REVIEW ARTICLE

Review of the Comparative Pharmacology and Clinical Activity of Cisplatin and Carboplatin

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Purpose: To review the pharmacodynamics, pharmacokinetics, toxicities, and relative clinical activities of cisplatin and carboplatin. Through a search of the MEDLINE database, we identified phase III clinical trials and pharmacologic studies comparing cisplatin and carboplatin published in the English language medical literature from January 1966 to December 1997.

Results: Prospective randomized trials comparing cisplatin to carboplatin were identified for ovarian (n = 12), germ cell (n = 4), non–small-cell lung (n = 1), small-cell lung (n = 3), and head and neck (n = 4) cancers. Carboplatin and cisplatin were equally effective in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer. One study each showed a trend toward better survival in favor of cisplatin for patients with optimally debulked ovarian and limited-stage small-cell lung cancers. These results were, however, based on subset analyses. In germ cell tumors, carboplatin was inferior because of lower relapse-free survival rates. Cisplatin produced superior response rates and survival in head and neck cancers. There are no published randomized phase III studies of bladder, cervical, endometrial, and esophageal cancers.

Conclusion: Carboplatin does not possess equivalent activity to cisplatin in all platinum-sensitive tumors. Carboplatin can replace cisplatin in chemotherapy regimens for suboptimally debulked ovarian cancer. Two ongoing studies will address the same question in optimally debulked disease. Carboplatin can also be substituted for cisplatin in the treatment of non–small-cell and extensive-stage small-cell lung cancers. Its role in limited-stage small-cell lung cancer needs to be investigated further. Carboplatin is inferior to cisplatin in germ cell, head and neck, and esophageal cancers. Randomized studies are needed to determine whether carboplatin has equivalent efficacy to cisplatin in bladder, cervical, and endometrial cancers.

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ROSENBERG AND CO-WORKERS[1,2] observed in 1965 that a current delivered between platinum electrodes inhibited *Escherichia coli* proliferation. These inhibitory effects were later found to be related to the formation of inorganic platinum-containing moieties in the presence of ammonium and chloride ions. Cisplatin (*cis*-diamminedichloroplatinum(II)) was the most active of these platinum complexes in experimental tumor systems and was introduced into clinical practice in the early 1970s.

Cisplatin has a broad spectrum of activity against epithelial cancers and has become the foundation of curative regimens in testicular and ovarian cancers. It also demonstrates significant activity against cancers of the lung, head and neck, esophagus, bladder, cervix, and endometrium. However, toxicities of cisplatin are substantial and include severe renal, neurologic, and emetogenic effects. Carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)), an analog of cisplatin, was introduced into clinical trials in 1981 to help circumvent some of the toxicities of cisplatin. Although carboplatin has replaced cisplatin in chemotherapy regimens of some diseases, such as ovarian carcinoma, it is still unclear whether carboplatin has equivalent efficacy to cisplatin across all disease types. In this review, we compare and contrast the pharmacology, toxicology, and clinical activity of these two platinum agents and give special attention to randomized trials investigating their comparative efficacies.

MECHANISM OF ACTION

Both cisplatin and carboplatin are platinum(II) complexes with two ammonia groups in the *cis* position. While cisplatin has two chloride ''leaving'' groups, carboplatin possesses a cyclobutane moiety (Fig 1). A large body of data suggests that the major cytotoxic target of cisplatin and carboplatin is DNA.

The pharmacologic behavior of cisplatin is determined largely by an initial aquation reaction in which the chloride groups are replaced by water molecules (Fig 2). This reaction is driven by the high concentration of water and low concentration of chloride in the tissues. The aquated plati-

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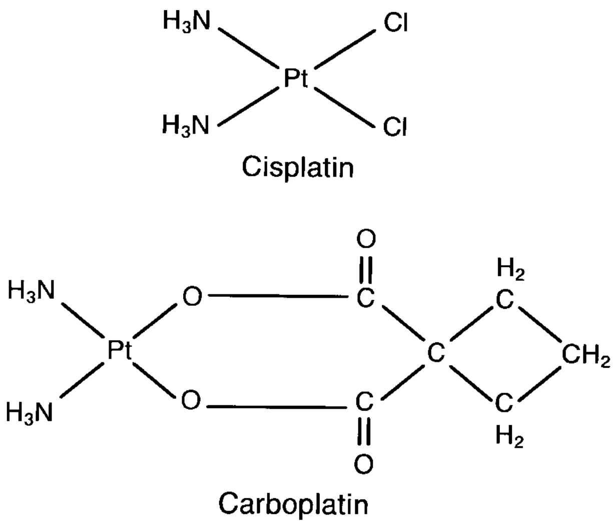

Fig 1. **Structure of cisplatin and carboplatin.**

num complex can then react with a variety of macromolecules. Cisplatin binds to RNA more extensively than to DNA and to DNA more extensively than to protein.[3] In intact DNA, cisplatin seems to bind preferentially to the N-7 position of guanine and adenine.[4] This may be due to the high nucleophilicity at this position. The cytotoxicity of cisplatin against cultured neoplastic cells correlates closely with platinum DNA interstrand cross-links and to the formation of intrastrand bifunctional N-7 adducts at d(GpG) and d(ApG).[5-7]

Despite the above data, the types of DNA lesions responsible for the cytotoxicity of cisplatin have not been clearly established. Various other effects of cisplatin in culture cell lines have been described. These effects include inhibition of sodium-potassium adenosine triphosphatase, transport of essential amino acids, calcium channel function, and mitochondrial function.[8-11]

Carboplatin has a mechanism of action similar to that of cisplatin. Hongo and co-workers[12] used the pUC18 plasmid DNA to demonstrate that carboplatin induced the same platinum-DNA adducts as those induced by cisplatin. They also showed that carboplatin required a 10 times higher drug concentration and 7.5 times longer incubation time than cisplatin to induce the same degree of conformational change on plasmid DNA. Also, the mutational outcome in the Chinese hamster *aprt* gene after exposure to cisplatin and carboplatin was found to be identical.[13]

In support of these data, although the cytotoxic aquated species of cisplatin and carboplatin are the same, the rate constant for the aquation of carboplatin in phosphate buffer with a pH of 7 and at 37°C is a 100-fold slower than that for cisplatin. Antibodies reacting with DNA-platinum adducts formed by cisplatin recognized adducts formed by carboplatin with similar affinity.[14,15]

MECHANISMS OF RESISTANCE

In vitro studies of cisplatin-resistant cell lines have provided some insights into the mechanisms of resistance to this drug. These mechanisms include reduced cellular drug accumulation, cytosolic inactivation of drug, and enhancement of DNA repair. More recent evidence implicates the role of certain genes and proteins in determining the sensitivity of cells to cisplatin.

A reduction in the intracellular accumulation of a drug can be due to either impaired influx through the cell membrane or enhanced efflux. A relationship between the amount of cellular cisplatin and sensitivity has been established in various cell lines.[16] The fundamental mechanism of cisplatin transport is, however, not completely understood because of conflicting data in the literature. Gately and Howell[17] proposed a working model in which cisplatin can enter the cell by way of either passive diffusion or a gated channel. The influx through this channel can be affected by various agents, including amphotericin B, dipyridamole, aldehydes, and sodium-potassium adenosine triphosphatase inhibitors, such as ouabain. Thus, these agents could be explored to reverse cisplatin resistance conferred by reduced drug influx. Enhanced efflux of cisplatin has also been observed in some cell lines.[18,19]

Thiol-containing compounds, notably glutathione and metallothioneins, can react with cisplatin intracellularly to inactivate it and prevent binding to DNA. There is ample evidence for this cytosolic inactivation.[20,21] Increased intracellular levels of glutathione and metallothionein are present in different cisplatin-resistant human carcinoma cell lines. However, not all studies have found the same correlations.[22] Two recent clinical studies demonstrated that tumor cell overexpression of metallothionein correlates with chemore-

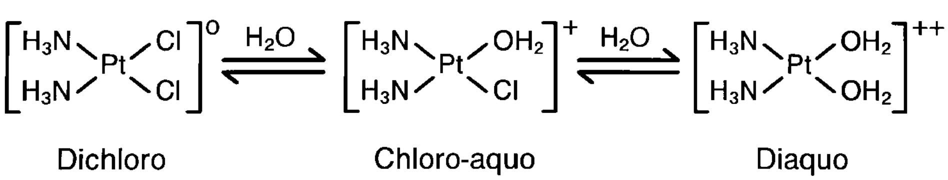

Fig 2. **Cellular activation of cisplatin. The presumed active platinum species is the positively charged diaquo compound, which is identical for both carboplatin and cisplatin.**

sistance and prognosis in esophageal and urothelial cancers.[23,24]

Preclinical studies have shown that some resistant tumor cell lines exhibit an enhanced ability to repair damaged DNA and that agents that inhibit DNA repair may reverse resistance.[25] This augmented capacity for repair is made possible either by platinum-DNA adduct removal, unscheduled DNA synthesis, repair synthesis, or host cell reactivation of cisplatin-damaged plasmid DNA.[26]

Several pharmacologic agents that inhibit DNA repair mechanisms have been studied, including DNA polymerase inhibitors (zidovudine, ganciclovir, and aphidicolin), topoisomerase II inhibitors (etoposide and novobiocin), and methylxanthines (caffeine and pentoxifylline). Other chemotherapeutic agents that exhibit synergism with cisplatin in experimental systems, including hydroxyurea, 5-FU, cytarabine, and pyrazoloacridine,[22,27] have been shown to inhibit the repair of DNA-platinum adducts.

Overexpression of various protooncogenes, including c-*ras*, c-*fos*, and c-*myc*, confers cisplatin resistance in vitro via modulation of one or more of the basic mechanisms described above.[28-30] Recently, nonfunctional p53 protein and loss of DNA mismatch repair were found to confer resistance through a failure to induce apoptosis.[31,32]

Cellular resistance to carboplatin is less well studied. Because carboplatin and cisplatin share a similar structure, undergo hydrolytic reaction leading to the same active intermediates, lead to the same DNA lesions, and are cross-resistant in most instances, it is assumed that similar mechanisms are involved in carboplatin resistance.

PHARMACOKINETICS

Measurable platinum compounds include ultrafiltrable platinum, which consists of non–protein-bound intact drug and metabolites, and total platinum, which represents all platinum species, both protein-bound or -unbound. Ultrafiltrable platinum is responsible for the antitumor activity and toxicity of both cisplatin and carboplatin.

After an intravenous bolus injection of 100 mg/m^2 cisplatin, a peak plasma level of approximately 6 μg/mL is reached immediately and decreases to less than 2 μg/mL within 2 hours.[33] Similar administration of 375 mg/m^2 carboplatin results in a peak plasma level of 39 μg/mL, which declines to approximately 9 μg/mL by the second hour.[34]

Clearance of platinum compounds is triphasic in nature, with a distribution half-life ($t_{1/2}$ alpha) of 13 min, elimination half-life ($t_{1/2}$ beta) of 43 min, and terminal half-life ($t_{1/2}$ gamma) of 5.4 days for total cisplatin.[35] The corresponding half-lives for carboplatin are 22 min, 116 min, and 5.8 days, respectively.[36] Approximately 25% of the cisplatin dose is eliminated from the body during the first 24 hours, with renal clearance accounting for more than 90%. Carboplatin is excreted primarily in the urine as unchanged drug, with approximately 90% clearance after 24 hours.[37] Unlike cisplatin, carboplatin is not significantly secreted by renal tubules; thus, renal clearance is similar to the glomerular filtration rate (GFR).

A drug's area under the concentration-time curve (AUC) is the ratio of the amount of a drug that reaches the systemic circulation and the clearance of the drug. The AUC of a drug, therefore, typically correlates with its toxicity and clinical efficacy. Carboplatin has relatively simple pharmacokinetics, with GFR accounting for almost all drug elimination. The remainder of the drug binds to body proteins.

Thus, the clearance of carboplatin is linearly related to the GFR,[38] so that GFR is related to the AUC of this drug. A formula has been derived to calculate the dose of carboplatin necessary to achieve a particular AUC. This formula has been validated in a prospective study and has been shown to predict AUCs with a margin of error of approximately 15%. This ‘‘Calvert formula'' is shown below.[39]

$$\textit{Dose}\ (\text{mg}) = \textit{Target AUC}\ (\text{mg/ml} \times \text{min}) \times [\textit{GFR}\ (\text{ml/min}) + 25]$$

In the original study, GFR was measured by the ^{51}Cr EDTA method. Estimation of GFR by creatinine clearance, which is more convenient, is now widely used, although this simplified approach has not been validated prospectively. Also, there is considerable controversy regarding the most accurate formula for calculating creatinine clearance with patients' serum creatinine values. Target AUC values of 5 and 7 mg/mL/min are recommended for single-agent carboplatin in previously treated and untreated patients, respectively. These doses have been shown to lead to acceptable thrombocytopenia (platelet nadirs of approximately 30% of the pretreatment value). Moreover, the efficacy of carboplatin is suboptimal at AUCs below 5 mg/mL/min and seems to plateau above an AUC of 7.5 mg/mL/min.

PRECLINICAL ACTIVITY

Cisplatin is broadly active against various tumors in cell culture, including ovarian, germ cell, lung, colon, pancreatic, and mammary carcinomas. Carboplatin, in general, shows a similar spectrum of in vitro activity, but it is consistently four- to 10-fold less potent in various tumor cell types. Tumor cell lines resistant to cisplatin are usually cross-resistant to carboplatin.[40] The comparative preclinical activity of these two agents is shown in Table 1.[41]

The observation that cisplatin enhanced radiosensitivity in bacterial spores led to preclinical studies of the use of

Table 1. Comparative In Vivo Antitumor Activities of Cisplatin and Carboplatin*

Implantation Site†	Cisplatin	Carboplatin
Intraperitoneal		
ADJ/PC6	+	++
C26	+	++
M109 lung	+	−
L1210 leukemia	++	+
B16 melanoma	+	+
Lewis lung	+	+
M5076 sarcoma	+	+
Intravenous		
Lewis lung	++	+
Subcutaneous		
Breast tumor xenograft	+	−
C26	+	+
C38	+	+
B16 melanoma	+	+
CD8F, mammary	+	+
Colon tumor xenograft	+	+
Lung tumor xenograft	−	−
M109 lung	−	−
M5076 sarcoma	+	+
Intracerebral		
Ependymoblastoma	+	−
B16 melanoma	−	−
Subrenal capsule		
Colon tumor xenograft	+	−
Lung tumor xenograft	−	−
Breast tumor xenograft	+	+

Symbols: +, active; −, inactive; ++, more active.

*All nonxenografts are murine tumor models.

†Dosages of platinum used in the tumor models (mg/kg/injection, route) at different implantation sites: intraperitoneal, 12.5 to 200 IP × three to nine doses or 25 to 200 IV × two to five doses; intravenous, six to 25 IP × nine doses; subcutaneous, 12.5 to 200 IP × two to 30 doses; intracerebral, 32 IP × five doses; subrenal capsule, 12.5 to 50 SC × 10 doses or 12.5 to 50 IP × three doses.

cisplatin as a radiosensitizer. Carboplatin has also been evaluated in this setting.[42] It is, however, unclear whether results observed with platinum-radiation combinations are due to radiation potentiation by either of these platinum agents rather than to simple additive effects. Dewit[43] convincingly demonstrated marked synergistic cell killing in only a few tumor systems.

TOXICITY

Nausea and Vomiting

Immediate ($\leq$ 24 hours after treatment) or delayed ($>$ 24 hours after treatment) nausea and vomiting are the most common and most dreaded side effects of cisplatin-based chemotherapy. In one study, after a dose of 120 mg/m^2 cisplatin, all patients who had not received premedication with antiemetics developed an average of 11 emetic episodes.[44] The discovery of the role of the serotonergic pathway in the pathophysiology of chemotherapy-induced emesis has led to the development of 5-hydroxytryptamine (5-HT3) receptor antagonists. These agents have significantly reduced cisplatin-related acute emesis. In one study, there was complete control of emesis (no episode) in almost 50% and major responses (two or fewer episodes) in approximately 75% of the treatments.[45] The effectiveness of the 5-HT3 antagonists seems to be less marked for delayed nausea and vomiting and diminishes across repeated days and sometimes after repeated chemotherapy cycles.[46] There is significantly less control over nausea than there is over emesis, with incomplete nausea control persisting in approximately half of patients receiving cisplatin. The effect of the 5-HT3 antagonists is enhanced by the concomitant administration of corticosteroids.

In contrast to cisplatin-related nausea and vomiting, carboplatin-related nausea and vomiting is much less severe and frequent. In a retrospective analysis of clinical toxicities of 1,893 patients previously treated with carboplatin alone before the 5-HT3 receptor antagonist era, emesis was found in 20% of patients, 20% did not have any emetogenic side effects whatsoever, and 15% developed nausea only. Treatment was interrupted in fewer than 1% of the courses because of gastrointestinal intolerance.[47]

Nephrotoxicity

Nephrotoxicity was dose-limiting for cisplatin in early clinical trials, with effects ranging from reversible azotemia to irreversible renal failure requiring dialysis. It has been shown that early proximal tubular damage causes decreased reabsorption of sodium and water.[48] Subsequent events, including impairment of distal tubular reabsorption, renal blood flow, and glomerular filtration, result in enhanced excretion of enzymes, proteins, and other electrolytes, including magnesium and potassium.[49]

Hydration with normal saline, hypertonic saline infusion, and mannitol- or furosemide-induced diuresis has been used to effectively decrease this toxicity.[50-53] It is believed that the mechanism of cisplatin-induced nephrotoxicity is similar to its tumor cytotoxicity, ie, formation of highly reactive aquated platinum species that cross-link DNA. This aquation reaction is dependent upon ambient chloride concentrations. Hydration and diuresis can reduce urinary concentration of cisplatin whereas forced chloruresis provides high chloride levels in the kidneys, thus minimizing the aquation of cisplatin in renal tubules. In the presence of pre-existing renal insufficiency, cisplatin should not be used if the GFR is less than 30 mL/min. Full-dose cisplatin can be used if the GFR is above 50 mL/min. Dosage adjustment is required for GFRs between 30 mL/min and 50 mL/min.[54] Dose reduction should be proportional to the reduction in GFR (normal GFR is assumed to be 100 mL/min). Thus at a GFR of 40 mL/min, 40% of the full dose of cisplatin should be given.

Thiol-containing compounds have also been used to reduce cumulative renal toxicity. The most promising agent to date is amifostine (WR-2721, S-2 (3-amino-propylamino) ethylphosphorothioic acid). It is a pro-drug that is preferentially taken up and metabolized by normal cells. The active thiol moiety acts as a nucleophile, which can inactivate carbonium ions generated by alkylating agents and prevent DNA damage.[55] In various trials, pretreatment with amifostine conferred protection against cisplatin-induced nephrotoxicity without compromising antitumor efficacy. A reduction in other cisplatin-related toxicities, including myelosuppression and neurotoxicity, was noted as well.[56,57]

Renal impairment is rare with the administration of carboplatin, except at extremely high doses. There seems to be no significant cumulative damage after long-term follow-up, as seen in a series of treated germ cell tumor patients.[58] Because it is excreted primarily as an unchanged drug in the kidneys, carboplatin is not directly toxic to the renal tubules. However, the presence of renal impairment significantly increases its plasma level, which leads to other systemic toxicities. Dosage according to the desired AUC is then modified using the Calvert formula.

Neurotoxicity

Neuropathy is now the major dose-limiting toxicity of cisplatin. This toxicity includes peripheral sensory neuropathy, which is the most common, hearing loss, autonomic neuropathy, Lhermitte's sign (electric shock-like sensation transmitted down the spine upon neck flexion), seizures, and encephalopathy. It is dose-dependent and occurs in approximately 85% of patients with a cumulative dose greater than 300 mg/m^2.[59] In 30% to 50% of cases, neuropathy is irreversible.

Platinum-DNA adducts are found in various tissues of the body, including the peripheral nerves.[60] The highest levels of platinum concentrations in nervous tissues are found in the dorsal root ganglia of autopsied patients. This is consistent with the predominant presentation of sensory neuropathy. The amount of histopathologic changes and clinical neurotoxicity correlate closely with the concentration of cisplatin present in nervous tissue.[61] Ototoxicity, usually manifested as high-frequency hearing loss, is thought to be caused by damage to the outer hair cells in the organ of Corti.[62] Neuropathy is additive when cisplatin is administered with other neurotoxic agents, including paclitaxel and docetaxel.[63,64] Interestingly, in a study involving non–small-cell lung cancer, when cisplatin was added to vinorelbine, the incidence of severe neuropathy was not increased above that of vinorelbine alone.[65]

Different types of agents are currently being explored to reduce or protect patients from cisplatin-induced neurotoxicities. They include nucleophilic sulfur thiols, neurotropic factors, phosphonic acid antibiotics, and free oxygen radical scavengers.[66]

Neurotoxicity is infrequent as a result of carboplatin treatment. Peripheral neuropathies develop in approximately 3% of patients. In patients with existing cisplatin-induced neuropathy, symptoms did not worsen in two thirds of cases after further treatment with carboplatin. The incidence of clinically evident ototoxicity resulting from carboplatin treatment is approximately 1%.[47]

Myelosuppression

Myelosuppression, particularly thrombocytopenia, is the dose-limiting toxicity of carboplatin. It is cumulative in nature. Severe (grade 3 or 4) neutropenia occurs in approximately 18% of treated patients, whereas severe thrombocytopenia occurs in approximately 25% of cases. Platelet count nadirs can be delayed up to 21 days after treatment with carboplatin and may sometimes preclude dosing every 3 weeks. Infectious and bleeding complications are unusual, however ($<$ 6%).[47] The degree of myelosuppression correlates strongly with carboplatin clearance by the kidneys.

Cisplatin-induced cytopenias are usually mild. All three hematopoietic cell lines can be affected. These cytopenias are dose-related and reversible. The incidence of severe leukopenia or thrombocytopenia is approximately 5% to 6%.[67]

CLINICAL ACTIVITY

Ovarian Cancer

Cisplatin is considered the most active chemotherapeutic agent, and it is an integral part of standard regimens for the treatment of advanced ovarian cancer. However, the majority of patients who respond to cisplatin-based therapy will relapse and ultimately die from their disease.[68] Because current treatments are mostly noncurative, measures to minimize clinical toxicities are essential.

At least 12 randomized trials[69-80] have compared cisplatin with carboplatin either as single agents or in combination chemotherapy in the treatment of ovarian cancer (Table 2). Ten of the trials showed equivalent response rates (15% to 30%) as well as median survival times (15 months to 35 months) for both platinum analogs. The dosages of cisplatin used were between 50 mg/m^2 and 100 mg/m^2, whereas the dosages of carboplatin were between 300 mg/m^2 and 400 mg/m^2. Both drugs were administered on the same schedule. None of the trials calculated the dose of carboplatin on the basis of renal function. The majority of patients enrolled had

Table 2. Randomized Trials in Ovarian Cancer

First Author	No. of Patients	Regimen	Platinum Dose	cOR (%)	cCR (%)	MS (months)
Kato[69]	42	CyAP	50 mg/m^2	35	1	—*
		v	q 28d	NS		NS
		CyAC	250 mg/m^2	42	0	—*
			q 28d			
ten Bokkel Huinink[70]	264	CyAHP	20 mg/m^2/d d1-5	49	29	25
		v	q 35d × 6	NS	NS	NS
		CyAHC	350 mg/m^2/d	47	28	25
			q 35d × 6			
Adams[71]	80	P	100 mg/m^2/d	48	15†	—*
		v	q 28d × 5	NS	NS	NS
		C	400 mg/m^2/d	66	20†	—*
			q 28d × 5			
Mangioni[72]	163	P	100 mg/m^2/d	73	NA	—*
		v	q 28d × 5	NS		NS
		C	400 mg/m^2/d	61	NA	—*
			q 28d × 5			
Edmonson[73]	103	CyP	60 mg/m^2/d	NA‡	NA	27
		v	q 28d × 12			S
		CyC	150 mg/m^2/d	NA	NA	20
			q 28d × 12			
Gurney[74]	74	CyP	100 mg/m^2/d	73	23	19
		v	q 28d × 6	NS	NS	NS
		CyC	300 mg/m^2/d	67	46	24
		v	q 28d × 6			
		CyI	240 mg/m^2/d	64	21	18
			q 28d × 6			
Conte[75]	144	CyAP	50 mg/m^2/d	67	28	23
		v	q 28d × 6	NS	NS	NS
		CyAC	200 mg/m^2/d	63	21	23
			q 28d × 6			
Swenerton[76]	417	CyP	75 mg/m^2/d	57	36	25
		v	q 28d × 6	NS	NS	NS
		CyC	300 mg/m^2/d	59	27	28
			q 28d × 6			
Alberts[77]	291	CyP	100 mg/m^2/d	52	30	17
		v	q 28d × 6	NS	NS	NS
		CyC	300 mg/m^2/d	61	33	20
			q 28d × 6			
Belpomme[78]	144	CyAP	75 mg/m^2/d	73	—†	28
		v	q 28d × 6	S	S	S
		CyAC	300 mg/m^2/d	47	—†	21
			q 28d × 6			
Taylor[79]	104	P	100 mg/m^2/d	54	—†	20
		v	q 28d × 10	NS	NS	NS
		C	400 mg/m^2/d	38	—†	13
			q 28d × 10			
Meerpohl[80]	158	CyP	80 mg/m^2/d	63	50	37
		v	q 28d × 6	NS	NS	NS
		CyC	350 mg/m^2/d	73	55	35
			q 28d × 6			

NOTE. In most studies, carboplatin showed more hematologic toxicity and cisplatin showed more nonhematologic toxicities.

Abbreviations: cOR, clinical overall response; cCR, clinical complate response; MS, median survival; Cy, cyclophosphamide; A, doxorubicin; P, cisplatin; C, carboplatin; H, hexamethylmelamine; I, iproplatin; NS, not significant; S, significant.

*Actual figures not provided by authors.

†Complete pathologic response.

‡Trial terminated because of superior progression-free survival in cisplatin arm at interim analysis.

suboptimal residual disease (tumor size ≥ 1 cm). Five trials had at least 4 years of follow-up.

The largest study was conducted by Swenerton et al.[76] This study compared the regimen of cyclophosphamide 600 mg/m^2 in combination with either cisplatin 75 mg/m^2 or carboplatin 300 mg/m^2 given every 4 weeks for six cycles in 417 women with postoperative macroscopic residual disease. Most patients had stage III, grade 3 tumors and bulky residual disease. The results in both arms were similar, including clinical and pathologic response rates and median survival times. Only two trials concluded that carboplatin was inferior to cisplatin. The study by Edmonson et al[73] was terminated before full accrual because interim analysis showed superior progression-free survival for the cisplatin arm. Both platinum agents were given in combination with cyclophosphamide. Although both regimens produced equal myelosuppression, the dosage ratio of carboplatin to cisplatin was less than the optimal 4:1 (150 mg/m^2 *v* 60 mg/m^2). A report in abstract form by Belpomme et al,[78] who investigated a combination of cyclophosphamide, doxorubicin, and either 75 mg/m^2 cisplatin per cycle or 300 mg/m^2 carboplatin per cycle, showed a significantly higher pathologic complete response rate and median survival time in favor of the cisplatin arm.

A meta-analysis by the Advanced Ovarian Cancer Trialist Group[81] concluded that cisplatin and carboplatin were equally effective when used as single agents or in combination with other drugs. Interim analysis of a phase III trial comparing regimens of paclitaxel with either cisplatin or carboplatin revealed no significant difference in efficacy.[82]

From the above data, it is evident that carboplatin is equivalent to cisplatin in the treatment of suboptimally debulked ovarian cancer. Its use in optimally debulked residual disease, where cure is a realistic goal, has been questioned. In a subset analysis of patients with less than 1 cm of residual tumor in the trial by ten Bokkel Huinink et al,[70] both overall survival and progression-free survival separated in favor of the cisplatin arm. This did not reach statistical significance, however, and further analysis was limited by the small number of patients in this subgroup. Two ongoing studies, one from the Gynecologic Oncology Group (GOG) and another from a German group[83] comparing paclitaxel/cisplatin versus paclitaxel/carboplatin combinations, will address this issue.

Germ Cell Tumors

Since the introduction of cisplatin, 70% to 80% of patients with advanced germ cell tumors can now be cured. Prognostic factors have been identified that are useful in classifying different risk groups, thus making it possible for appropriate treatment decisions to be made on the basis of risk stratification. The most frequently used classifications are those developed by Memorial Sloan Kettering Cancer Center, Indiana University, and the European Organization for Research and Treatment of Cancer. Recently, the International Germ Cell Cancer Collaborative Group put together a new consensus classification.[84] The good-prognosis category includes seminomatous tumors of any primary site without extrapulmonary visceral metastases and nonseminomatous tumors of testicular or retroperitoneal primary tumors, without nonpulmonary visceral metastases and low levels of tumor markers. The 5-year overall survival rates are 86% and 92% for seminoma and nonseminoma tumors, respectively. One focus in current germ cell tumor research is to modify the standard chemotherapeutic regimens to minimize toxicities in these good-prognosis patients without compromising efficacy.

Four trials[85-88] have compared cisplatin and carboplatin in good-risk germ cell tumors (Table 3). Bajorin et al[86] enrolled 270 patients with good-risk germ cell tumors (seminoma and nonseminoma) by using Memorial Sloan Kettering Cancer Center criteria. Two hundred sixty-five patients were assessable and were randomized to receive four cycles of either etoposide/cisplatin or etoposide/carboplatin. Cisplatin was given at a dose of 20 mg/m^2/d for 5 days, carboplatin at 500 mg/m^2 on day 1, and etoposide 100 mg/m^2/d for 5 days. Complete response rates were equivalent. However, after a median follow-up of 22 months, more patients in the etoposide/carboplatin arm relapsed (12% *v* 3%). Overall

Table 3. Randomized Trials in Germ Cell Tumors

First Author	No. of Patients	Platinum Regimen	Dose	CR (%)	Relapse (%)	Overall Survival (%)
Tjulandin[85]	62	EP	20 mg/m^2/d d1-5	87	9	—
		v	q 21d × 4	NS	S	NS
		EC	350 mg/m^2	87	30	—
			q 28d × 4			
Bajorin[86]	265	EP	20 mg/m^2/d d1-5	90	3	—
		v	q 21d × 4	NS	S	NS
		EC	500 mg/m^2	80	12	—
			q 28d × 4			
Bokemeyer[87]	54	PEB	20 mg/m^2/d d1-5	81	13	—
		v	q 21d × 3	NS	S	NS
		CEB	AUC 5	76	32	—
			q 21d × 4			
Horwich[88]	598	PEB	100 mg/m^2	94	5	97*
		v	q 21d × 4	S	S	S
		CEB	AUC 5	87	15	90*
			q 21d × 4			

NOTE. There was significantly more hematologic toxicity in the carboplatin arm and more nonhematologic toxicities in the cisplatin arm.

Abbreviations: CR, complete response; E, etoposide; P, cisplatin; C, carboplatin; B, bleomycin; AUC, area under the concentration-time curve; S, significant; NS, not significant.

*Three-year survival.

survival was not different. A similar study was conducted in Russia by Tijulandin et al[85], using the same eligibility criteria. Carboplatin was given at a lower dose of 350 mg/m^2. Results were similar: the etoposide/cisplatin arm had a better relapse-free survival rate.

Two European studies used the triple-drug regimens of etoposide, bleomycin, and either cisplatin or carboplatin. The total cisplatin dose used per cycle was 100 mg/m^2, whereas carboplatin was given to achieve an AUC of 5 mg/mL/min. Only nonseminomatous tumors were included in the study. Response rates were similar in both studies, but the etoposide/bleomycin/carboplatin regimen was inferior because of more treatment failures in this arm, including relapse and treatment-related deaths. In the study by Horwich et al,[88] which enrolled almost 600 patients, complete response to chemotherapy and overall survival were also significantly better in the cisplatin arm after a median follow-up of 36 months.

On the basis of the consistent results of these randomized trials, one can firmly conclude that cisplatin is superior to carboplatin in the treatment of germ cell tumors.

Table 4. Randomized Trials in Small-Cell Lung Cancer

First Author	No. of Patients	Regimen	Platinum Dose	OR/CR (%)	MS (months)
Wolf[90]	350	AIO/EP	90 mg/m^2	60/17	10
		v	q 56d × 2	NS	NS*
		AIO/EC	300 mg/m^2	65/18	10
			q 56d × 2		
Skarlos[91]	143	EP + RT	50 mg/m^2/d d1-2	69/31	13
		v	q 21d × 6	NS	NS
		EC + RT	300 mg/m^2	78/29	12
			q 21d × 6		
Lassen[92]	475	P arm†	35 mg/m^2/d d2, 3	63/31	12
		v	q 28d × 5	NS	NS
		C arm†	150 mg/m^2/d d2, 3	72/37	10
		v	q 28d × 5		
		arm III‡			

NOTE. There was a similar incidence of myelosuppression but significantly more nonhematologic toxicities in the cisplatin arm.

Abbreviations: OR, overall response; CR, complete response; MS, median survival; A, doxorubicin; I, ifosfamide; E, etoposide; P, cisplatin; C, carboplatin; RT, radiotherapy; NS, not significant.

*Better survival in limited-stage disease.

†Four alternating regimens.

‡Three alternating regimens.

Small-Cell Lung Cancer

Although cisplatin is the mainstay of treatment in small-cell lung cancer, clinical studies have demonstrated that carboplatin is a very active drug in this disease as well. In phase II trials, an average overall response rate of 34% was observed (59% in patients without prior chemotherapy and 17% in patients with prior treatment). The carboplatin and etoposide combination has produced overall response rates of 87% and 61%, as well as complete response rates of 49% and 13%, in limited and extensive stages of small-cell lung cancer, respectively.[89]

Three trials[90-92] compared the use of both platinum agents (Table 4). Skarlos et al[91] used the combinations of cisplatin/etoposide and carboplatin/etoposide. Additional thoracic and prophylactic cranial irradiation was given only to complete responders. Lassen et al[92] used an alternating chemotherapy regimen of nine different drugs and replaced cisplatin with carboplatin in one of the study arms. Both trials showed equal rates of overall and complete responses as well as equal median survival times. A German multicenter trial conducted by Wolf et al[90] evaluated 350 patients randomized to receive doxorubicin, ifosfamide, and vincristine alternating with either cisplatin/etoposide or carboplatin/etoposide. Preliminary analysis revealed an advantage of the cisplatin regimen in limited disease, with a median survival time of 14 months versus 12 months, but there was no difference in extensive disease. This study had the largest number of patients per treatment arm and is the only study that analyzed response rates and survival according to disease extent and treatment.

On the basis of the results presented here, carboplatin can replace cisplatin in extensive-stage disease regimens with equivalent efficacy. Cisplatin should still be used in limited-stage disease until future studies prove the equivalence of carboplatin to cisplatin in this subset of potentially curable patients.

Non–Small-Cell Lung Cancer

Primary chemotherapy in advanced non–small-cell lung cancer remains a big challenge. Response rates with standard cisplatin-based regimens in large trials are in the range of 30%, with few complete responses and only a modest impact on overall survival. A meta-analysis of 52 randomized clinical trials showed a benefit of cisplatin-based chemotherapy over supportive care alone, with an absolute improvement in survival of 10% at 1 year and a modest increase in median survival of 1.5 months.[93] Because of significant treatment-related toxicities, it is general practice that chemotherapy be offered only to patients with good performance status, with improvement in quality of life as one of the major goals.

Only one randomized trial[94] has addressed the substitution of carboplatin for cisplatin in combination chemotherapy (Table 5). Two hundred twenty-eight patients were randomized by Klatersky et al[94] to receive 120 mg/m^2 cisplatin per cycle or 325 mg/m^2 carboplatin per cycle in

Table 5. Randomized Trial in Non–small-Cell Lung Cancer

First Author	No. of Patients	Regimen	Platinum Dose	OR/CR (%)	MS (months)
Klatersky[94]	228	EP*	120 mg/m²	27/2	8
		v	q 21-28d†	NS	NS
		EC	325 mg/m²	16/1	7
			q 21-28d†		

Abbreviations: OR, overall response; CR, complete response; MS, median survival; E, etoposide; P, platinum; C, carboplatin; NS, not significant.

*Hematologic and nonhematologic toxicities were significantly increased in the cisplatin arm.

†Until progression or no further response.

combination with etoposide in locally advanced unresectable or metastatic non–small-cell lung cancer. There was a 27% objective response in the cisplatin arm and a 16% objective response in the carboplatin arm. This reached borderline statistical significance ($P = .07$). Survival was equivalent. There were fewer toxicities, including treatment-related deaths, in the carboplatin group. However, the dosage of carboplatin used was not equitoxic to the dose of cisplatin and may account for the lower response rate.

Paclitaxel-based combinations have now become commonly used regimens in advanced lung cancer in the United States. An Eastern Cooperative Oncology Group phase III trial was completed recently comparing cisplatin/etoposide with two paclitaxel/cisplatin regimens.[95] Both paclitaxel regimens produced better response rates (31% and 26% *v* 12%) and superior survival in a preliminary analysis. In phase II studies, paclitaxel/carboplatin combinations have yielded response rates of 12% to 62%.[96] It is hoped that two ongoing Eastern Cooperative Oncology Group and European Organization for Research and Treatment of Cancer trials incorporating both paclitaxel/cisplatin and paclitaxel/carboplatin regimens in the treatment arms will provide the answer to whether these two regimens are equivalent in activity.

As the role of chemotherapy in non–small-cell lung cancer is mostly palliative, substitution of cisplatin by carboplatin is reasonable based on the very limited data available.

Head and Neck Cancer

Advanced-stage, recurrent, or metastatic head and neck cancers have a poor prognosis, with a median survival time of approximately 6 months. A meta-analysis has shown that combination chemotherapy provides higher response rates than single agents do, with improvement in survival.[97] However, this improved survival is at the cost of increased toxicity. The most widely used combination chemotherapy is the fluorouracil (5-FU)/cisplatin regimen. Fluorouracil with carboplatin in phase II studies produced response rates between 20% and 85%.[98]

There are three randomized studies[98-100] reported in the literature (Table 6). Welkoborsky et al[99] studied 60 patients with advanced carcinomas of the oropharynx and hypopharynx. Fluorouracil was given with either cisplatin 100 mg/m² or carboplatin 400 mg/m² every 3 to 4 weeks for three cycles. Overall response rates were similar (67% *v* 63%), but there were more complete responses in the cisplatin arm (20% *v* 3%). Median survival was not reported.

Two other studies compared 5-FU/cisplatin and 5-FU/carboplatin in the neoadjuvant setting. In the trial by Ebeling et al,[100] who used 100 mg/m² cisplatin per cycle and 360 mg/m² carboplatin per cycle, overall and complete response rates and median survival times were higher in the cisplatin arm but did not reach statistical significance. De Andres et al[98] enrolled a larger number of patients but used 400 mg/m² carboplatin per cycle. The cisplatin arm not only showed a significantly higher rate of overall response (92% *v* 76%) and complete response (27% *v* 20%), but 5-year survival (49% *v* 25%) was better as well.

Overall, these studies, although small in size, suggest that carboplatin is inferior to cisplatin in the systemic treatment of head and neck cancer.

Other Cancers

Currently, there are no published phase III randomized trials comparing the substitution of cisplatin by carboplatin in established combination regimens in bladder, cervical, endometrial, and esophageal cancers.

Table 6. Randomized Trials in Head and Neck Cancer

First Author	No. of Patients	Regimen	Platinum Dose	OR/CR (%)	MS (months)
Welkoborsky[99]	60	5-FU/P	100 mg/m²	67/20	NA
		v	q 21-28d × 3	NS/S	
		5-FU/C	400 mg/m²	63/3	NA
			q 21-28d × 3		
Ebeling[100]	73	5-FU/P	100 mg/m²	83/29	27*
		v	q × 3	NS	NS
		5-FU/C	360 mg/m²	77/22	24*
			q × 3		
De Andres[98]	95	5-FU/P	100 mg/m²	92/27	—
		v	q 21d × 3	S	S
		5-FU/C	400 mg/m²	76/20	—
			q 21d × 3		

Abbreviations: OR, overall response; CR, complete response; MS, median survival; 5-FU, fluorouracil; P, cisplatin; C, carboplatin; RT, radiotherapy; NS, not significant; S, significant; NA, not available.

*Disease-free survival.

†There was significantly more hematologic toxicity in the carboplatin arm and more nonhematologic toxicities, including mucositis, in the cisplatin arm.

Bladder cancer. In bladder cancer, cisplatin-containing chemotherapeutic regimens have produced encouraging results, with overall response rates between 50% and 70%, complete responses in 10% to 20% of patients, median survival times of approximately a year, and long-term survival in 10% of patients with metastatic disease.[101] The methotrexate, vinblastine, doxorubicin, and cisplatin regimen (M-VAC) remains the only regimen that has been shown to be superior to single-agent cisplatin.[102] Nevertheless, toxicities are considerable. Bellmunt et al[103] reported a randomized phased III trial comparing M-VAC with a carboplatin-containing three-drug regimen of methotrexate, carboplatin, and vinblastine (M-CAVI). The latter regimen is, however, different because in addition to the substitution of cisplatin by carboplatin, doxorubicin has been dropped. Forty-seven patients were evaluated. The overall response rate was higher in patients treated with M-VAC (52% *v* 39%) but did not reach statistical significance. Three complete responses were observed in the M-VAC group and none were seen among patients in the methotrexate/carboplatin/vinblastine group. The M-VAC regimen was more toxic but produced a significantly longer median disease-related survival time (16 months *v* 9 months). A randomized phase II study[104] compared a similar regimen, methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC), with carboplatin-substituted M-VECa in 57 patients with recurrent or metastatic bladder cancer. The overall response (71% *v* 41%) and complete response (25% *v* 11%) were significantly in favor of M-VEC. These results have to be confirmed in a phase III trial.

Cervical cancer. Surgery and radiotherapy are used as the primary modalities in the treatment of cervical cancer, even in the locally advanced setting. Chemotherapy has mostly been used in recurrent or disseminated diseases. Duration of response is usually shorter than 6 months, and impact on overall survival is not significant. Cisplatin is the most commonly used single agent. There is no firm evidence that cisplatin-based regimens are better than cisplatin alone. In a phase III GOG trial,[105] single-agent cisplatin resulted in an 18% overall response. Although the cisplatin/ifosfamide combination regimen had a better response rate (31%), it did not result in a better survival. Carboplatin used alone in phase II studies has generally shown response rates between 15% and 30% at a dose of 400 mg/m^2 every 4 weeks.[106-108]

Endometrial cancer. In endometrial cancer, resection of the primary tumor with adjuvant radiotherapy is the mainstay of treatment. Both platinum agents are active in this disease. A GOG study[109] reported superior progression-free survival when cisplatin was added to doxorubicin, which is the most active agent in endometrial cancer. An average overall response rate of 31% (28% to 33%) was found in three phase II trials testing carboplatin. These results are comparable to those obtained for cisplatin.[110-112] However, the role of carboplatin in combination chemotherapy is still undefined.

Esophageal cancer. The combination of cisplatin and 5-FU is the most active chemotherapeutic regimen in esophageal cancer producing response rates of 25% to 35% in metastatic disease and 50% to 60% in locally advanced stages. Carboplatin, either as a single agent or in combination therapy, has been tested in squamous cell carcinoma and adenocarcinoma of the esophagus with poor results. Response rates have been less than 10%.[113] Thus, carboplatin should not be used in this disease. It is unlikely that future comparative studies will be performed.

CONCLUSION

Cisplatin is one of the most active drugs in the treatment of solid tumors. Its narrow therapeutic index has led to the development of the less toxic analog carboplatin, which has the additional advantage of easier administration and individualized dosing. Although carboplatin has a similar mechanism of action and preclinical spectrum of activity as cisplatin, it does not have the same clinical efficacy in all platinum-sensitive tumors. Carboplatin can substitute for cisplatin in the treatment of suboptimally debulked ovarian cancer. Studies are ongoing to determine whether this also holds true for optimally debulked disease. In germ cell tumors, carboplatin therapy results in more relapses and, thus, should not be used. Cisplatin is still the agent of choice in head and neck cancer. On the basis of limited comparative randomized trials, carboplatin can probably substitute for cisplatin in non–small-cell and extensive-stage small-cell lung cancer. Its use in limited-stage small-cell lung cancer requires further investigation. As phase II esophageal cancer studies generally showed poor responses, carboplatin should not be substituted for cisplatin in the treatment of this disease. Future studies are needed to determine whether carboplatin is as effective as cisplatin in advanced bladder, cervical, and endometrial cancers.

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