatin in children. *Acta Otolaryngol Suppl* 1997; **529**:90–94.

95 Kretschmar CS, Warren MP, Lavally BL, Dyer S, Tarbell NJ. Ototoxicity of preradiation cisplatin for children with central nervous system tumors. *J Clin Oncol* 1990; **8**:1191–1198.

96 Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V, *et al*. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT′91. *Int J Radiat Oncol Biol Phys* 2000; **46**:269–279.

97 Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, *et al*. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys* 2002; **52**:599–605.

98 Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediat Blood Cancer* 2008; **51**:110–117.

99 Bitner-Glindzicz M, Rahman S. Ototoxicity caused by aminoglycosides. *BMJ* 2007; **335**:784–785.

100 Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, Barhdadi A, *et al*. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. *Nat Genet* 2009; **41**:1345–1349.

101 Ad Hoc Committee on Audiologic Management of Individuals Receiving Ototoxic and/or Vestibulotoxic Drug Therapy. Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA* 1994; **35 (Suppl)**:11–19.

102 Nagy JL, Adelstein DJ, Newman CW, Rybicki LA, Rice TW, Lavertu P. Cisplatin ototoxicity: the importance of baseline audiometry. *Am J Clin Oncol* 1999; **22**:305–308.

103 Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J. Prospective of validation of a pharmacologically-based dosing scheme for the cis-diamminedichloroplatin (II) analogue cis-diammine-cyclobutane-dicarboxylato platinum (II). *Cancer Res* 1985; **45**:6502–6506.

104 Nowrousian MR, Schmidt CG. Effects of cisplatin on different haemopoietic progenitor cells in mice. *Br J Cancer* 1982; **46**:397–402.

105 Rothmann SA, Weick JK. Cisplatin toxicity for erythroid precursors. *N Engl J Med* 1981; **304**:360.

106 Levi A, Aroney RS, Dalley DN. Haemolytic anaemia after cisplatin treatment. *Br Med J* 1981; **282**:2003–2004.

107 Fouladi M, Blaney SM, Poussaint TY, Freeman BB III, McLendon R, Fuller C, *et al*. Phase II study of oxaliplatin in children with recurrent or refractory medulloblastoma, supratentorial primitive neuroectodermal tumors, and atypical teratoid rhabdoid tumors. *Cancer* 2006; **107**:2291–2297.

108 Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. *Toxins (Basel)* 2010; **2**:2490–2518.

109 Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. *Am J Med Sci* 2007; **334**:115–124.

110 Ciarimboli G, Deuster D, Knief A, Sperling M, Holtkamp M, Edemir B, *et al*. Organic cation transporter 2 mediates cisplatin-induced oto- and nephrotoxicity and is a target for protective interventions. *Am J Pathol* 2010; **176**:1169–1180.

111 Filipski KK, Mathijssen RH, Mikkelsen TS, Schinkel AH, Sparreboom A. Contribution of organic cation transporter 2 (OCT2) to cisplatin-induced nephrotoxicity. *Clin Pharmacol Ther* 2009; **86**:396–402.

112 Hanigan MH, Gallagher BC, Taylor PT Jr, Large MK. Inhibition of gamma-glutamyl transpeptidase activity by acivicin in vivo protects the kidney from cisplatin-induced toxicity. *Cancer Res* 1994; **54**:5925–5929.

113 Qian W, Nishikawa M, Haque AM, Hirose M, Mashimo M, Sato E, *et al*. Mitochondrial density determines the cellular sensitivity to cisplatin-induced cell death. *Am J Physiol Cell Physiol* 2005; **289**:1466–1475.

114 Lieberthal W, Triaca V, Levine J. Mechanisms of death induced by cisplatin in proximal tubular epithelial cells: apoptosis vs. necrosis. *Am J Physiol* 1996; **270**:700–708.

115 Ramesh G, Reeves WB. TNF-alpha mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. *J Clin Invest* 2002; **110**:835–842.

116 Yamate J, Machida Y, Ide M, Kuwamura M, Kotani T, Sawamoto O, *et al*. Cisplatin-induced renal interstitial fibrosis in neonatal rats, developing as solitary nephron unit lesions. *Toxicol Pathol* 2005; **33**:207–217.

117 Ali BH, Al Moundhri MS. Agents ameliorating or augmenting the nephrotoxicity of cisplatin and other platinum compounds: a review of some recent research. *Food Chem Toxicol* 2006; **44**:1173–1183.

118 Cornelison TL, Reed E. Nephrotoxicity and hydration management for cisplatin, carboplatin, and ormaplatin. *Gynecol Oncol* 1993; **50**:147–158.

119 Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol* 2003; **23**:460–464.

120 Launay-Vacher V, Rey JB, Isnard-Bagnis C, Deray G, Daouphars M. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. *Cancer Chemother Pharmacol* 2008; **61**:903–909.

121 Skinner R, Parry A, Price L, Cole M, Craft AW, Pearson AD. Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. *Eur J Cancer* 2009; **45**:3213–3219.

122 Skinner R, Pearson AD, English MW, Price L, Wyllie RA, Coulthard MG, *et al*. Cisplatin dose rate as a risk factor for nephrotoxicity in children. *Br J Cancer* 1998; **77**:1677–1682.

123 Erdlenbruch B, Pekrum A, Roth C, Grunewald RW, Kern W, Lakomek M. Cisplatin nephrotoxicity in children after continuous 72-h and 3 × 1-h infusions. *Pediatr Nephrol* 2001; **16**:586–593.

124 Morgan KP, Buie LW, Savage SW. The role of mannitol as a nephroprotectant in patients receiving cisplatin therapy. *Ann Pharmacother* 2012; **46**:276–281.

125 Willox JC, McAllister EJ, Sangster G, Kaye SB. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. *Br J Cancer* 1986; **54**:19–23.

126 Jones DP, Spunt SL, Green D, Springate JE. Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 2008; **51**:724–731.

127 English MW, Skinner R, Pearson AD, Price L, Wyllie R, Craft AW. Dose-related nephrotoxicity of carboplatin in children. *Br J Cancer* 1999; **81**:336–341.

128 Gordon SJ, Pearson AD, Reid MM, Craft AW. Toxicity of single-day high-dose vincristine, melphalan, etoposide and carboplatin consolidation with autologous bone marrow rescue in advanced neuroblastoma. *Eur J Cancer* 1992; **28**:1319–1323.

129 Linch M, Cunningham D, Mingo O, Stiles A, Farquhar-Smith WP. Renal tubular acidosis due to oxaliplatin. *Ann Oncol* 2007; **18**:805–806.

130 Ta LE, Espeset L, Podratz J, Windebank AJ. Neurotoxicity of oxaliplatin and cisplatin for dorsal root ganglion neurons correlates with platinum-DNA binding. *Neurotoxicology* 2006; **27**:992–1002.

131 Gregg RW, Molepo JM, Monpetit VJ, Mikael NZ, Redmond D, Gadia M, *et al*. Cisplatin neurotoxicity: the relationship between dosage, time, and platinum concentration in neurologic tissues, and morphologic evidence of toxicity. *J Clin Oncol* 1992; **10**:795–803.

132 Chválová K, Brabec V, Kaspárková J. Mechanism of the formation of DNA-protein cross-links by antitumor cisplatin. *Nucleic Acids Res* 2007; **35**:1812–1821.

133 Zhu C, Raber J, Eriksson LA. Hydrolysis process of the second generation platinum-based anticancer drug cis-amminedichlorocyclohexylamineplatinum (II). *J Phys Chem B* 2005; **109**:12195–12205.
134 McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. *Mol Cancer Ther* 2009; **8**:10–16.
135 Heinzlef O, Lotz JP, Roullet E. Severe neuropathy after high dose carboplatin in three patients receiving multidrug chemotherapy. *J Neurol Neurosurg Psychiatry* 1998; **64**:667–669.
136 Van den Bent MJ, van Putten WL, Hilkens PH, de Wit R, van der Burg ME. Retreatment with dose-dense weekly cisplatin after previous cisplatin chemotherapy is not complicated by significant neuro-toxicity. *Eur J Cancer* 2002; **38**:387–391.
137 Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. *Chemother Res Pract* 2011; **2011**:843019.
138 Cavaletti G, Minoia C, Schieppati M, Tredici G. Protective effects of glutathione on cisplatin neurotoxicity in rats. *Int J Radiat Oncol Biol Phys* 1994; **29**:771–776.
139 Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, *et al*. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003; **21**:927–931.
140 Granowetter L, Rosenstock JG, Packer RJ. Enhanced cis-platinum neurotoxicity in pediatric patients with brain tumors. *J Neurooncol* 1983; **1**:293–297.
141 Weickhardt A, Wells K, Messersmith W. Oxaliplatin-induced neuropathy in colorectal cancer. *J Oncol* 2011; **201593**.
142 Grothey A. Oxaliplatin-safety profile: neurotoxicity. *Semin Oncol* 2003; **30 (Suppl)**:5–13.
143 Saif MW. Does OPTIMOX strategy ('stop-and-go' approach) also work in treatment of pancreatic cancer with oxaliplatin-based regimens? *JOP* 2008; **9**:658–663.
144 Grothey A. Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* 2005; **1 (Suppl)**:38–46.
145 Durand JP, Deplanque G, Montheil V, Gornet JM, Scotte F Mir O, *et al*. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol* 2012; **23**:200–205.
146 Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer* 2008; **51**:110–117.