

## REVIEWS

# Cisplatin and solid tumors: Still working, after all these years

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Cisplatin, like many anti antineoplastic agents, has a rich and interesting history. It was first discovered in 1845 by Dr. Michele Peyrone and given the full chemical name cis-diamminedichloroplatinum (II), also called cis-DDP, though at the time of its discovery was called 'Peyrone's salt' <sup>[1]</sup>. The discovery <sup>[2]</sup> of its cellular toxic effects was not until more than a century later in experiments with bacteria using platinum electrodes to study the effects of bacterial growth in an electrical field. Growth was noted to be stunted, with bacteria left alive, but not replicating. After two years, cisplatin was discovered to be similar to the compounds used in the electrodes and capable of stopping cell growth. This gave rise to experiments in animals testing the antineoplastic properties of cisplatin and eventually to human trials. Phase I trials began in 1971 and the drug was FDA approved for use in 1978 <sup>[3]</sup>. Cisplatin is the prototype of the chemotherapy class of platinum drugs that include carboplatin and oxaliplatin. They cause cell death by binding to DNA to form DNA adducts, preventing further replication <sup>[4]</sup>.

## Side effects

Among other side effects, the emetogenicity of cisplatin is legendary. It has been used as the prototype for high-risk emetic chemotherapeutic drugs in the development of modern anti-emetics. Without prophylaxis, cisplatin administration will cause emesis in more than 90% of patients <sup>[5]</sup>. Now, with the use of more modern antiemetics, including neurokinin-1 (NK-1) antagonists, selective type three 5 hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists and steroids, 90% of patients treated with high dose cisplatin do not experience acute emesis and 80% of patients avoid delayed emesis as well <sup>[6]</sup>. Guidelines <sup>[7]</sup> recommend the combination of a 5-HT<sub>3</sub> receptor antagonist, an NK-1 antagonist and dexamethasone given on day one to prevent acute emesis and days 2-4 for delayed emesis. Dosing of dexamethasone is dependent on whether an NK-1 antagonist is given. If an NK-1 antagonist is used, dexamethasone is recommended at 12 mg on day one and 8 mg on days 2-4. If an NK-1 antagonist is not used, dexamethasone 20mg is given on day one and 8 mg twice per day on days 2-4.

Cisplatin is associated with hair thinning, rather than complete alopecia. One of the major and dose limiting toxicities of cisplatin is nephrotoxicity. It is related to dose and may worsen with subsequent dosing. Approximately 30% of patients treated with a cisplatin dose of 50mg/m<sup>2</sup> or higher will see some decrease in their renal function <sup>[8]</sup>. Damage is done on the tubular level and is associated with electrolyte wasting. Administration of cisplatin is therefore done with the use of intravenous saline and diuretics, most commonly mannitol or furosemide. Electrolyte monitoring and repletion is also recommended. As with other cytotoxic agents, myelosuppression is seen, affecting all three cell lines and can be dose limiting. With cumulative doses of cisplatin, a peripheral neuropathy can develop, which can be irreversible. Anaphylactic type reactions, which are a class effect, have also been described. Hearing loss is a well-known side effect of cisplatin and

tends to affect hearing in the high frequency range. It affects about one third of patients and may be more pronounced in children <sup>[9]</sup>.

## Lung cancer

Lung cancer is the leading cause of cancer related mortality in the United States <sup>[10]</sup> and though many treatment advances have been made, cisplatin remains an integral part of the oncologic treatment of lung cancer. In non-small cell lung cancer (NSCLC), postoperative cisplatin based chemotherapy has been shown to improve survival compared with observation in several randomized trials as well as a meta-analysis <sup>[11]</sup>. In the meta-analysis, at five years, there was an absolute survival benefit of 5.4% in the patients that were treated with chemotherapy corresponding to a hazard ratio of death of 0.89 (95% CI, 0.82 to 0.96,  $P=0.005$ ). The trials included in this meta-analysis paired cisplatin with various other cytotoxic agents including vinorelbine, etoposide, vindesine, mitomycin and vinblastine. National Comprehensive Cancer Network (NCCN) guidelines recommend cisplatin based therapy in the adjuvant setting, with carboplatin and paclitaxel recommended for use in patients whose comorbidities preclude the use of cisplatin <sup>[12]</sup>.

Locally advanced and stage III NSCLC is characterized by local invasion and/or mediastinal node involvement. Combined chemotherapy and radiation is the treatment of choice for such patients with or without surgery <sup>[13]</sup>. NCCN guidelines recommend cisplatin based therapy as “preferred” for the use of concurrent chemotherapy and radiation in this setting <sup>[14]</sup>. Clinical trials are now addressing whether other full dose platinum based regimens have similar outcomes.

In patients with stage IV NSCLC, chemotherapy is the treatment of choice, as it offers both palliative benefit, as well as a modest survival benefit. In this setting, several cisplatin and carboplatin based regimens have been shown to be comparable in efficacy, though differ with respect to side effects <sup>[15]</sup>. In the Eastern Cooperative Oncology Group (ECOG) 1594 trial, cisplatin plus gemcitabine, cisplatin plus docetaxel, cisplatin plus paclitaxel and carboplatin plus paclitaxel were compared. There was no difference in overall survival, though cisplatin and gemcitabine had the longest median time to progression of 4.2 months (95% CI, 3.7-4.8,  $P=0.001$  compared with cisplatin and paclitaxel). However, a significantly higher number of patients withdrew from the study because of toxic effects in the cisplatin and gemcitabine group (27% vs. 15%,  $P<0.001$  compared with cisplatin and paclitaxel). Citing the lack of overall survival benefit between the regimens and the toxicity profile, ECOG chose carboplatin and paclitaxel to be their reference regimen for future studies. Cisplatin however, remains in use in the metastatic setting and is the more commonly used regimen in European based studies.

Small cell lung cancer represents approximately 15% of lung cancers. Disease that can be adequately treated with radiation is optimally treated in a combined modality fashion with chemotherapy with cisplatin being the treatment of choice when radiation is used <sup>[16,17]</sup>. In extensive or metastatic disease, platinum based therapy remains the standard of care, though both cisplatin and carboplatin are considered acceptable choices. Small cell carcinoma can present in extrapulmonary sites such as the gastrointestinal tract prostate among others and treatment is similar to small cell carcinoma of the lung.

## Mesothelioma

Malignant mesothelioma is an unusual, but often devastating cancer involving the covering or serosal surfaces of the lung as well as in the abdomen. Exposure to asbestos predisposes to this type of cancer by a number of potential mechanisms including that of irritation and pleural reaction that can become malignant, DNA damage, an increase in oxidative factors that can induce DNA damage and activation of cellular growth pathways <sup>[18]</sup>. Patients often present with a pleural effusion as well as shortness of breath or chest pain. Treatment with extensive surgery represents the only option for cure. Chemotherapy is the mainstay of treatment for more advanced disease, or, in some centers as part of trimodality therapy to increase the chances of cure. Neoadjuvant chemotherapy often consists of the active doublet of cisplatin plus pemetrexed for four cycles prior to surgery, which has yielded a response rate of 32.5% in a phase II study involving several major mesothelioma centers. Patients who were fit and able then went on to extra-pleural pneumonectomy followed by radiation. In this series, median survival was 16.8 months for all patients, but 29.1 months in patients who were able to complete all

of the therapy <sup>[19]</sup>. For inoperable patients, chemotherapy is the treatment of choice, though goals are palliative. The combination of cisplatin and pemetrexed has been shown to be superior to cisplatin alone and is considered the standard of care in this setting. In this trial, 456 patients were randomized to cisplatin alone versus the combination. The combination arm was associated with a response rate of 41.3% in the combination arm versus 16.7 in the control arm ( $P < 0.0001$ ) and a better median survival of 12.1 months vs. 9.3 months ( $P = 0.020$ , HR 0.77).

## Bladder cancer

Most bladder cancers are transitional cell carcinoma histology. Localized disease is often managed with transurethral resection with or without intravesicular therapy <sup>[20]</sup>. When the disease invades into the muscularis layer of the bladder, the risk of recurrence and distant metastases is significant. In patients with muscle invasive or more extensive disease, consideration is given to neoadjuvant treatment with a cisplatin based regimen prior to cystectomy <sup>[21]</sup>. In patients with T3 disease (invasion into the perivesicular tissues), it is strongly recommended. In a phase III study of surgery alone for T2-T4a bladder cancer compared with neoadjuvant therapy with methotrexate, vinblastine, adriamycin and cisplatin (MVAC), the use of chemotherapy was found to be associated with higher percent of patients with no residual cancer at the time of resection (38% vs. 15,  $P < 0.001$ ) and a longer median survival (77 months vs. 46,  $P = 0.06$ ) compared with surgery alone <sup>[22]</sup>.

The MVAC regimen can be challenging for patients in terms of tolerability and toxicity. Cisplatin and gemcitabine have emerged as a comparable regimen, particularly in the setting of inoperable or metastatic disease based on a large phase III study comparing the two regimens. In this study, 405 patients with at least T4, N2 or M1 disease were randomized to cisplatin plus gemcitabine or MVAC for a maximum of six cycles. The regimens were found to be comparable with five year progression free survival rates of 9.8% in the cisplatin/gemcitabine arm compared with 11.3%, in the MVAC arm ( $P = 0.63$ ) and in terms of overall survival at five years (13.0 vs. 15.3,  $P = 0.53$ ) <sup>[23]</sup>. Cisplatin and gemcitabine was found to be less toxic with decreased rates of grades 3 or 4 neutropenia, febrile neutropenia, neutropenic sepsis and mucositis <sup>[24]</sup>. With comparable efficacy and similar outcomes, cisplatin plus gemcitabine has become the standard of care in advanced or metastatic bladder cancer and is also used as neoadjuvant therapy.

The administration of the MVAC regimen in a high dose (HD) fashion has resulted in less toxicity and equivalent, if not better outcomes compared with standard dosing in patients with advanced or metastatic transitional cell cancer <sup>[25]</sup>. The HD-MVAC regimen had better progression free survival compared with standard MVAC (9.1 months vs. 8.2 months,  $P = 0.037$ ; HR 0.75; 95% CI 0.58-0.98), but no significant difference in overall survival. HD-MVAC includes the use of growth factor as part of the regimen and was also found to be less toxic than classic MVAC. Neutropenia and neutropenic fever was less common with HD-MVAC, as was mucositis.

## Testicular cancer

Cisplatin is an integral part of the treatment for both seminomatous and non seminomatous germ cell tumors. It is used as post-operative therapy in more advanced germ cell tumors generally either in combination with etoposide alone for 4 cycles or with bleomycin and etoposide for 3 cycles <sup>[26,27]</sup>. Early studies tried the substitution of carboplatin for cisplatin, but in one larger series, 265 patients with good risk germ cell tumors were randomized to receive 4 cycles of cisplatin plus etoposide or carboplatin plus etoposide. Overall survival was not different, but the carboplatin group was associated with a decreased event free and relapse free survival <sup>[28]</sup>. Testicular cancer remains a highly curable disease and cisplatin is an integral part of the therapy, particularly in more advanced stages.

## Head and neck cancer

Cancers of the head and neck are treated with a multidisciplinary approach and depending on the tumor location and stage, may be treated with surgery, radiation, chemotherapy, or any combination of those modalities. For locally advanced disease that is not amenable to surgical resection, there are two approaches: Induction chemotherapy followed by

combined chemotherapy and radiation or combined chemotherapy and radiation from the start. The two approaches have not been directly compared and the choice of regimen may be institutional preference or tumor bulk. For both approaches, cisplatin is an integral part of the chemotherapy regimen. In one of the pivotal trials of the use of induction therapy by Posner et al<sup>[29]</sup>, 501 patients were randomized to the regimen of docetaxel, cisplatin and fluorouracil (TPF) or cisplatin and fluorouracil (PF). The TPF arm had significantly longer median survival (71 months vs. 30 months,  $P = 0.006$ ) and better locoregional control. It was also associated with increased rates of hematologic toxicity and febrile neutropenia, while non-hematologic toxicity was similar, with the exception of fatigue, which was higher in the PF group.

Combined therapy with the use of cisplatin as upfront and definitive therapy has been shown to be superior to radiation alone. In one series<sup>[30]</sup> of 295 patients, the use of cisplatin was associated with an improvement in the projected 3 year survival of 23% in the radiation alone arm compared with 37% with the addition of cisplatin concurrent with radiation ( $P = 0.14$ ). The addition of infusional 5-FU did not offer significant advantage over cisplatin alone. NCCN guidelines recommend the use of cisplatin therapy as the preferred (and category 1) recommendation for the use of concurrent chemotherapy for definitive primary therapy and for post-operative chemoradiation<sup>[31]</sup>.

## Esophageal cancer

Early stage esophageal cancer is treated with surgery or local ablation. However, the majority of patients present with more advanced cancer. In higher stage disease, starting with T2 disease (cancer that invades into the muscularis layer), consideration is given to preoperative chemoradiation, chemotherapy alone or definitive chemoradiation<sup>[32]</sup>. Though it has been challenging to study in a large phase III study, smaller series have shown a survival benefit to the use of preoperative chemoradiation for more advanced esophageal cancer. In one series<sup>[33]</sup> of 56 patients randomized to chemoradiation followed by surgery or surgery alone, survival was 39% at five years for the combined treatment group, compared with 16% for the surgery alone group. The chemotherapy regimen used in this study was a standard regimen of cisplatin at 100mg/m<sup>2</sup> d given on days 1 and 29 with infusional 5 FU given on days 1-4 and 29-32 starting with radiation therapy. Several different regimens are used in the preoperative setting as well as with definitive chemoradiation, though cisplatin remains a category 1 recommendation in this group in the NCCN guidelines.

## Gastric cancer

Many distal esophageal cancers and cancers found at the esophagogastric (GE) junction are treated as gastric cancers and many clinical trials include such tumor types in gastric cancer trials. Early stage gastric cancer may be treated with endoscopic resection or surgery, but tumors that have invaded through at least the muscularis propria (T2) or are node positive warrant further discussion for therapy in addition to surgery, or in the case of metastatic disease, for systemic therapy<sup>[34]</sup>. For resectable tumors, several approaches have been tried; though have not been compared directly. One approach, primarily studied in Europe uses neoadjuvant chemotherapy with the so called ECF regimen (epirubicin, cisplatin and 5-FU). In the pivotal trial of this approach<sup>[35]</sup>, 503 patients were randomized to either perioperative chemotherapy and surgery or surgery alone. In the group randomized to chemotherapy, three cycles of ECF was given preoperatively and postoperatively. Surgical complications and 30 day mortality was similar in the two groups. Survival was improved in the group randomized to chemotherapy with a hazard ratio for death of 0.75 (95% CI, 0.60 to 0.93;  $P = 0.009$ ) and a five year survival rate of 36% vs. 23%. Another approach is upfront surgery followed by 5FU based chemotherapy and chemoradiation. This approach has recently been compared to a course incorporating the ECF regimen. In a small single arm study, 54 patients with resected adenocarcinoma of the stomach or esophagogastric cancer were treated with one cycle of ECF followed by chemotherapy and radiation with 5FU followed by two cycles of ECF. Febrile neutropenia was seen in 7.4% of participants and grade 3 or 4 toxicity gastrointestinal toxicity was seen in 28%. At three years, 61.9% of patients were alive. This approach was tested in Cancer and Leukemia Group B (CALGB) study 80101 comparing the addition of ECF to a 5FU based postoperative regimen<sup>[36]</sup>. In this study, patients with gastric or GE junction tumors were randomized to 5FU given for one cycle followed by administration with concurrent radiation therapy followed by two additional cycles of 5FU alone. This standard regimen was compared with a course of ECF given for one cycle followed by 5FU concurrent with radiation followed by two dose reduced cycles of ECF. Overall toxicities favored

the ECF arm, with grade 4 toxicity seen in 40% of patients in the 5FU arm compared with 26% in the ECF containing arm ( $P < 0.001$ ). Survival was comparable with median overall survival of 37 months in the 5FU arm compared with 38 months in the ECF containing arm (HR 1.03; 95% CI, 0.80-1.34;  $P = 0.80$ ).

## Biliary tract cancer

Biliary tract cancers include gall bladder cancer, cholangiocarcinoma and ampullary carcinoma. Historically, biliary tract cancer has been treated with gemcitabine or 5FU based regimens with no clear standard of care. That changed when a randomized phase III trial by the ABC-02 investigators<sup>[37]</sup> found that the combination of cisplatin and gemcitabine improved outcomes over gemcitabine alone. In this study, 410 patients were randomized to cisplatin 25mg/m<sup>2</sup> and gemcitabine 1000mg/m<sup>2</sup> given on days 1 and 8 of a 3 week cycle or gemcitabine alone at 1000mg/m<sup>2</sup> given on days 1, 8, and 15 every four weeks. Toxicity was similar with the exception of more neutropenia in the combined therapy arm, though no difference in neutropenic infections was noted. Median overall survival was better in the combined therapy arm: 11.7 months in the combined therapy group compared with 8.1 months in the gemcitabine alone arm (HR, 0.64; 95% CI, 0.52 to 0.80;  $P < 0.001$ ).

## Ovarian cancer

The use of cisplatin in ovarian cancer has largely been replaced by carboplatin and the initial recommended chemotherapy for advanced stage epithelial ovarian cancer is combination carboplatin and paclitaxel. With new data, there has been a resurgence in the use of intraperitoneal chemotherapy for this disease, primarily using cisplatin based therapies. In a phase III study conducted by the Gynecologic Oncology Group (GOG), patients with stage III ovarian or primary peritoneal carcinoma after maximal debulking (no mass larger than 1 cm) were randomized to paclitaxel given intravenously with either intraperitoneal (IP) or<sup>[38]</sup> intravenous (IV) cisplatin given on day 2. Cisplatin in the IV group was given at 75mg/m<sup>2</sup>, intraperitoneal at 100mg/m<sup>2</sup>, both on day 2. On day 8, in the intraperitoneal group also received 60mg/m<sup>2</sup> of paclitaxel. A special peritoneal catheter was required in the intraperitoneal group. The intraperitoneal regimen was found to be more toxic with more grade 3 and 4 hematologic, neurologic, gastrointestinal, metabolic toxicity as well as fatigue. However, outcomes were also improved with progression free survival in the IV group of 18.3 months compared with 23.8 months in the IP group. Overall survival was also better with 49.7 months in the IV arm, 65.6 months in the IP arm.

## Cervical cancer

While early stage cervical cancer can be managed surgically, tumors that are more advanced are treated primarily with radiation and chemotherapy. Cisplatin is the most widely used chemotherapy used in combination with radiation as a radiosensitizer. The GOG has shown that cisplatin based chemotherapy improves outcomes in this setting. In one series of 526 women<sup>[39]</sup>, patients were assigned to radiation with cisplatin or hydroxyurea based chemotherapy. Cisplatin was given either weekly at 40mg/m<sup>2</sup> or on days 1 and 29 combined with 5FU and hydroxyurea. One arm consisted of hydroxyurea alone. Overall survival was significantly better in the arms containing cisplatin with relative risk of death of 0.61 (95% CI 0.44 to 0.85) in the cisplatin only arm and 0.58 (95% CI 0.41 to 0.81) in the combination arm compared with hydroxyurea alone.

## Breast cancer

Though cisplatin has been used less in breast cancer outside of the metastatic setting in recent history, it is now being looked at again, particularly in triple negative breast cancer-cancer which does not carry receptors to estrogen or progesterone and does not overexpress HER2. This type of breast cancer may be more sensitive to the mechanism of action of cisplatin. In one small series<sup>[40]</sup>, women with triple negative stage II or III breast cancer were treated with four cycles of neoadjuvant cisplatin at 75mg/m<sup>2</sup>. Most patients had some response with 50% experiencing a good pathologic response, 22% of those were pathologic complete responses. Low BRCA expression predicted for response, further supporting the

idea that low levels of this DNA repair enzyme, whether sporadic or inherited, may be sensitive to therapies that damage DNA like cisplatin.

## Predictive markers

In the era of personalized medicine, attempts have been made to find markers or changes within tumors that predict for responsiveness to cisplatin. ERCC1<sup>[41]</sup> is a DNA repair enzyme that repairs cross links that form and prevent transcription. High levels of this enzyme are associated with a better prognosis, but low levels may predict for better response to cisplatin, presumably because tumors are less able to repair the damage done by the drug. An analysis of tumor tissue from the International Adjuvant Lung Trial found that low levels of ERCC1 was predictive of response to adjuvant cisplatin based chemotherapy (hazard ratio (HR) 0.73 for chemotherapy versus control,  $P = 0.02$ ). Studies are ongoing as to how to incorporate this into practice.

## Shortages

Practicing oncologists are facing a new challenge with drugs such as cisplatin: shortages of the medication and uncertainty about its availability in the future. The FDA website<sup>[42]</sup> lists cisplatin on the drug shortage list and cites manufacturing delays and increased demand as factors in the shortage. One company has stopped production of the drug. This has an obvious impact on patient care, but may also affect clinical trials as well<sup>[43]</sup>. The extent to which the shortage has affected patient care or clinical trials is unknown. For patients, it may mean substituting a drug that may not be as effective, such as carboplatin. For clinical trials, it may mean a compromise in trial results if patient schedules change or regimens are different between arms. Many cancer advocacy groups remain focused on this issue and efforts are ongoing to improve access.

## Conclusion

Though cisplatin is one of the oldest antineoplastic agents in use in oncology today, it remains a critical part of the treatment of a variety of cancers and, importantly, is an integral part of many curative therapy regimens. Its use spans many cancer types and, in many cancer types, modern randomized phase III trials support its continued importance. Cisplatin continues to be incorporated into new therapies and regimens, even as we are learning how better to predict who will respond best to this important drug.

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