Is There a Role for Platinum Chemotherapy in the Treatment of Patients With Hormone-Refractory Prostate Cancer?

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Docetaxel chemotherapy is the current standard of care for metastatic hormone-refractory prostate cancer (HRPC). Platinum chemotherapy drugs, such as cisplatin and carboplatin, have moderate single-agent activity in HRPC. Next-generation platinum drugs, including satraplatin and oxaliplatin, may have additional activity in the management of HRPC. Furthermore, neuroendocrine differentiation may play a role in disease progression, providing a rationale for platinum-based chemotherapy in the management of HRPC. The authors reviewed the MEDLINE database for reports related to platinum-based chemotherapy in patients with advanced prostate cancer and evaluated studies that reviewed the role of neuroendocrine differentiation in the progression of HRPC. Older studies from the 1970s and 1980s suggested a lack of activity of cisplatin and carboplatin; however, those studies were flawed at least in part by their methods of response assessment. More recent Phase II studies of carboplatin suggested a moderate level of clinical and palliative activity when it was used as a single agent. However, when carboplatin was combined with a taxane and estramustine, high response rates were observed in several recent clinical trials. In addition, a randomized trial suggested that satraplatin plus prednisone improved progression-free survival compared with prednisone alone. For patients who progressed after docetaxel, no standard options existed in the literature that was reviewed. Several preliminary reports suggested that carboplatin and oxaliplatin may have activity as second-line chemotherapy. Platinum chemotherapy drugs historically have been considered inactive in HRPC, although a review of the data suggested otherwise. Carboplatin, in particular, induced very high response rates when it was combined with estramustine and a taxane, but it also appeared to have activity in patients who progressed after docetaxel. Satraplatin plus prednisone is being investigated in a large Phase III trial as second-line chemotherapy for HRPC. Targeting neuroendocrine cells may provide a new therapeutic approach to HRPC. Cancer 2007;109:477–86. © 2006 American Cancer Society.

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the early 1990s, it was reported that cytotoxic chemotherapy had dismal response rates of approximately 4% to 8%. However, recent studies of chemotherapy in HRPC have demonstrated greater evidence of benefit, both because of new drugs and because of changes in how activity is assessed in Phase II and III trials. For instance, reductions >50% in prostatic-specific antigen (PSA) levels correlated with improvements in pain and disease control and were associated with improvements in survival. In the middle 1990s, 2 groups of investigators demonstrated that mitoxantrone and corticosteroids had a palliative benefit compared with steroids alone in patients with HRPC. Consequently, mitoxantrone was approved for the palliative treatment of bone pain from metastatic prostate cancer.

Taxanes represented the next important milestone in the treatment of HRPC. Phase II trials of paclitaxel and docetaxel, with or without estramustine, demonstrated promising response rates. In 2004, 2 large, randomized, Phase III trials demonstrated for the first time a survival benefit to docetaxel-based chemotherapy in HRPC. In Southwest Oncology Group (SWOG) trial 9916, the regimen of docetaxel 60 mg/m² every 3 weeks plus estramustine 280 mg 3 times daily on Days 1 through 5 was compared with the regimen of mitoxantrone 12 mg/m² every 3 weeks plus prednisone 5 mg twice daily in patients with HRPC. In the TAX 327 study, 1006 patients with HRPC were randomized to 1 of 3 arms: docetaxel 75 mg/m² every 3 weeks for 10 cycles, docetaxel 30 mg/m² weekly (for 5 of 6 weeks) for 5 cycles, or mitoxantrone 12 mg/m² every 3 weeks for 10 cycles. All 3 groups received prednisone 5 mg twice daily. Together, those studies demonstrated a significant improvement in overall survival, time to disease progression, pain control, and PSA response with docetaxel-based chemotherapy given every 3 weeks compared with mitoxantrone. Because of those trials, docetaxel every 3 weeks with prednisone recently obtained approval from the U.S. Food and Drug Administration (FDA) as a standard, first-line chemotherapy regimen for patients with HRPC.

Despite such progress, the median survival benefit in each of those trials was between 2 months and 3 months, and survival remained disappointingly short. In addition, a significant proportion of patients did not benefit from docetaxel-based chemotherapy, notably those with measurable disease. In both SWOG 9916 and TAX 327, the proportions of patients with measurable disease who experienced at least a partial response were 17% and 12%, respectively, which was not statistically significantly better than mitoxantrone. Thus, opportunities clearly exist to improve the outcome of patients with HRPC who receive treatment with docetaxel-based chemotherapy.

Platinum drugs have a long history of use in many cancers, including prostate cancer. Although earlier studies suggested a lack of activity, more recent studies using palliation and PSA endpoints have suggested a greater degree of clinical benefit. In addition, several recent clinical trials have combined carboplatin with taxanes and demonstrated promising results. Finally, a new platinum analogue, satraplatin, has demonstrated intriguing activity in HRPC and is being tested in a large randomized study in the second-line chemotherapy setting.

The mechanisms by which advanced prostate cancer progresses from a hormone-sensitive state to a hormone-refractory state remain unclear. Many potential mechanisms have been proposed by which prostate cancer proliferates in the androgen-deprived environment, including amplification of the androgen receptor (AR) gene, increased AR protein stability with hypersensitivity to low androgen levels, and activation of mutant AR by different ligands. Growth factors and cytokines also may activate AR. Recently, neuroendocrine (NE) differentiation has been proposed as an important factor that contributes to the emergence of HRPC.

The link between the biology of NE differentiation in prostate cancer and the activity of platinum-based chemotherapy has been explored in at least 1 study. However, much remains to be understood about the extent to which NE differentiation contributes to a potential clinical subtype of cancer for which platinum drugs may have a role. Therefore, the objectives of the current study were to review the biology of NE differentiation in prostate cancer, to review trials that evaluated platinum as single agents or in combination, and to look to the future of platinum agents in the management of HRPC.

NE DIFFERENTIATION IN HRPC

The concept of NE differentiation of prostate cancer has caused confusion among clinicians and needs to be defined more clearly. Epithelial components of the normal prostate include luminal secretory cells, basal cells, and a third minor component of NE cells. NE cells are distributed widely in the normal prostate with only an occasional cell per gland or duct. In addition, NE cells are present in prostate cancer specimens. An uncommon scenario is one in which all cancer cells of the prostate show NE differentiation. These scenarios include small cell carcinoma and carcinoid tumor, both of which are observed rarely in the prostate. In a more general sense, NE differentiation of prostate cancer refers to the presence of scattered, individual NE cells or small nests of NE cells among the more abundant, non-NE secretory-type cancer cells in conventional adeno-
carcinomas. \footnote{48,49} According to the latter definition, nearly all adenocarcinomas of the prostate demonstrate some degree of NE differentiation. \footnote{20}

NE cancer cells, unlike non-NE, secretory-type cancer cells, do not express AR. \footnote{51} Consequently, although ADT induces apoptosis of the androgen-dependent, secretory-type cancer cells (which express AR), ADT actually may enrich for NE cancer cells, which appear to be postmitotic. Therefore, ADT cannot eliminate all cancer cells, and it generally is not considered curative. Furthermore, NE cells that survive in this androgen-deprived environment may establish paracrine networks to stimulate androgen-independent proliferation of the secretory-type cancer cells, leading to progressive HRPC.

Similarly, results from other studies suggest that ADT may induce NE differentiation and that NE differentiation contributes to the emergence of HRPC. \footnote{52–55} For instance, NE differentiation is increased in high-grade and high-stage localized tumors \footnote{48,56,57} and is increased even more in androgen-deprived \footnote{52} and hormone-refractory cancers. \footnote{53} In addition, it has been demonstrated that levels of circulating chromogranin A (CgA), which is a product of prostate NE cells, are higher in patients with prostate cancer than in patients with benign prostatic conditions. In patients with prostate cancer, CgA correlates with both clinical disease stage and the degree to which the cancer has become hormone refractory. \footnote{58} Positive immunohistochemical staining of tumor tissue for CgA is an independent predictor of cancer progression in well differentiated and moderately differentiated prostate cancers. \footnote{59} In patients with hormone-refractory disease, elevated serum CgA is a significant predictor of poor prognosis independent of serum PSA and other prognostic factors. \footnote{53,54,58,60–63} Finally, in a gene-expression profiling experiment of primary prostate cancers, Singh et al demonstrated that the gene for CgA is one of 5 genes that correlate strongly with Gleason score and that this 5-gene-expression model alone accurately predicted outcome after radical prostatectomy. \footnote{64}

The function of NE differentiation has been studied extensively. NE cells secrete biogenic amines, neuropeptides, and cytokines, \footnote{46} and the non-NE tumor cells express receptors for many NE cell products. \footnote{65–71} In vitro, some NE cell products stimulate the proliferation of prostate cancer cells. \footnote{47,56,72} For instance, interleukin 8 (IL-8), which is an angiogenic and mitogenic factor for many tumors, promotes androgen-independent proliferation of prostate cancer cells in vitro. \footnote{73} Tissue studies similarly have demonstrated that NE cells in prostate cancer produce IL-8 and that non-NE tumor cells express increased levels of the IL-8 receptor, CXCR1, \footnote{74} suggesting that NE differentiation may be one of the factors that contribute to the progression of prostate cancer in a paracrine fashion. \footnote{75–77}

In addition to cell culture and tissue studies, transgenic and xenograft mouse models have provided additional evidence for the significance of NE differentiation in prostate cancer. \footnote{78,79} In the CWR22 xenograft tumor model, there was a significant increase in the number of NE cells after castration that preceded the increase in tumor cell proliferation. \footnote{79} In the transgenic adenocarcinoma of the mouse prostate (TRAMP) tumor model, recurrent tumors after castration also were associated with increased NE differentiation. \footnote{78} LNCaP xenograft tumors normally do not survive in castrated hosts, but an allograft mouse NE tumor (NE-10) implanted on the opposite flank could support LNCaP xenograft tumor in castrated mice, providing strong evidence for the function of NE differentiation in androgen-independent proliferation of prostate cancer. \footnote{80} In an uncastrated host, the same NE cells appear to enhance migration and invasion of LNCaP tumor cells. \footnote{81}

Targeting NE cells in HRPC, thus, may provide a novel approach to the treatment of this disease. It is known that platinum has activity against epithelial cancers with NE differentiation. Together with etoposide or irinotecan, it generates the highest response rates in small cell lung cancer and is the established first-line treatment option for this disease. \footnote{82} Pure small cell carcinoma of the prostate is a rare disease, and its management generally is similar to that for other extrapulmonary small cell carcinomas. Because most patients with pure small cell prostate carcinoma present with metastatic disease at diagnosis, treatment usually consists of cisplatin and etoposide.

It is noteworthy that certain NE carcinomas, such as carcinoids, pancreatic islet cell tumors, and paragangliomas, generally are not sensitive to platinum agents. \footnote{83,84} In contrast to small cell carcinomas, this second group of tumors usually involves the gastrointestinal tract and generally has a more indolent clinical course, although this may be widely variable. Generally, somatostatin analogues and surgery represent the mainstay of treatment for such metastatic NE tumors, and chemotherapy drugs like streptozocin, dacarbazine, 5-fluorouracil, and doxorubicin demonstrate modest response rates. \footnote{83,84} A notable subset of patients with pancreatic endocrine or carcinoid tumors, however, will demonstrate an atypical presentation with numerous mitoses and areas of necrosis. Two trials of cisplatin and etoposide in 45 and 32 evaluable patients produced response rates of 67% and 53%, respectively. \footnote{85,86}

Whether there is a distinct clinical phenotype of a more NE-differentiated cancer remains unknown. Patients with poorly differentiated prostate cancers who are diagnosed later with unusual visceral metastases, such as hepatic or brain, are often assumed to have some component of NE differentiation but rarely
undergo biopsy. Lymph node metastases are more common, but it remains unclear whether there is greater NE differentiation in HRPC in these metastatic sites. In addition, patients with either low or no PSA production per volume of cancer also are considered to fit this phenotype. Clinical trials of prostate cancer sometimes exclude patients who have very low PSA values; thus, it is possible that the true efficacy of current drugs has been underestimated in clinical trials. If the importance of NE differentiation of prostate cancer is confirmed over time, then the use of chemotherapies that are targeted specifically against NE cells may be a reasonable, added option in the armamentarium for the treatment of prostate cancer, providing a rationale for combining platinum drugs with other drugs that are directed more specifically at the non-NE epithelial cancer cells.

**PLATINUM DRUGS AS FIRST-LINE CHEMOTHERAPY IN PROSTATE CANCER**

**Single-Agent Cisplatin and Carboplatin**

Platinum-based chemotherapy has been evaluated both as a single agent and in combination regimens for the treatment of HRPC (Table 1). In the pre-PSA era, most trials used cisplatin. In 1979, Yagoda et al treated 25 HRPC patients with 50 to 75 mg/m² of single-agent cisplatin every 3 weeks and reported a measurable partial response rate of 12%.87 When National Prostate Cancer Project criteria were used, 24% of patients achieved stable disease. In a subsequent study that used a lower dose of 50 mg/m² every 3 weeks, no responses were reported among 18 patients, and the investigators concluded that the regimen was not active.88 However, 4 contemporaneous studies that employed weekly cisplatin reported measurable response rates ranging from 10% to 43%.26,27,29,31 In a 1993 review article that summarized results from 209 patients who received cisplatin, Yagoda and Petrylak calculated an overall 12% partial response rate (95% confidence interval, 4–20%).4 However, closer examination of the 2 trials that evaluated every-3-week cisplatin suggests that the chemotherapy dose used was low and that patient selection likely influenced the activity level. For instance, in studies that used a higher dose (1 mg/kg per week) for 6 weeks, responses were reported in multiple soft tissue sites, including lymph nodes, liver, and lung, in addition to the more common site of bone.26,29

Carboplatin is second-generation platinum chemotherapy that has a toxicity profile distinct from cisplatin. The Eastern Cooperative Oncology Group (ECOG) treated 29 patients who had HRPC with doses of carboplatin ranging from 250 mg/m² to 400 mg/m² based on renal function and prior radiation.89 One of 5 patients (20%) who had bidimensionally measurable disease in that study had a partial response, 1 of 24 patients who had an abnormal bone scan had >50% regression in the number of sites with abnormal tracer uptake, and 3 of 24 patients experienced an improvement in their clinical status. In that trial, although the investigators concluded that carboplatin had no significant activity, the dose used was low by today’s standards and was not administered according to current area under the curve (AUC) methods. In addition, most of the patients in that study, in contrast to prior studies with cisplatin, had bone metastases and, thus, were not evaluable by the standard, cross-sectional imaging techniques that were available at the time.

In the post-PSA era, 4 clinical trials have been performed with weekly carboplatin, and all of those studies showed evidence of activity as measured by clinical ben-

**TABLE 1**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients</th>
<th>PSA response rate, %</th>
<th>Measurable response rate, %</th>
<th>Duration of response, median, mo</th>
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<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merrin, 197826</td>
<td>21</td>
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<td>54</td>
<td>—</td>
<td>31.4</td>
<td>7</td>
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<tr>
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<td>25</td>
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<td>12</td>
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<td>18</td>
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<td>29</td>
<td>—</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Carboplatin</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trump et al., 199089</td>
<td>29</td>
<td>—</td>
<td>20</td>
<td>3</td>
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<td>25</td>
<td>12</td>
<td>17</td>
<td>7</td>
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<td>27</td>
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</table>

PSA indicates prostate-specific antigen; NR, not reported.
efit, measurable response, or declines in PSA. Canobbio et al demonstrated that weekly carboplatin at a dose of 150 mg/m² allowed greater dose intensity compared with a schedule of every 3 or 4 weeks. Responses in that study represented a composite of both measurable and evaluable disease (using PSA and prostatic acid phosphatase) and were reported in 17% of patients. In another study, Miglietta et al used the same weekly schedule in 35 patients and reported that 10 patients (28%) had a decline in PSA, and the mean response duration was 6.6 months. In a third study by Jungi et al, 27 patients with HRPC received carboplatin at a dose of 400 mg/m² once every 28 days. Decreased pain, an improved performance status, and stabilization of metastases were observed in 13 patients, and the investigators reported a clinical benefit response rate of 48%. This included patients who demonstrated improvements in performance status, reductions in pain, and stable metastases. In addition, 2 of 24 evaluable patients (8%) in that study demonstrated a PSA response, although the investigators reported no clear association between clinical benefit and PSA response.

Castagneto et al recently reported a study at the 2006 Prostate Cancer Symposium in San Francisco. Twenty-seven patients with HRPC received carboplatin at a dose of 150 mg weekly for 3 of 4 weeks, and 26.9% of patients experienced a decline ≥50% in PSA after therapy. Hence, it appears that carboplatin has definite though moderate activity in HRPC, whether it is administered weekly or monthly and even when it is dosed by nonrenal methods. No recent trials of carboplatin alone have been reported using AUC dosing.

**Multiagent Regimens that Include Cisplatin and Carboplatin**

Earlier trials combined cisplatin with other drugs that were believed to be active in HRPC. For instance, in a Phase II trial of doxorubicin and cisplatin, significant improvements were demonstrated in prostatic acid phosphatase in 21% of patients, and clinical improvement was observed in 24% of patients. Additional trials have combined cisplatin with doxorubicin plus 5-flourouracil, with strontium-89 (89Sr), with etoposide plus pirarubicin, with mitoxantrone, with estramustine plus etoposide, and with calcitriol plus dexamethasone. Some regimens have been targeted specifically against small cell carcinoma, with cisplatin and etoposide as the core elements of the regimen. For instance, Papandreou et al treated 38 patients with metastatic pure or mixed small cell carcinoma of the prostate with doxorubicin, etoposide, and cisplatin and reported a 61% partial response rate. However, in that study, the addition of doxorubicin also increased toxicity significantly, and the regimen was not considered tolerable.

A randomized Phase III trial compared the radiopharmaceutical drug 89Sr alone or in combination with cisplatin in 70 patients with HRPC and painful bone metastases. Cisplatin was infused 3 times over 11 days up to a total dose of 50 mg/m² prior to and after 89Sr. Study endpoints were palliation of bone pain at 2 months, new onset of bone pain, progression of bone metastases, and survival. Pain improvement at 2 months was reported as 91% versus 63% favoring combination therapy. Progression of bone metastases was 64% in the combination arm versus 27% with radioisotope alone. There was no difference in new onset of painful bone lesions or survival.

In the past decade, docetaxel with or without estramustine became a platform on which other drugs were added, although recent randomized trials have questioned the role of estramustine. A series of contemporary clinical trials added carboplatin to a taxane (either docetaxel or paclitaxel) and estramustine in the management of HRPC (Table 2). Results have been encouraging in Phase II trials, with PSA declines ≥50% in 60% to 100% of patients and objective response rates from 45% to 65% in the subset of patients with measurable dis-

<table>
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<th>TABLE 2</th>
<th>Recent Trials of Estramustine, Carboplatin, and Taxane Chemotherapy</th>
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<tr>
<td>Author, year</td>
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</tr>
<tr>
<td>Kelly et al., 2001</td>
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</tr>
<tr>
<td>Urakami et al., 2002</td>
<td>II</td>
</tr>
<tr>
<td>Solit et al., 2003</td>
<td>II</td>
</tr>
<tr>
<td>Oh et al., 2003</td>
<td>II</td>
</tr>
<tr>
<td>Oh et al., 2005</td>
<td>I/II</td>
</tr>
<tr>
<td>Berry et al., 2006</td>
<td>II</td>
</tr>
<tr>
<td>Total</td>
<td></td>
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</tbody>
</table>

PSA indicates prostate-specific antigen.

* At the recommended Phase II dose, the PSA response rate was 75% in 12 patients, and measurable responses were observed in 2 of 5 patients (40%).

† Reported as a pooled endpoint of measurable and/or PSA response.
eases. The measurable response rate gives a further indication that carboplatin may have a role in the front-line management of certain patients with HRPC. Of course, care in interpreting these trials is needed, because these were small Phase II trials with highly selected patients, many of whom had a good performance status.

One of those Phase II trials was a multicenter trial conducted by the Cancer and Leukemia Group B evaluating the activity of estramustine, docetaxel, and carboplatin in patients with metastatic HRPC. The regimen included 5 days of estramustine, docetaxel at 70 mg/m², and carboplatin AUC (5) administered every 3 weeks. Because of the myelosuppression associated with this combination, prophylactic granulocyte-colony stimulating factor was used in all patients. Forty patients were enrolled and received a median of 7 cycles of chemotherapy. PSA declines >50% were noted in 68% of evaluable patients, whereas measurable responses were noted in 52% of the 21 patients with measurable disease, including 1 patient who had a complete measurable response to therapy. Grade 3 or 4 toxicity was uncommon and included neutropenia in 23% of patients, thrombocytopenia in 13% of patients, and fatigue in 13% of patients. Febrile neutropenia occurred only in 1 patient (3%). The median time to progression was 8.1 months, and overall survival was 19 months. Although the regimen seemed promising and was tolerated reasonably well, it remains unclear from this and other Phase II trials the extent to which carboplatin enhances the efficacy of docetaxel and estramustine. No Phase III trials currently are ongoing to determine whether carboplatin enhances response or survival when it is added to docetaxel used as first-line chemotherapy.

**Novel Platinum Drugs Including Satraplatin**

Newer formulations of platinum drugs are in clinical development for the management of HRPC and other cancers. An excellent recent review has been published that summarizes newer platinum compounds and the different strategies to improve platinum formulations. Satraplatin and oxaliplatin represent 2 drugs that are based on novel structures with altered, stable ligands and demonstrate activity in cisplatin-resistant cancers. Both react with DNA at the same sites as cisplatin and carboplatin, but they form DNA adducts that have different chemical structures.

Satraplatin is the first orally available platinum drug that has shown cytotoxic activity in vitro in cisplatin-resistant cell lines. A planned Phase III trial of satraplatin plus prednisone versus prednisone alone was initiated several years ago by the European Organization for Research and Treatment of Cancer but was stopped early because of withdrawal of support from the sponsor. However, 50 patients had been enrolled at the time of study closure. An intriguing report on the clinical outcomes of those 50 patients suggested a significant benefit in progression-free survival that attained statistical significance. On the basis of these promising data and the lack of cross-resistance with other chemotherapy drugs typically used in this setting, a large, randomized Phase III trial was initiated with satraplatin as second-line chemotherapy, as noted below.

Oxaliplatin is a newer platinum agent that has a more favorable toxicity profile and evidence of activity in cisplatin-resistant cell lines. Droz et al performed a multicenter Phase II trial in 54 patients with metastatic HRPC who were randomized to receive oxaliplatin either alone or with 5-fluorouracil. Greater than 50% of those patients had received prior chemotherapy, including some who received cisplatin (although none had received prior docetaxel or paclitaxel). Despite such heavy pretreatment, PSA declines were noted in 11% and 19% of patients in each arm. Hematologic toxicity was mild to moderate, and single-agent oxaliplatin, in particular, was well tolerated.

Other platinum-based chemotherapy drugs have been studied in patients with metastatic cancer. ZD-0473 is a novel platinum compound that has demonstrated activity in cisplatin-resistant ovarian and lung cancer cell lines. Modest response rates have been reported in patients with platinum-resistant ovarian and small cell lung cancers. Lobaplatin is another novel platinum compound that appears to have some activity in cisplatin-resistant cancer cell lines.

An alternative method for improving the efficacy of platinum drugs is to improve delivery of the drug to the tumor itself. One approach is to incorporate the agent into a liposome, whereas another approach is to attach the active agent to an inert compound. Two liposomal platinum drugs in development are aroplatin and SPI-77. Like other novel platinum agents, both liposomal formulations have shown activity in cisplatin-resistant cell lines and are in clinical development. Early-phase trials have demonstrated minimal myelosuppression, although efficacy studies are ongoing. Two platinum polymers in clinical development include AP-5280 and AP-5346. AP-5280 is platinum complex linked to a polymer compound and has been evaluated in a Phase I trial. The polymer conjugate appears to decrease clearance of drug in plasma, but it did not appear to enhance toxicity.

**PLATINUM DRUGS AS SALVAGE CHEMOTHERAPY FOR HRPC**

At the time of disease progression after first-line chemotherapy with docetaxel and prednisone, there is no sec-
ond-line regimen that is considered a single standard of care.
In the absence of a clinical trial in the second-line setting, mito-
xantrone and prednisone after failure on docetaxel, and vice versa, has been considered a reason-
able choice. However, several recent reports describing the response to second-line mito-
xantrone chemotherapy have suggested that overall activity is modest and ranges from 5% to 15% using PSA declines of ≥50% as the primary endpoint. Other cytotoxic agents have been used, including vinorelbine, etoposide, doxorubicin, estramustine, and cyclophosphamide. Data supporting their use remain limited or nonexistent, but expected response rates are from <10% to 20%, and response duration is likely to be short. Other nonresearch options for this patient population include radiopharmaceuticals, further second-line hormone manipulation, and supportive care only.

In this environment of limited choices, patient participa-
tion in clinical trials remains a priority. Nonetheless, some patients are unable or unwilling to enroll in a cli-
nical trial. In this context, we treated 4 consecutive patients who had not responded to or progressed on taxane-
based chemotherapy and noted what appeared to be greater than expected responses to docetaxel plus low-
dose carboplatin chemotherapy. Treatment consisted of docetaxel at a dose of 60 mg/m² to 70 mg/m² and car-
boblatin AUC (4 or 5) every 3 weeks. All 4 patients experi-
cenced declines >50% in PSA and survived another 4.5 to 12 months after starting this regimen.

Because of these observations, we initiated a pro-
spective, multicenter clinical trial of docetaxel 60 mg/
m² and carboplatin AUC (4) every 3 weeks in patients who progressed on prior docetaxel chemotherapy. Patients were required to have received ≥2 cycles of docetaxel and demonstrated PSA or clinical progression of disease while on treatment or within 45 days of their last dose. Final analysis of that trial will attempt to cor-
relate response to serum markers of NE differen-
tiation, including CgA and neuron-specific enolase.

Satraplatin is being investigated as second-line che-
motherapy in a Phase III, international, randomized trial called Satraplatin and Prednisone Against Refrac-
tory Cancer (SPARC). In total, 912 patients have been 
randomized at a 2:1 ratio to receive satraplatin plus prednisone versus prednisone alone. The primary end-
point is time to progression using a composite endpoint, and secondary endpoints include overall survival and time to pain progression. It is noteworthy that patients are not required to have received docetaxel as first-line chemotherapy, because this trial was initiated prior to FDA approval of docetaxel for this indication.

In September 2006, preliminary results of SPARC were released and suggested a 40% reduction in the risk of disease progression in the satraplatin-treated group compared with the control group. A notably better progression-free survival was observed in the satraplatin arm and was highly statistically significant (P < .00001). Benefit was reported whether or not patients had received prior docetaxel, and toxicity was considered mild to moderate. Final data are pending.

**CONCLUSIONS**

Platinum chemotherapy has been used for many de-
cades for many cancers and has demonstrated clear ben-
efit in the palliative and/or curative treatment of diseases like testicular, ovarian, and lung cancers. Its ac-
tivity in prostate cancer has been a subject of uncer-
tainty. Early reports from the 1980s and early 1990s suggested that cisplatin and carboplatin had no mean-
ingful clinical activity. However, those trials were con-
ducted in the pre-PSA era and used ineffective methods for determining response, particularly in patients w ho had prostate cancer that involved bone. In the middle 1990s, results from several small trials suggested that carboplatin provided some palliative benefit and in-
duced declines in PSA comparable to other active agents in this disease, such as mitoxantrone and vinorelbine. Based on a belief that carboplatin offered some additional benefit, at least 6 clinical trials involving 272 patients added carboplatin to estramustine and a taxane have been reported in the past 7 years and showed high response rates. The question that has not been answered is whether and the degree to which carbopla-
tin actually improves progression-free or overall survival in patients with HRPC.

So, is there a role of platinum chemotherapy in the management of HRPC? We believe that there is a body of evidence to support the use of platinum drugs in patients with prostate cancer. In patients with advanced pure or predominant small cell cancers of the prostate, cisplatin-based regimens represent the standard of care. In more typical patients with HRPC who have progres-
sive, metastatic disease, docetaxel chemotherapy repre-
sents the current standard of care. Although combi-
inations of docetaxel with carboplatin have shown promising activity in the initial chemotherapeutic man-
agement of HRPC, such combinations have not de-
monstrated a clear additional benefit in this situation. However, in the second-line chemotherapeutic man-
agement of HRPC, there is no accepted standard of care, and carboplatin may have clinically relevant activity in this setting. An ongoing Phase III trial of the novel platinum satraplatin will be reported soon in the sec-
ond-line chemotherapy setting.

Because we recognize that a specific subtype of patients with HRPC may benefit more from platinum agents than others, ongoing efforts will help to clarify
these distinct phenotypes. Currently, we are conducting a pooled analysis of the Phase II trials of taxanes with estramustine and carboplatin to assess whether specific subgroups are more likely to respond to these regimens. We also are completing the trial mentioned above in which we are attempting to correlate response to docetaxel plus carboplatin with serum markers of NE differentiation.

REFERENCES

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