New Perspectives on an Old Friend: Optimizing Carboplatin for the Treatment of Solid Tumors

DAVID S. ALBERTS, ROBERT T. DORR
University of Arizona, Arizona Cancer Center, Tucson, Arizona, USA

Key Words. Carboplatin · Cisplatin · Paclitaxel · Etoposide · Ovarian cancer · Non-small cell lung cancer · Small cell lung cancer · Solid tumors · Pharmacokinetics · Pharmacodynamics

ABSTRACT

Background. Since its clinical introduction in 1981, carboplatin has proved a feasible alternative to cisplatin for the treatment of many solid tumors, especially ovarian cancer. Because the pharmacokinetics and, ultimately, the pharmacodynamics of carboplatin are highly dependent on the status of renal function, fixed dosing based on body surface area has led to carboplatin overdosing or, especially, underdosing. This has resulted in less than optimal treatment results compared with cisplatin in a variety of solid tumor types. Only in the past few years has the optimal dosing method for carboplatin—individualizing the dose (area under the concentration-versus-time curve [AUC]) rather than conventional use of body surface area—been adopted by clinical oncologists.

Methods. An extensive review of the oncology literature has been performed to update both carboplatin dosing guidelines as well as its present role in solid tumor chemotherapy. Initial efforts to devise a dosing formula for carboplatin focused on reducing myelotoxicity (especially thrombocytopenia). Subsequently, a simple formula was developed to adjust the carboplatin dose according to renal function. By targeting a carboplatin AUC rather than empirically dosing according to body surface area, doses of carboplatin can be individualized to fall within the drug’s therapeutic index.

Results. The use of carboplatin dosing guidelines based on renal function has led to optimization of its pharmacodynamic effects both with respect to its safety profile and its ultimate impact on solid tumor response and patient survival. Since carboplatin has little neurotoxicity, it has become the platinum agent of choice in combination with paclitaxel for therapy of previously untreated ovarian cancer. Carboplatin plus etoposide and carboplatin plus paclitaxel have been studied in phase II and III trials, with the latter combination demonstrating improved activity against advanced non-small cell lung cancer. Additional trials in patients with other solid tumors have shown that carboplatin is more cost-effective and less toxic than cisplatin.

Conclusions. Dosing based on renal function and a targeted serum AUC, rather than on body surface area, has resulted in the optimal utilization of carboplatin in cancer chemotherapy. Its predictable toxicity and clinical efficacy equivalent to cisplatin make carboplatin the drug of choice for selected tumor types. The Oncologist 1998;3:15-34

INTRODUCTION

Since its clinical introduction in 1981, carboplatin has proved a feasible alternative to cisplatin for the treatment of many solid tumors, especially ovarian cancer, an indication that was approved by the United States FDA in the late 1980s [1, 2]. As a second-generation analog of cisplatin, carboplatin shares many structural and pharmacologic features with cisplatin, yet it has an improved toxicity profile. These characteristics have made carboplatin an ideal candidate for not only dose-intensive chemotherapy but also combination therapy with newer agents such as paclitaxel.

Only recently was the optimal dosing method for carboplatin—individualizing the dose (area under the concentration-versus-time curve, [AUC]) rather than conventional use of body surface area (BSA)—recognized. The FDA approval within the past year of individualized dosing for carboplatin marks the beginning of a new era for this drug. Although its effectiveness in many tumors was similar to that of cisplatin,
even when carboplatin was suboptimally dosed, the results of recent trials that use individualized dosing of carboplatin are just now maturing. Because of its lower toxicity and equivalent efficacy, as compared to cisplatin, carboplatin is the platinum analog of choice for selected tumor types.

**Clinical Pharmacology**

Both carboplatin and cisplatin exert their therapeutic effects primarily by forming intrastrand DNA adducts with adjacent guanine residues in tumor-cell DNA [3]. Although the platinum-containing moieties of carboplatin and cisplatin are identical (Fig. 1), it is the unique leaving groups of each that ultimately facilitate DNA binding. In the case of carboplatin, the carboxylate groups are much more stable adducts than the chloride groups of cisplatin. This decreases the chemical reactivity of carboplatin relative to cisplatin and significantly lengthens the time required for its aquation and subsequent DNA-adduct formation [4, 5]. Despite these time-course differences, both carboplatin and cisplatin appear to induce an equivalent number of DNA cross-links, which determines the extent to which they are cytotoxic [5].

**Pharmacokinetics of Carboplatin**

After i.v. infusion of carboplatin in the dose range 20-1,600 mg/m², the disposition of platinum typically is followed by measuring the free platinum—the therapeutically active form of the drug—present in plasma ultrafiltrate, the protein-bound platinum, and the total platinum, a composite of free and protein-bound platinum plus metabolites. After carboplatin is distributed throughout the body, total platinum concentrations found in various tissues are higher than those found in plasma, with the highest concentrations in liver, kidney, skin, and tumors [5, 6].

Carboplatin is excreted almost exclusively by the kidneys. The total body clearances of ultrafiltrable platinum and that of the parent carboplatin molecule are roughly equivalent and correlate linearly with the pretreatment glomerular filtration rate (GFR). Approximately 65%-70% of the total platinum dose is eliminated as intact carboplatin in the urine during the first 12-16 hours after administration, while the remaining 30%-35% of the dose, which is protein-bound and inactive, is eliminated slowly over the next five days [4, 7, 8].

The extent of the pharmacodynamic effects of carboplatin on the body is directly related to the amount of drug delivered to the tissues, which is determined by its plasma concentration. Because physiologic variables, such as renal function, can affect the plasma concentration of carboplatin in proportion to its total body clearance, the AUC should comprise a more accurate reflection of the actual exposure of body tissues (especially the tumor) to carboplatin than should a single empiric dose based solely on the BSA [9]. Because AUC dosing is adjusted for pharmacokinetic variables within each individual, it should achieve a more standardized level of drug delivery than empiric dosing based entirely on BSA.

**Administration and Dosing**

**Administration**

Carboplatin is easily administered in the outpatient setting because, unlike cisplatin, it does not require hydration or prophylactic diuretics. Additionally, it can be delivered in a bolus i.v. dose over as short a period as 15 min. In contrast, cisplatin, owing to its renal toxicity, must be administered much more slowly (generally at a rate of 1 mg/min) with saline and a diuretic such as the osmotic nonmetabolized sugar mannitol [10, 11]. Because cisplatin is also far more emetogenic than carboplatin, and its administration requires considerably more time, carboplatin should cost significantly less to administer [2, 12].

Although oral administration of carboplatin has been studied, the low bioavailability of the drug with this route and its untoward gastrointestinal side effects preclude oral administration. On the other hand, the response of tumors located within the peritoneal cavity, such as ovarian cancer, could potentially benefit from intraperitoneal (i.p.) administration of carboplatin. Although the theoretical advantages of enhanced carboplatin exposure after i.p. administration have been investigated [13, 14], pharmacokinetic studies revealed that despite the slower clearance of carboplatin from the peritoneal cavity than from plasma, and the resultant 10-fold
higher i.p. AUC, the benefits of i.p. administration of carboplatin were unfounded. The transit of carboplatin through extracellular space is less efficient than that of cisplatin because of its larger molecular size, which prevents penetration beyond a depth of 1-2 mm of tumor tissue [13-16].

**Individualized Dosing**

The conventional method of dosing carboplatin by BSA is being replaced by pharmacokinetically individualized dosing based on the desired plasma concentration versus time curve (AUC). Carboplatin is considerably less toxic than cisplatin, but its dose-limiting toxicity is myelosuppression, particularly thrombocytopenia. Initial efforts by Egorin and Jodrell at the University of Maryland to devise a dosing formula for carboplatin focused exclusively on reducing the drug’s myelotoxicity, since the percentage reduction in platelet count was shown to correlate linearly with the AUC [9]. Subsequently, Calvert and colleagues at the Royal Marsden in the United Kingdom developed a simple formula for adjusting the carboplatin dose according to renal function [9, 17-21]. This formula was based on the GFR, calculated using the clearance of radiolabeled chromium-EDTA, a test not available in the United States. This formula was based on the observation of a high correlation of measured GFR with renal clearance of carboplatin, which is its primary mode of elimination. The nonrenal contribution to carboplatin clearance was relatively constant at 25 ml/min, and thus the AUC of carboplatin varied solely as a function of renal clearance, reflected in the measured GFR values. The total carboplatin dose could then be measured in milligrams.

\[
\text{Total dose (mg) = target AUC (mg/ml \cdot \text{min})} \\
\times (\text{GFR [ml/min]} + 25)
\]

The value of 25 ml/min is a constant that used to correct for the nonrenal clearance of irreversibly tissue-bound carboplatin [17].

By targeting a carboplatin AUC, rather than empirically dosing according to BSA, doses of carboplatin can be individualized to a target AUC, which should be within the drug’s therapeutic index. This is believed to fall within the range of AUCs of 5-7 in nonpretreated patients receiving single-agent carboplatin and 3-5 in heavily pretreated patients or those receiving concomitant myelosuppressive agents, although the ideal targeted AUC determination would be based on studies exploring a relationship with tumor response and toxicity [23].

Much of the work on target AUC has been done on ovarian cancer and would be different for other cancers. However, if one knows that the total dose of carboplatin is equal to the AUC × [creatinine clearance – 25], this equation should theoretically allow the AUC to be determined for any cancer.

However, at AUC values >5-7, there may be no increase in carboplatin efficacy, despite the occurrence of greater thrombocytopenia, which is the case in ovarian cancer [23]. For example, patients who have a BSA of 1.7 m² and are dosed empirically might experience a wide range of AUCs (AUC 3-11.1), depending on their GFR (Table 1). However, since the Calvert formula is based on the GFR value, a specific AUC can be targeted for specific cancers. Thus, recommended target AUC values are 5 mg/ml × min when carboplatin is used in combination, 6 mg/ml × min when it is used as a single agent in previously treated patients, and 7 mg/ml × min when it is used as a single agent in previously untreated patients because they are associated with manageable levels of hematologic toxicity [4, 17, 18, 22].

A parallel rise in hematologic toxicity with an increasing carboplatin AUC—as evidenced by a reduced platelet count two weeks after carboplatin administration—has been shown empirically by Calvert (Table 2A) [17]. Similarly, Canetta observed an inverse relationship between myelosuppression and GFR—as the GFR decreases, the incidence of WHO grade 3-4 neutropenia and thrombocytopenia induced by carboplatin increases (Table 2B) [22]. The relationship between the carboplatin AUC during the first course of chemotherapy and the degree of myelosuppression also has been retrospectively evaluated in 450 chemotherapy-naïve and 578 previously treated ovarian cancer patients who were given single-agent carboplatin [23]. There was a

| Table 1. Comparison of formulaic and empiric dosing as exemplified by two patients with a body surface area of 1.7 m² and with different glomerular filtration rates |
|-------------------|-------------------|-------------------|-------------------|
| **Target dose**   | **Patient 1**     | **Patient 2**     |
|                   | **Empiric**       | **Formulaic (AUC)** | **Empiric**       | **Formulaic (AUC)** |
|                   | 360 mg/m²         | AUC = 5           | 360 mg/m²         | AUC = 6            |
| Glomerular filtration rate (ml/min) | 30 | 30 | 120 | 120 |
| Dose administered (mg) | 612 | 275 | 612 | 870 |
| Carboplatin plasma concentration-versus-time curve (AUC) (mg/ml × min) | 11 | 5 | 4 | 6 |
significant correlation between the carboplatin AUC and the degree of thrombocytopenia and leukopenia. Regression analysis also indicated that increases in the exposure to carboplatin to an AUC of 5 to 7 were associated with significant improvements in the objective response rate. A similar relationship between AUC and response rate was demonstrated for single-agent carboplatin in patients with germ cell tumors. In a phase I/II study, 88% of those who received an AUC above 6.5 achieved a durable complete remission compared with 20% of those who experienced a carboplatin AUC below 6.5 [24].

Although the associations between tumor response, median survival, time to progression, and AUC are not as definitive as the relationship between toxicity and AUC, the ability to preselect an AUC based on GFR confers several benefits:

- Avoidance of subtherapeutic dosing in patients with high renal clearance values [17];
- Avoidance of overdosing in patients with impaired renal function, especially older patients with reduced bone marrow reserve [17];
- Usefulness regardless of previous or concurrent therapy [25], and
- High association between target AUC values and manageable thrombocytopenia [4, 17, 20, 23, 26].

One question of great concern is whether the AUC for carboplatin is affected by concurrent administration of other agents. In most cases, it does not appear to be. For example, in studies combining carboplatin with cyclophosphamide [4, 25], with etoposide [9, 27], or with methotrexate and vinblastine [28], the AUC of carboplatin was identical to its single-agent AUC. However, the addition of other agents can alter the degree of myelosuppression. Leukopenia and thrombocytopenia at a given AUC of carboplatin are greater when carboplatin is used alone [29, 30]. When carboplatin is combined with paclitaxel, paclitaxel appears to exert a protective effect on platelets, and severe thrombocytopenia is reduced to levels considerably below those for single agent carboplatin at the same AUC. This positive interaction occurs without altering the pharmacokinetics of either drug. Although the mechanism of this platelet-sparing effect is unknown, it increases commensurate with the paclitaxel dose [31-38].

Measuring GFR by Creatinine Clearance

The most accurate methods for determining the GFR use radioisotopes. Perhaps the most common direct measurement of GFR in the United Kingdom is obtained by i.v. injection of chromium-tagged ethylenediaminetetraacetic acid (\(^{51}\)Cr-EDTA), a chemically stable compound that is eliminated only by glomerular filtration. However, the need for a nuclear medicine facility, the expense of this technique, and the exposure of the patient to radiation limit the utility of this approach for routine practice [26].

Because creatinine is eliminated primarily through glomerular filtration, creatinine clearance (CrCl) can be determined from steady-state serum creatinine (Scr) levels and substituted for the GFR in the Calvert formula. Alternatively, the AUC can be derived from a simple dosing chart based on the Calvert formula (Table 3). Four methods have been developed to estimate CrCl. The urine-collection method, although less invasive than isotope injection, also has its drawbacks. Either a timed urine collection or a 24-h complete urine collection can be time consuming to collect, and are typically incomplete, yielding inaccurate estimates of CrCl and renal function [26]. Nevertheless, CrCl may be calculated from a 24-h total urine collection using the following equation:

\[
\text{CrCl} = \frac{\text{Volume of urine after 24 h (ml)} \times \text{urine creatinine concentration (µM)}}{\text{Serum creatinine concentration (µM)} \times 1,440 \text{ (min)}}
\]

Another equation for estimating CrCl was developed by Jelliffe as a simple bedside method that does not require urine collections. It includes an adjustment for sex because the lower muscle mass in women produces less creatinine than in men. For women, a value of 90% of the predicted CrCl for men is used. Additionally, including an adjustment for BSA did not produce a major change in CrCl estimates. This implies that even though BSA is important for dosing many drugs, it is not

<table>
<thead>
<tr>
<th>Observed AUC (mg/ml/h)</th>
<th>Median platelet count (× 10^9/l)</th>
<th>% of pretreatment platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–6</td>
<td>103</td>
<td>27</td>
</tr>
<tr>
<td>6–8</td>
<td>113</td>
<td>18</td>
</tr>
<tr>
<td>&gt;8</td>
<td>51</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glomerular filtration rate (ml/min)</th>
<th>Patients with neutropenia (%)</th>
<th>Patients with thrombocytopenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥120</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>100–119</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>80–99</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>60–79</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>40–59</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>&lt;40</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>
the primary determinant for renally eliminated drugs [40]. The Jelliffe equation is:

\[
CrCl (\text{ml/min}/1.73 \text{ m}^2) = \frac{98 - 0.8(Age - 20)}{\text{Scr}}
\]

Another commonly used CrCl estimation method uses age, weight, and sex. Cockcroft and Gault devised this method shortly after Jelliffe, in which the CrCl should be reduced by 15% for women [41]:

\[
CrCl = \frac{(140 - \text{Age}) \times \text{Wt (kg)}}{72 \times \text{Scr (mg/100 ml)}}
\]

Chatelut et al. more recently developed a fourth method for estimating the clearance of carboplatin which mathematically integrates several patient variables into the calculation [42]:

\[
\text{Cl}_{\text{carbo}} = 0.134 \times \text{Wt} + [218 \times \text{Wt} \times (1 - 0.00457 \times \text{Age}) \times (1 - 0.314 \times \text{sex})] / \text{creatinine expressed in } \mu \text{M (with weight in kg, age in years, and sex = 0 if male and sex = 1 if female)}
\]

\[
\text{Scr (}\mu \text{M)}
\]

Importantly, this method has been prospectively validated in a small patient population receiving carboplatin [42].

Several studies comparing the accuracy of these four methods of estimating CrCl have yielded equivocal results. In a comparison of the Jelliffe and the Cockcroft-Gault equations, the Cockcroft-Gault equation was found to be better suited for nonelderly patients with normal Scr values, while the Jelliffe equation was better for men with elevated Scr values (>1.5 mg/dl) [39]. The Cockcroft-Gault estimation of CrCl also compared well with the GFR determined by diethyleneetriamine pentaacetic acid (DPTA) [43]. Finally, a comparison of 24-h urine collection, the Cockcroft-Gault equation, and the Chatelut equation demonstrated the latter to be both precise and unbiased [36]. In all likelihood, all four methods produce acceptable results when performed correctly, although recent studies indicate that the Chatelut equation may be the most accurate [44-48]. Single-sample assays have also been developed for determining the carboplatin AUC, primarily from studies using retrospective analyses [49-51].

Toxicity

One of the driving forces behind developing cisplatin analogs was to mitigate the extensive toxicities of cisplatin while preserving its antitumor efficacy. For the treatment of many solid tumors, carboplatin has satisfied this goal. Carboplatin causes significantly less nephrotoxicity than cisplatin, eliminating the need for hydration during administration, except in patients with impaired renal function or those receiving dose-intensive carboplatin (>800 mg/m²) [52-55]. Whereas renal tubular damage is the acute dose-limiting toxicity of cisplatin, the cumulative dose-limiting effect of cisplatin is peripheral (sensory) neuropathy. These peripheral sensory neuropathies manifest as hearing loss and foot and hand numbness, eventually leading to an inability to hear high frequencies or an inability to walk. This is virtually absent with carboplatin. At conventional doses (360 mg/m²) carboplatin is associated with a low incidence of hearing loss, and it is considerably less ototoxic than cisplatin [5, 55-59].

Cisplatin is one of the most emetogenic chemotherapeutic agents, whereas carboplatin is considerably less emetogenic. Carboplatin-induced dose-related nausea or vomiting is also of shorter duration and is highly manageable with standard antiemetic therapy [5, 55]. This lessens the need for extensive antiemetic drug combination therapy with carboplatin. When combined with the lack of need for prophylactic hydration and diuretics, there is much greater cost-effectiveness with carboplatin. In general, carboplatin-induced emesis is completely prevented by combining a serotonin-3 receptor antagonist with a glucocorticoid such as dexamethasone. For example, a study to develop a cost-effective antiemetic regimen for carboplatin demonstrated that when low-dose granisetron (0.5 mg) was combined with dexamethasone, emesis was completely or mostly controlled in 96% of patients at a reasonable cost [60].

Hematologic toxicity is the dose-limiting toxicity of conventional carboplatin therapy, with thrombocytopenia being more severe than leukopenia or anemia. Although carboplatin-induced myelosuppression appears to be reversible, its severity may be cumulative with successive cycles. Platelet nadirs usually occur between 14 and 28 days after administration, and recovery ensues 7-10 days thereafter [5, 55, 61, 62]. Because
of the relationship between the carboptatin AUC, the degree of myelotoxicity, and the therapeutic activity of carboptatin, platelet- and neutrophil-count nadirs can be used to determine whether the dosage (or targeted AUC) of single-agent carboptatin is appropriate. The platelet count nadir should lie between 50,000/µl and 100,000/µl, and the neutrophil count nadir should lie between 500/µl and 1,000/µl after carboptatin treatment. If the nadirs are above these levels, the carboptatin dose should be escalated during subsequent cycles, whereas if the nadirs are below these levels, the carboptatin dose should be reduced by 25% [12].

When high-dose carboptatin therapy (>1,200 mg/m²) is given, 90% of patients experience WHO grade 4 thrombocytopenia and neutropenia. This often delays the administration of repeated cycles and thereby reduces dose intensity [54, 55]. Because the low nonhematologic toxicity profile of carboptatin is well suited for dose-intensive therapy, numerous trials have investigated the use of natural and synthetic hematopoietic agents—erythropoietin, the cytokines, amifostine, and the colony-stimulating factors—to mitigate the myelosuppressive effects of carboptatin [56, 63-74]. Of these, erythropoietin, interleukin 1 alpha (IL-1α), IL-6, and amifostine have been shown to reduce the leucopenia and granuloctopenia associated with carboptatin. Except for the sulphydrl-based cytoprotectant amifostine [75], these growth factors have little effect on the thrombocytopenia. In the randomized study of Budd et al. [75], administration of amifostine markedly reduced cumulative carboptatin-induced thrombocytopenia and preserved carboptatin dose intensity. The probable mechanism of amifostine’s beneficial interaction with carboptatin involves a primary stimulation of primitive bone marrow progenitor cell growth [76, 77]. Growth factors are effective in limiting thrombocytopenia after carboptatin therapy when they are used to augment the collection of peripheral blood progenitor cells (PBPCs), and their use also may reduce the overall cost of high-dose therapy by lessening the need for blood cell support [78].

In contrast, thanks to its natural platelet-sparing ability when used in concert with carboptatin, paclitaxel significantly reduces the thrombocytopenic effects of carboptatin. For example, in a study of ovarian cancer patients, ten Bokkel Huinink and colleagues found that as the dose of carboptatin was escalated from 300 mg/m² to 600 mg/m², higher doses of paclitaxel yielded higher platelet nadirs [32]. This same effect was also found when Siddiqui and colleagues treated ovarian cancer patients with increasing doses of paclitaxel plus a fixed dose of carboptatin (AUC = 7 mg/ml × min) [33]. Moreover, the administration of high-dose carboptatin plus a 3-h infusion—rather than a 24-h infusion—of paclitaxel may eliminate the need for concurrent G-CSF to reduce neutropenia [79, 80]. Based on phase II study results, the combination of paclitaxel plus carboptatin appears highly active in patients with advanced ovarian cancer, resulting in an overall response rate of 75% and only mild myelotoxicity [81].

**Carboptatin Treatment of Solid Tumors**

**Non-Small Cell Lung Cancer**

**Metastatic Non-Small Cell Lung Cancer**

In patients with Stages IIIIB (with pleural effusion) or IV (metastatic) non-small cell lung cancer (NSCLC), curative therapy is not available, and providing palliation with chemotherapy and extending survival continue to be major challenges. One reason is that in NSCLC, an improved therapeutic response has not always been accompanied by an improved outcome—in this case, longer survival. Thus, the results of randomized clinical trials in this population of NSCLC patients have been difficult to interpret because the response rates are low and do not translate into longer survival [2]. An equally important consideration in patients with advanced disease is the quality of survival, since chemotherapeutic agents are not curative but their toxicity might diminish the quality of life without adding any survival advantage.

Thus, the low toxicity profile of carboptatin renders it a promising treatment for patients with metastatic disease, especially when carboptatin is optimally dosed. Indeed, the benefits of single-agent carboptatin were borne out in a phase III clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) in which 699 patients with Stage IV NSCLC were randomized to receive either single-agent carboptatin or iproplatin, followed by mitomycin/vinblastine/cisplatin (MVP) at time of disease progression, or three other cisplatin-based combination regimens, MVP, VP, or MVP alternated with cyclophosphamide/doxorubicin/methotrexate/procarbazine (CAMP) [2, 82-85]. Despite the low response rate of 9% with single-agent carboptatin treatment compared with the response rates with the combination regimens (20% with MVP, 13% with VP, and 13% with MVP/CAMP), patients treated with carboptatin had significantly longer median durations of survival (31 weeks, p = 0.008), longer times to disease progression (p = 0.01), and fewer adverse effects (p < 0.0001). Moreover, as shown in Table 4, the response rate was inversely related to the duration of survival, since the drug combinations with the highest response rates yielded the shortest mean survivals. In the carboptatin arm, crossover to MVP after disease progression did not significantly affect either survival duration or time to progression, since patients who received carboptatin without subsequent MVP had a mean survival of 29.3 weeks compared with 22.7 weeks for those who received MVP as primary treatment. Likewise, the median time to progression for the whole study population
was 23.6 weeks, compared with 29.0 weeks for patients who received carboplatin. The reason for the superior outcomes is unclear, but the lower toxicity of carboplatin may contribute to improved survival.

The European Organization for Research and Treatment of Cancer (EORTC) compared the efficacy of etoposide plus carboplatin or cisplatin in a phase III trial of 239 patients with advanced-stage NSCLC [2, 83, 86-88]. Although the cisplatin regimen tended to have a higher response rate—objective response rate of 16% for carboplatin/etoposide versus 27% for cisplatin/etoposide (p = 0.07)—the survival durations were similar (i.e., 27 weeks versus 30, respectively) and the carboplatin/etoposide regimen was significantly less toxic. This led to fewer toxic deaths and a lower incidence and severity of leukopenia, ototoxicity, and nephrotoxicity for the carboplatin/etoposide combination. When combined with etoposide, carboplatin appeared to have activity similar to that of cisplatin in metastatic NSCLC and was better tolerated.

Carboplatin plus etoposide was also studied in several phase II trials (Table 5) [71, 89-91], highlighting the question of which agent(s) may have superior activity when added to carboplatin in two-drug combinations. Various trials have explored different drug combinations [92-95]. A number of dose-escalation studies are listed in Table 5 [96-98]. For both response rate and survival, the combination of paclitaxel and carboplatin appears to be as active as any other platinum-based regimen for metastatic NSCLC, yet toxicity is manageable.

### Locally Advanced Unresectable NSCLC

Historically, the standard of care for Stage IIIA and IIIB unresectable NSCLC has been radiotherapy, although it results in a median survival of only about 10 months. In recent years, cisplatin-based chemotherapy has been added to radiotherapy, extending the median survival by a few months [82]. The dose and fractionation schedules for radiation have also shifted from continuous or split-course therapy, which does not enhance long-term survival, to hyperfractionation, whereby a small dose of radiation is delivered continuously a few times per day up to standard cumulative dose limits [99]. Another strategy for treating nonresectable NSCLC disease is neoadjuvant therapy, in which patients are initially treated with chemotherapy (with or without radiotherapy) to stem

### Table 4. Median survival and response rate in NSCLC after chemotherapy in the ECOG trial EST 1583 [84]

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Median survival (wk)</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>VP</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>MVP/CAMP</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Carboplatin/MVP</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Iproplatin/MVP</td>
<td>26</td>
<td>6</td>
</tr>
</tbody>
</table>

| MVP  = Mitomycin/vinblastine/cisplatin; VP = vinblastine/cisplatin; CAMP = cyclophosphamide/doxorubicin/methotrexate/procarbazine; NSCLC = non-small cell lung cancer. |

### Table 5. Carboplatin-based trials in patients with metastatic NSCLC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonomi et al. [84]</td>
<td>699</td>
<td>MVP</td>
<td>20</td>
<td>23 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VP</td>
<td>13</td>
<td>25 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MVP/CAMP</td>
<td>13</td>
<td>25 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin/MVP</td>
<td>9</td>
<td>32 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iproplatin/MVP</td>
<td>6</td>
<td>26 wk</td>
</tr>
<tr>
<td>Sculier et al. [96]</td>
<td>121</td>
<td>Cisplatin</td>
<td>23</td>
<td>26 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin/carboplatin</td>
<td>22</td>
<td>28 wk</td>
</tr>
<tr>
<td>Klastersky et al. [87]</td>
<td>228</td>
<td>Cisplatin/etoposide</td>
<td>27</td>
<td>30 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin/etoposide</td>
<td>16</td>
<td>27 wk</td>
</tr>
<tr>
<td>Schiller [89]</td>
<td>25</td>
<td>Cisplatin/vinblastine/amifostine</td>
<td>64</td>
<td>17 mo</td>
</tr>
<tr>
<td>Frasci et al. [71]</td>
<td>39</td>
<td>Carboplatin/oral etoposide/G-CSF</td>
<td>38.5*</td>
<td>10 mo*</td>
</tr>
<tr>
<td>Hsieh et al. [91]</td>
<td>33</td>
<td>ICE</td>
<td>27.3</td>
<td>8 mo</td>
</tr>
<tr>
<td>Langer et al. [93–95]</td>
<td>53</td>
<td>Paclitaxel/carboplatin/G-CSF</td>
<td>62</td>
<td>12.5 mo</td>
</tr>
<tr>
<td>Belani et al. [97]</td>
<td>26</td>
<td>Paclitaxel/carboplatin/G-CSF</td>
<td>50</td>
<td>Not reported</td>
</tr>
<tr>
<td>Vafai et al. [98]</td>
<td>44</td>
<td>Paclitaxel/carboplatin</td>
<td>61</td>
<td>10</td>
</tr>
</tbody>
</table>

| NSCLC = non-small cell lung cancer; MVP = mitomycin/vinblastine/cisplatin; VP = vinblastine/cisplatin; CAMP = cyclophosphamide/doxorubicin/methotrexate/procarbazine; G-CSF = granulocyte colony-stimulating factor; ICE = ifosfamide/mesna/carboplatin/etoposide; AUC = area under the concentration-versus-time curve. There was a 66% response rate with an AUC of 8 and a 16.5-month median survival rate with an AUC of 4 to 8.1. |
local growth and make subsequent surgical resection possible. This is followed by an intensive radiotherapy program including prophylactic central nervous system irradiation. In clinical trials, neoadjuvant therapy has reduced tumor burden sufficiently to allow surgical resection in approximately 50% of patients [82].

Like cisplatin, carboplatin is an experimental radiosensitizer and has been incorporated as such into recent radiotherapy trials. In a phase III study, 100 patients were randomized to receive either conventional radiotherapy (60 Gy in six weeks), accelerated radiotherapy (60 Gy in three weeks), conventional radiotherapy plus carboplatin (350 mg/m² during weeks 1 and 5 of radiotherapy), or accelerated radiotherapy plus carboplatin (350 mg/m² during week 1 of radiotherapy) [100]. Although the toxicity in both radiotherapy/chemotherapy arms was considerably worse than with radiotherapy alone—more severe neutropenia, thrombocytopenia, and esophagitis—the median overall survival duration for the study was relatively long at 17.1 months [100].

Another randomized trial was conducted in 169 patients using hyperfractionated radiotherapy with carboplatin plus etoposide [101]. Patients were randomized to receive either hyperfractionated radiation alone consisting of 64.8 Gy in hyperfractionated doses of 1.2 Gy twice daily (group 1), hyperfractionated radiation plus 100 mg carboplatin on days 1 and 2 and 100 mg etoposide on days 1-3 weekly during radiotherapy (group 2), or hyperfractionated radiation plus 200 mg carboplatin on days 1 and 2 and 100 mg etoposide on days 1-5 of weeks 1, 3, and 5 during radiotherapy (group 3). Compared with radiation alone (group 1), concomitant radiotherapy and chemotherapy (group 2) produced a significantly longer median survival of 18 months ($p = 0.0027$). This compares with 8 months for radiation alone (group 1) and only 13 months for simultaneous plus sequential chemotherapy with radiation (group 3). Patients in group 2 also had a slightly higher local recurrence-free survival than patients in group 1, although the concomitant treatment was somewhat more toxic than radiation therapy alone.

In a phase II randomized trial, cisplatin (60 mg/m²) was compared with carboplatin (300 mg/m²), each in combination with etoposide (100 mg/m² on days 1-3) and epirubicin (50 mg/m² on day 1). Four courses of chemotherapy were alternated with three cycles of local irradiation (15 Gy per course, delivered in five consecutive daily fractions) [102]. Among the 53 patients, the response rates for the carboplatin (59%) and cisplatin (62%) arms were similar, but those who received carboplatin had less severe leukopenia and emesis. Thus, carboplatin alone or in combination with etoposide, when administered concurrently with radiotherapy, appears to be a promising strategy in the treatment of locally advanced unresectable NSCLC.

Given that paclitaxel is more active than etoposide in NSCLC and is also an experimental radiosensitizer [103], the efficacy of paclitaxel plus carboplatin also should be evaluated in this population. In fact, several feasibility studies recently established that carboplatin plus a three-hour infusion of paclitaxel and radiotherapy is highly active in terms of response rates, although it is still too early to determine whether including carboplatin provides an added survival benefit [104-109].

**Resectable NSCLC**

In the rare patients diagnosed with Stage I disease, surgical resection alone is curative in 60%-70% of patients, and radiation is reserved for those who do not undergo surgery; chemotherapy does not confer any advantage. For those with Stages II or III NSCLC, the effectiveness of radiation is questionable because even though radiation eliminates local recurrence, it has little effect on distant recurrence or survival. On the other hand, adjuvant chemotherapy has been shown to increase disease-free survival by approximately seven months and is particularly warranted in patients who have undergone incomplete resection. Evidence of the efficacy of neoadjuvant therapy—for reducing the size of the primary tumor, enhancing the resectability rate, and eliminating systemic micrometastases—is more preliminary, and more trials are currently under way to test this [82, 99, 110, 111].

Few studies have evaluated the role of carboplatin in Stages I-IIIA NSCLC, but in a phase II trial, carboplatin-based neoadjuvant therapy effectively reduced tumor size, allowing surgery in more than 50% of patients whose tumors were previously only marginally resectable [112, 113]. The extremely promising results with paclitaxel plus carboplatin in advanced disease support further evaluation of this combination in both the neoadjuvant and adjuvant setting.

**Small Cell Lung Cancer**

Small-cell lung cancer (SCLC) is an aggressive disease characterized by a rapid tumor growth rate and early dissemination. When treated by surgery alone or with radiation, the two-year survival of patients with limited disease is less than 10% and the median survival is approximately 12 months [114]. The prognosis for patients with extensive disease is even more dismal, with a median survival of less than three months [114-117]. A combined modality approach that incorporates chemotherapy has stretched the survival time, although for extensive disease, survival has not been prolonged beyond six to nine months [115, 116].

Chemotherapy is the cornerstone of treatment for limited SCLC, but it is still far from ideal, since most patients relapse and die within two years of diagnosis [2, 118, 119]. Some of the newer agents, including carboplatin, when used alone or...
in combination, have considerably improved outcomes in patients with limited disease [2].

Carboplatin is one of the most active single agents for SCLC, yielding objective response rates of 25%-35% [82, 118, 119]. Its high activity provided the rationale for its inclusion in combination chemotherapy regimens, and it has been studied extensively in combination with etoposide [120]. Table 6 lists various studies of carboplatin plus etoposide.

Carboplatin and etoposide also form the foundation for other chemotherapeutic combinations (e.g., ifosfamide, vincristine, epirubicin) [124, 125], but modest gains in survival appear to be offset by increased morbidity and mortality [125]. Although the three- and four-drug regimens have produced responses, they have not been directly compared in the same trial [82, 126], and thus the efficacy of increasing the number of drugs is not established [127].

Approximately two-thirds of all patients with SCLC have extensive disease. Unfortunately, this group is incurable with current therapy, and, therefore, the therapeutic goal is palliation with the possibility of a modest survival benefit. Numerous studies have shown that chemotherapy, with or without radiation, can temporarily ameliorate the predominant symptoms of extensive SCLC [127].

Etoposide is one of the drugs most commonly combined with carboplatin for patients with extensive disease (Table 6) [117]. Response rates can range from 59%-88%, and the median survival varies from 4.6 to 10.4 months [128-131]. In one randomized trial that compared carboplatin with cisplatin, both in combination with etoposide, the two groups had equivalent complete responses and median survival durations, although the carboplatin-containing regimen was considerably less toxic [130].

### Table 6. Carboplatin-based combination chemotherapy trials in patients with SCLC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment (mg/m²)</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carboplatin versus cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evans et al. [130]</strong></td>
<td>Carboplatin (300)/etoposide (100) ED = 32</td>
<td>56</td>
<td>34.7 wk</td>
<td></td>
</tr>
<tr>
<td><strong>Kosmidis et al. [121]</strong></td>
<td>Carboplatin (300) or cisplatin (50) days 1-2, plus etoposide (100) days 1-3 and radiation LD = 82</td>
<td>49 carboplatin 29 cisplatin</td>
<td>LD = 14.1 mo ED = 10.4 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Carboplatin plus etoposide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ellis et al. [128]</strong></td>
<td>Carboplatin (600)/etoposide (120) days 1-3 ED = 28</td>
<td>93</td>
<td>9 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Pfeiffer et al. [122]</strong></td>
<td>Carboplatin (300)/etoposide (240 orally) days 1-3 and radiation LD = 44</td>
<td>89</td>
<td>15 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Smith et al. [123]</strong></td>
<td>Carboplatin (300)/etoposide (100) days 1-3 and radiation ED = 28</td>
<td>82</td>
<td>9.5 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Viren et al. [129]</strong></td>
<td>Carboplatin (450)/etoposide (100) days 1-3 ED = 56</td>
<td>59</td>
<td>4.6 mo</td>
<td></td>
</tr>
<tr>
<td><strong>3- and 4-drug regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gridelli et al. [126]</strong></td>
<td>Carboplatin (300), etoposide (100) days 1-3, epirubicin (50) day 1 LD = 23</td>
<td>96.5</td>
<td>14 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Joss et al. [134]</strong></td>
<td>Carboplatin (80), teniposide (80), versus cisplatin (30) days 1-3, Adriamycin (40), etoposide (100) days 1-3, cyclophosphamide (1,000), methotrexate (10) days 14 and 17, vincristine (1.4) day 1, lomustine (40) ED = 59</td>
<td>carb/ten 29 standard 65</td>
<td>147 days 260 days</td>
<td></td>
</tr>
<tr>
<td><strong>Prendiville et al. [125]</strong></td>
<td>Carboplatin (300), etoposide (120) days 1-2 and (240 orally) day 3, ifosfamide (5), and mesna, vincristine (1.0) midcycle, and radiation LD = 73</td>
<td>81</td>
<td>16.6 mo</td>
<td></td>
</tr>
<tr>
<td><strong>Wolff et al. [131]</strong></td>
<td>Ifosfamide (5,000), mesna, carboplatin (300), etoposide (50 orally) days 1-21 ED = 35</td>
<td>83</td>
<td>8.8 mo</td>
<td></td>
</tr>
</tbody>
</table>

LD = limited disease; ED = extensive disease.
In an effort to improve the median survival, three- and four-drug regimens based on carboplatin/etoposide have also been tested [132, 133]. However, the optimal balance between response, toxicity, and subjective well-being requires further study [134].

Ovarian Cancer

Carboplatin is one of the key agents in first-line therapy for advanced ovarian cancer. In fact, during the last few years, two separate groups have endorsed its use for this indication. A consensus development conference on ovarian cancer held in 1994 by the National Institutes of Health confirmed the important activity of combination chemotherapy with carboplatin and cyclophosphamide, both for its effectiveness and its acceptable toxicity [135, 136]. The previous year, an international group of leading researchers on chemotherapy for ovarian cancer issued a consensus statement acknowledging that carboplatin-based combinations are the appropriate choice in patients with suboptimal Stage III and IV ovarian cancer [137]. Another group, the Advanced Ovarian Cancer Trialists Group initiated by the British Medical Research Council, which conducted a meta-analysis of 45 randomized clinical trials that included 8,139 ovarian cancer patients, came to a similar conclusion [138-140].

Carboplatin also offers cost advantages over cisplatin in the overall cost of delivering care. Because the second-generation analog carboplatin is more expensive, a comparative cost analysis study was performed on retrospective information derived from the medical records of 94 ovarian cancer patients included in a phase III clinical trial comparing carboplatin and cisplatin plus cyclophosphamide conducted by the Southwest Oncology Group (SWOG). The results revealed that in the long run, carboplatin is significantly more cost-effective than cisplatin [141]. Because of its greater toxicity, cisplatin incurred higher administration costs (e.g., hospitalization, hydration, antiemetics) and midcourse toxicity-related hospitalizations that together amounted to $2,882.40 for six cycles of chemotherapy compared with $1,074.53 for carboplatin. This $1,807.87 toxicity-related cost differential exceeds the $1,254 difference in acquisition costs (in 1988) for the two drugs—$4,140 for carboplatin versus $2,286 for cisplatin—such that carboplatin may cost about $550 less per patient.

Some of the earlier randomized phase III trials that compared single-agent carboplatin and cisplatin in ovarian cancer are shown in Table 7 [58, 142-145]. Together they demonstrate that there is no significant difference between the two drugs in overall response rate, complete response rate, or median survival. A meta-analysis of three trials that compared carboplatin 400 mg/m² with cisplatin 100 mg/m², comprising a total of 385 patients, also demonstrated no significant difference in the effectiveness of the two agents: complete response rates of 23% for carboplatin versus 22% for cisplatin, median durations of complete response of 30 months versus 24 months, median time to progression of 14 months for both groups, and median survival times of 22 months versus 23 months [146-148]. On the other hand, the two agents had markedly different toxicity profiles (Table 8). Although myelosuppression occurred more frequently in patients treated with carboplatin, the incidence of nonhematologic toxicities—peripheral neuropathy, ototoxicity, renal impairment, and emesis—were considerably lower with carboplatin than with cisplatin [148].

Several phase III clinical trials in ovarian cancer have compared carboplatin and cisplatin in combination with other chemotherapeutic agents (Table 7). The SWOG and the National Cancer Institute of Canada (NCIC) conducted two pivotal trials comparing carboplatin and cisplatin plus cyclophosphamide, which together led to the general acceptance of carboplatin/cyclophosphamide as standard therapy for patients with advanced ovarian cancer [147, 148]. In the SWOG study (SWOG-8412), 291 patients with Stage III or IV disease were randomized to receive six courses of chemotherapy with cyclophosphamide (600 mg/m²) plus either carboplatin (300 mg/m²) or cisplatin (100 mg/m²) [149-151]. In the NCIC study, which was almost identical in design, 417 patients with optimal or suboptimal advanced ovarian cancer were randomized to receive six courses of chemotherapy with cyclophosphamide (600 mg/m²) plus either carboplatin (300 mg/m²) or cisplatin (75 mg/m²) [152]. Both studies demonstrated that carboplatin/cyclophosphamide and cisplatin/cyclophosphamide were equally effective with respect to median survival, overall response rate, and time to progression. Both studies also highlighted the differences in toxicity between the two regimens (Table 9). Treatment with cisplatin/cyclophosphamide generally resulted in more severe platinum-related side effects, particularly renal impairment, neuropathy, and ototoxicity. On the other hand, patients treated with carboplatin/cyclophosphamide were more likely to experience hematologic toxicity, especially thrombocytopenia, infection, and hemorrhage [151, 153]. Several other phase III trials have also compared cisplatin and carboplatin in ovarian cancer [153-156].

New chemotherapeutic strategies also have been developed that include paclitaxel, since the Gynecologic Oncology Group (GOG) showed that cisplatin/paclitaxel is significantly more effective than cisplatin/cyclophosphamide [157]. In a phase III trial conducted by the GOG (GOG-111), patients with advanced ovarian cancer who were treated with cisplatin/paclitaxel had a significantly greater complete response (54% versus 33%), longer median progression-free survival duration (18.0 months versus 12.9 months), and
### Table 7. Phase III trials comparing carboplatin and cisplatin in ovarian cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment (mg/m²)</th>
<th>Number of patients</th>
<th>Response rate (%)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams et al. [142]</td>
<td>Carboplatin (400)</td>
<td>40</td>
<td>CR 20, PR 48</td>
<td>&gt;25 mo</td>
</tr>
<tr>
<td></td>
<td>Cisplatin (100)</td>
<td>40</td>
<td>CR 15, PR 33</td>
<td>18 mo</td>
</tr>
<tr>
<td>Pecorelli et al. [143]</td>
<td>Carboplatin (400)</td>
<td>82</td>
<td>CR 27, PR 31</td>
<td>&gt;15 mo</td>
</tr>
<tr>
<td>Mangioni et al. [144]</td>
<td>Cisplatin (100)</td>
<td>81</td>
<td>CR 25, PR 47</td>
<td>&gt;15 mo</td>
</tr>
<tr>
<td>Wiltshaw et al. [58]</td>
<td>Carboplatin (400)</td>
<td>40</td>
<td>CR 23, PR 30</td>
<td>16.4 mo</td>
</tr>
<tr>
<td>Taylor et al. [145]</td>
<td>Cisplatin (100)</td>
<td>50</td>
<td>CR 24, PR 40</td>
<td>16.4 mo</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson et al. [153]</td>
<td>Carboplatin (300)</td>
<td>17</td>
<td>CR 41, PR 12</td>
<td>24 mo</td>
</tr>
<tr>
<td>Gurney et al. [154]</td>
<td>Cisplatin (100)</td>
<td>14</td>
<td>CR 21, PR 57</td>
<td>19 mo</td>
</tr>
<tr>
<td></td>
<td>Iproplatin (240)</td>
<td>19</td>
<td>CR 21, PR 53</td>
<td>18 mo</td>
</tr>
<tr>
<td>Alberts et al. [148]</td>
<td>Carboplatin (300)</td>
<td>61</td>
<td>CR 33, PR 33</td>
<td>23 mo</td>
</tr>
<tr>
<td>Hannigan et al. [149]</td>
<td>Cisplatin (100)</td>
<td>62</td>
<td>CR 27, PR 29</td>
<td>17 mo</td>
</tr>
<tr>
<td>Swenerton et al. [152]</td>
<td>Carboplatin (300)</td>
<td>71</td>
<td>CR 27, PR 32</td>
<td>110 wk</td>
</tr>
<tr>
<td></td>
<td>Cisplatin (75)</td>
<td>75</td>
<td>CR 36, PR 21</td>
<td>100 wk</td>
</tr>
<tr>
<td>Chiara et al. [155]</td>
<td>Carboplatin (200)</td>
<td>76</td>
<td>CR 22, PR 43</td>
<td>23 mo</td>
</tr>
<tr>
<td>Conte et al. [156]</td>
<td>Cisplatin (50)</td>
<td>74</td>
<td>CR 36, PR 34</td>
<td>23 mo</td>
</tr>
</tbody>
</table>

CR = Complete response (complete disappearance of all known disease); PR = partial response (50% or greater reduction of lesion mass).

### Table 8. Comparative toxicity of single-agent carboplatin versus cisplatin in patients with advanced ovarian cancer (adapted from [147])

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Carboplatin % of patients with grade</th>
<th>Cisplatin % of patients with grade</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 3 4</td>
<td>2 3 4</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13 7 2</td>
<td>0 1 0</td>
<td>0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>27 3 0</td>
<td>18 0 0</td>
<td>0.001</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>26 8 0</td>
<td>15 3 0</td>
<td>0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>25 5 2</td>
<td>16 1 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td>% of total patients</td>
<td>% of total patients</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction (&lt;60 ml/min creatinine clearance)</td>
<td>25</td>
<td>44</td>
<td>0.001</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 17</td>
<td>17 17</td>
<td>0.001</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>2 13</td>
<td>13 13</td>
<td>0.001</td>
</tr>
<tr>
<td>Emesis (grades 2 and 3)</td>
<td>53 69</td>
<td>53 69</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Analysis of toxicity used World Health Organization criteria whenever applicable and was limited to myelosuppression, emesis, neurologic manifestations, and alterations in kidney and liver function tests in first-line chemotherapy.
longer median survival duration (37.5 months versus 24.4 months) than patients treated with cisplatin/cyclophosphamide (Table 10) [157, 158]. As a result, cisplatin/paclitaxel has replaced cisplatin/cyclophosphamide as standard therapy for advanced ovarian cancer [158-160].

Unfortunately, the neurotoxicity of combination therapy with cisplatin and paclitaxel can be unacceptably high. This was particularly evident in a recent study of paclitaxel 175 mg/m² (3-h infusion) plus cisplatin 75 mg/m², in which 16 (42%) of the 38 patients with gynecologic malignancies experienced grade 2 or higher peripheral neuropathy [161, 162]. This contrasts with the 13% incidence of grade 2 or higher peripheral neuropathy in GOG-111.

As a result, studies are now under way to compare the effectiveness and toxicity of carboplatin/paclitaxel with cisplatin/paclitaxel. An initial phase I/II dose-intensification study by the GOG showed that the maximum tolerated dose (MTD) of carboplatin, when used with paclitaxel, is targeted AUC of 7.5, and the MTD of paclitaxel is 175 mg/m² [79, 81, 163-165]. Among the 24 study participants with measurable disease, the overall response rate was 75%, the complete response rate was 67%, and the median survival time has not yet been reached after >60 weeks [81].

As the current platinum-based regimen of choice, paclitaxel plus carboplatin holds great promise in the treatment of ovarian cancer. A phase III study now being conducted by the GOG (GOG-158) is designed to compare the effectiveness of cisplatin or carboplatin combined with paclitaxel. In an effort to minimize the toxicity of cisplatin/paclitaxel, paclitaxel is delivered over a 24-h period. Ovarian cancer patients with optimal Stage III disease are randomized to receive either paclitaxel 175 mg/m² (3 h) plus carboplatin (AUC = 7.5) or paclitaxel 135 mg/m² (24 h) plus cisplatin 75 mg/m². When the results of GOG-158 are mature, they...
should provide a more complete picture of comparative outcomes with carboplatin/paclitaxel and cisplatin/paclitaxel.

Other Solid Tumors

Carboplatin has been used to treat several other solid tumors, both as a single agent and with other drugs, with varying degrees of success.

Germ Cell Tumors

In germ cell tumors, although carboplatin appears promising because of its low toxicity, recent data suggest that cisplatin is more effective [167]. In a randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in 598 patients with good-risk nonseminomatosus germ cell tumors, combination therapy based on cisplatin was superior to that based on carboplatin [167]. Because the cure rate in men with metastatic germ cell tumors is 70%-80%, studies have focused on patients with good-risk disease—those with the highest probability of a cure—in a search for ways to diminish treatment toxicity without sacrificing cure rate [2]. In one large randomized trial, the effectiveness of carboplatin (500 mg/m²) plus etoposide (100 mg/m² on days 1-5) was compared with that of cisplatin (20 mg/m² on days 1-5) plus etoposide in 265 patients [168, 169]. Despite equivalent complete response rates (88% for carboplatin versus 90% for cisplatin), responses were less durable in the carboplatin group, and event-free and relapse-free survival were inferior with the carboplatin combination. Although carboplatin may have been given at suboptimal doses because the AUC formula dosing was not used, cisplatin appears to be the platinum analog of choice for germ cell tumors [167].

Carboplatin also has been used as adjuvant therapy for germ cell tumors. In one study, a carboplatin AUC of 7 was administered along with radiation to 51 patients, and there were only two relapses during a five-year follow-up; both patients are currently in remission. Another 63 patients who were only two relapses during a five-year follow-up; both patients are currently in remission. Another 63 patients who were given two cycles of ICE (ifosfamide 2 gm/m², carboplatin 400 mg/m², and etoposide 20 mg/kg, for three days, plus mesna) plus hematopoietic support (bone marrow or peripheral stem cells or both). After a median follow-up of 45 months, nine patients (45%) remained alive and disease-free. The regimen was well tolerated, which is particularly important for this poor-prognosis population [170]. In the second study, prognostic variables for response and survival were retrospectively determined in 310 patients with poor-prognosis germ cell tumors who were treated with high-dose chemotherapy plus hematopoietic support. Adverse prognostic factors included progressive disease before high-dose chemotherapy, mediastinal nonseminomatous primary tumor, disease refractory to conventional-dose cisplatin, and greater than 1,000 U/l of chorionic gonadotropin before high-dose chemotherapy [171].

Bladder Cancer

In urothelial cancer, single-agent carboplatin produces only low response rates of approximately 15%. However, when combined with methotrexate, much higher response rates are attained (36%), toxicity is manageable, and median survival times exceed one year [172, 173]. Carboplatin at an AUC of 6 also has been combined with a 3-h infusion of paclitaxel in a phase I/II trial in patients with advanced bladder cancer [174]. The response rate was 50%, although the survival and response duration data are not yet mature. Thus, carboplatin-based combination chemotherapy—especially with paclitaxel—holds promise in the treatment of bladder cancer.

Head and Neck Cancer

Carboplatin also may have a role in treating head and neck cancer. The SWOG conducted a phase III trial comparing carboplatin/fluorouracil, cisplatin/fluorouracil, and methotrexate in the treatment of 277 patients with metastatic and recurrent head and neck cancer. The response rate for the carboplatin/fluorouracil was 21% versus 32% for cisplatin/fluorouracil and 10% for methotrexate. Nonetheless, all three regimens were equivalent with respect to median survival, which averaged five to six months [175, 176].

The concurrent use of chemotherapy and radiotherapy may improve outcomes in patients with head and neck cancer [177]. In a phase II trial in which single-agent carboplatin was administered with concurrent radiotherapy, a 66% complete remission rate and 98% overall response rate were achieved, and 53 of the 56 patients remained disease-free with a median survival of >25 months [178]. In a second phase II trial that compared single-agent carboplatin or cisplatin, each administered with radiotherapy, complete response rates and overall response rates were similar for both platinum agents, as were the estimated one- and two-year overall and disease-free survival rates. Clinical toxicities were significantly lower on the carboplatin arm. Carboplatin produced outcomes similar to those with cisplatin but with less toxicity, when combined with radiation therapy [179].

Paclitaxel also has shown activity in head and neck cancer and currently is being tested in combination with carboplatin [180]. In one phase II study, 11 patients were treated with radiotherapy plus paclitaxel (60 mg/m²) and carboplatin (AUC = 2) [181]. Despite the high toxicity, 10 patients responded (91% response rate), five of whom had a complete
response. Tolerance improved after carboplatin was reduced to AUC = 1. In another phase I dose-escalation study, the systemic exposure to carboplatin was held constant at AUC = 7.5, and a 3-h infusion of paclitaxel was increased from 150 mg/m² to 250 mg/m² in 21 patients [182]. The overall response rate was 62%, with 29% showing a complete response. Although the results are preliminary, carboplatin plus paclitaxel may prove advantageous in treating head and neck cancer.

Breast Cancer
Carboplatin also offers some advantages in the treatment of breast cancer. Although its use as a single agent with AUC dosing shows moderate activity in previously untreated patients, its inclusion with mitoxantrone, methotrexate, and vincristine (MIMOC) shows enhanced activity in advanced breast cancer. In a phase II trial of 51 patients with Stage IIIB and IV breast cancer, the objective response rate to the MIMOC combination was 60%, and the median time to disease progression was 12 months [183, 184]. Another active combination for advanced breast cancer is continuous infusion of carboplatin plus 5-fluorouracil and epirubicin. In a phase II study of 52 patients, the overall response rate was 81%, with a complete response rate of 17% in patients with metastatic disease and of 56% in patients with locally advanced disease [185]. Patients with metastatic breast cancer had a median survival time of 14 months, which is similar to outcomes for infusional therapy with cisplatin/fluorouracil/epirubicin [185], although carboplatin offered the advantage of reduced toxicity.

Cervical and Endometrial Cancer
In cervical cancer, cisplatin continues to be the primary platinum-containing analog used in treating advanced disease. However, carboplatin also has activity in endometrial cancer, producing objective response rates in 30%-35% of patients [186], and its favorable toxicity profile may make carboplatin superior to cisplatin for treating these older patients [2]. In a phase II study of 32 patients with advanced endometrial cancer conducted by the SWOG, carboplatin (400 mg/m²) yielded an overall response rate of 30%, with four of the responding patients remaining alive 839+ and 987+ days after starting treatment [187].

DISCUSSION
A large body of evidence suggests that carboplatin, when properly dosed, holds a key place at the forefront of first-line therapy for many solid tumors. Its role will likely be redefined in the coming years, as researchers replace BSA dosing with optimal AUC dosing. Despite the fact that results based on BSA dosing have negatively biased carboplatin performance, this drug appears equivalent in activity to cisplatin in most solid tumors and is more easily tolerated. As the results emerge from recent studies in which carboplatin is optimally dosed in combination with other active agents, such as paclitaxel, carboplatin may well prove to be more active than cisplatin in ovarian and lung cancer and at least equivalent to cisplatin in other tumor types. Germ cell tumors remain an exception and are most sensitive to cisplatin.

In combination with paclitaxel, carboplatin appears to have at least an additive cytotoxic effect. Because their toxicities are complementary, they can be administered together without exacerbating their individual toxicity profiles. This is often not possible with cisplatin, which has additive dose-limiting neuropathy. In contrast, paclitaxel appears to have a protective effect on thrombocytopenia, the normally dose-limiting toxicity of carboplatin. Furthermore, this highly active combination does not require the concomitant use of growth factors when paclitaxel is administered as a 3-h infusion. Thus, carboplatin/paclitaxel will likely displace other chemotherapeutic regimens for sensitive solid tumors, based on its activity, good tolerability, and potentially lower administration costs. Indeed, the combination of AUC-dosed carboplatin and 3-h infusions of paclitaxel may well become a standard chemotherapeutic regimen once large-scale phase III studies of its activity are completed in patients with advanced cancer of the ovary or lung. Further studies of carboplatin, in combination with newly approved cytotoxic agents, must be pursued to determine the future role of carboplatin in the treatment of solid malignancies.

REFERENCES


15 Markman M, Reichman B, Hakes T et al. Evidence supporting the superiority of intraperitoneal cisplatin compared to intraperitoneal carboplatin for salvage therapy of small-volume residual ovarian cancer. Gynecol Oncol 1993;50:100-104.


38 Aisner J, Belani CP, Kearns C et al. Feasibility and pharmacokinetics of paclitaxel, carboplatin, and concurrent radiotherapy...


52 Cornelison TL, Reed E. Nephrotoxicity and hydration management for cisplatin, carboplatin, and oxaliplatin. Gynecol Oncol 1993;50:147-158.

78 Elias AD, Ayash L, Tepler I et al. The use of G-CSF or GM-CSF mobilized peripheral blood progenitor cells (PBPC) alone or to augment marrow as hematologic support of single or multiple cycle high-dose chemotherapy. J Hematother 1993;2:377-382.


34 Optimizing Carboplatin for Solid Tumors


161 Markman M, Connely B, Kennedy A et al. Cisplatin (75 mg/m²) plus 3-hour infusional taxol (135 or 175 mg/m²): unexpected high incidence of peripheral neuropathy. Gynecol Oncol 1996;60:98-99.


186 Alberts DS, Garcia DJ. Salvage chemotherapy in recurrent or refractory squamous cell cancer of the uterine cervix. Semin Oncol 1994;21(suppl 7):37-46.