

Cisplatin Nephrotoxicity in A Patient With Metastatic Testicular Choriocarcinoma: A Case Report and Review of the Literature

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Abstract

Choriocarcinoma is an aggressive and uncommon germ cell testicular tumour which represents only 1 to 3% of all germ cell testicular tumours. It is a tumour that has a propensity for early haematogenous dissemination, which is why it often presents itself as a disseminated disease at diagnosis. In the advanced stages of the disease, treatment must be systemic, and for this there are different chemotherapy regimens. All treatment regimens contain platinum as a fundamental chemotherapeutic agent in this type of tumours. One of the most frequent adverse effects in these treatment regimens is cisplatin nephrotoxicity. The case report presents a 28 year old man with metastatic testicular choriocarcinoma treated with platinum-based chemotherapy that presented nephrotoxicity as an adverse effect, making treatment with cisplatin impossible. Despite using the corresponding support measures for this type of situations, the recovery of renal function was prolonged up to several weeks. During this time of recovery, it was not possible to continue with the chemotherapeutic treatment. As a result, since it was an aggressive disease, the disease progression led to the death of the patient due to multiple organ failure. This case report is intended to emphasize the importance of monitoring renal function to ensure adequate dosing of chemotherapeutic agents and the early detection of nephrotoxicity.

Introduction

Testicular neoplasms comprise the most common solid malignancy affecting males between the ages of 15 and 35, although they represent only approximately 1% of all solid tumours in men. Testicular cancer can be broadly divided into Germ Cell Tumours (GCTs), which account for 95% of cases, and Non-Germ Cell Tumours (NGCTs).

Accurate histological evaluation of testicular cancer and staging will help determine if a patient should be treated surgically (Orchiectomy, Retroperitoneal Lymph Node Dissection) and whether chemotherapy is indicated. GCTs are more sensitive to systemic chemotherapy than any other adult solid tumor. Cisplatin is an integral component of the most effective chemotherapy regimens and can cure up to 80 percent of patients with disseminated GCTs [1]. Advanced disease should be treated with a cisplatin-based combination regimen Bleomycin, Etoposide, and Cisplatin (BEP) or Etoposide and Cisplatin (EP). Patients who relapse or have refractory disease can be cured by high-dose chemotherapy.

Cisplatin is renally excreted and can produce nephrotoxicity. Its use is generally limited to patients with a Creatinine Clearance (CrCl) >60 mL/min; however, cisplatin-induced nephrotoxicity is common and may limit dosing and/or dose intensity. The overall prevalence of cisplatin induced nephrotoxicity approaches one third of treated patients [2,3] and typically presents approximately 10 days after treatment. Hydration and other measures significantly reduce and improve nephrotoxicity due to cisplatin [4]. This adverse effect can compromise the course of chemotherapy protocols and the patients' vital prognosis.

This is a real problem for the clinician. To minimize treatment-related toxicity from conventional and high-dose chemotherapy has become a prime concern. With the present case report the authors wish to influence the importance of preventing or diagnosing and treating early nephrotoxicity by cisplatin, demonstrating the consequences that can be derived not only at the renal level but also the vital commitment that it can imply for patients who need a platinum-based chemotherapy regimen as a fundamental treatment strategy. To this end, we have reviewed the literature on cisplatin nephrotoxicity and the support measures that must be carried out to prevent and / or treat this adverse effect.

Case Report

A 28 year old man with a personal history of nephrectomy in childhood due to renal lithiasis was presented with acute onset of hematemesis in our centre. He only referred constitutional syndrome of 3 months of evolution. The endoscopic exam of the upper gastrointestinal tract detected a bleeding duodenal mass that was biopsied. Shortly after that, the patient presented a massive

intra-abdominal bleeding and an urgent laparotomy was performed. An extensive infiltrating mass was resected. The image evaluation showed multiple liver and pulmonary nodes, retroperitoneal lymph nodes and a right testicular mass. The pathological review confirmed a choriocarcinoma. Preoperative levels of Alpha-FetoProtein (AFP: 3.0 ng/ml), Human Chorionic Gonadotropin (HCG: >2x106 IU/L), and Lactate Dehydrogenase (LDH: 2500 U/L) were high. Renal function at diagnosis showed a Glomerular Filtration Rate (GFR) of 63 mL/min, due to massive bleeding with hemoglobin of 6 g/dl in a patient with a single kidney. He required 4 red cell transfusions. Renal function improved, with a GFR of 75 mL/min.

Having obtained diagnosis of disseminated testicular choriocarcinoma with factors of poor prognosis and vital compromise due to hepatic insufficiency secondary to metastatic infiltration (bilirubin 5mg/dl, hypertransaminasemia x 2 times the normal value), we decided to start treatment with cisplatin 75 mg/m2 with a 25% dose reduction and bleomycin 30 mg/m2 every 21 days. Etoposide was not administered due to liver failure (BEP regimen). After the third course of chemotherapy, our patient persisted with generalized clinical deterioration. His renal function was maintained with a GFR >65 mL/min. Moreover the first computerized tomography to evaluate the disease showed clear disease progression. The patient also presented elevation of HCG > 3x106 IU / L. In the absence of response and disease progression to a first line of chemotherapy and due to the existent contraindications to administer full doses of bleomycin, cisplatin and etoposide according to the chemotherapy scheme BEP, we decided to start a second line of treatment according to Taxol, Ifosfamide and Cisplatin regimens (TIP) with a 25% dose reduction.

On day 7 of the first cycle of TIP treatment our patient developed an acute renal failure with signs of glomerular and tubular impairment viewed in blood control analysis (GFR 45 mg/dl, Hypomagnesemia 0.8 mg/ml, Hypoalbuminaemia 2.6 g/dl and Proteinuria 450 mg/24 h) attributed to cisplatin toxicity.

Renal function was recovered after several weeks of hospitalization and supportive treatment with hydration, magnesium supplementation orally, albumin intravenous replacement, and daily evaluation and treatment adjustment by the nephrology department. This unforeseen difficulty caused a significant delay in the chemotherapy schedule. In the end, the patient died due to a progression of his malignant disease that originated a multiple organ failure.

Discussion

The kidney disease is a common complication of cancer and its therapy. Renal failure in oncologic patients may be multifactorial: related to the patients and their comorbidities, the toxicity of cancer treatments and other associated medications or direct tumour compression. The majority of chemotherapy treatments and other associated medications such as bisphosphonates and the novelties immune checkpoint inhibitors are potentially nephrotoxic. The kidneys are a major elimination pathway for many anti-neoplastic drugs and their metabolites.

Despite the tremendous advances in the field of oncology, cisplatin, approved as an anti-neoplastic agent in 1978, plays a central role in cancer chemotherapy, especially for testicular cancer, whose global cure rate exceeds 90% and is nearly 100% for early stages. Cisplatin and carboplatin, a platinum-based therapeutics, have been used for many years to treat a wide variety of tumours and is currently an important and effective therapy for genitourinary cancer, oesophageal, head and neck, lung, among many others [5]. Cisplatin use is mainly limited by two factors: acquired resistance to cisplatin and adverse effects in normal tissues [6,7]. The molecular mechanism of cisplatin resistance has been studied extensively, which may involve decreased uptake or increased efflux of cisplatin, neutralization of cisplatin by glutathione and other sulphur-containing molecules, increased DNA repair, and defective apoptotic signalling in response to DNA damage [7-10].

The other major limiting factor in the use of cisplatin is the side effects in normal tissues, which include neurotoxicity, ototoxicity, nausea and vomiting, and its major side effect, the nephrotoxicity. For years, various approaches have been attempted to curtail these side effects. One strategy is to synthesize and screen for novel cisplatin analogues that have lower toxicity in normal tissues. In this direction, several cisplatin analogues, such as carboplatin, have been identified with less severe side effects [11].

Despite its more favourable toxicity profile, carboplatin should not be routinely used in the treatment of testicular GCTs. Several randomized trials have demonstrated an inferior outcome with carboplatin [12-14]. Another approach that has been used with some success is to hydrate the patients during cisplatin treatment. Despite these efforts, the side effects of cisplatin, particularly nephrotoxicity, remain a major factor that limits the use and efficacy of cisplatin in cancer therapy [5].

Table 1: Risk factors for cisplatin nephrotoxicity.

Factors related to the patient	Factors related to the cisplatin chemotherapeutic agent
Age	High dose (greater 50 mg/m2)
Performance status	Cumulative dose
Hydroelectrolytic disturbances	Frequency of administration
Comorbidity (chronic diseases: diabetes mellitus, hypertension)	Cumulative dose
Chronic kidney disease	Hydration with cisplatin administration
Nephrotoxic drugs (aminoglycoside antibiotics, nonsteroidal antiinflammatory drugs, radiographic contrast)	Bolus administration
Toxic habits (alcoholism, smoking)	
Malnutrition	
Plasma albumin	

The prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment [2]. Cisplatin nephrotoxicity is often seen after 10 days of cisplatin administration and is manifested as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels. The long-term effects of cisplatin on renal function are not completely understood, but it is believed that cisplatin treatment may lead to subclinical but permanent reduction in glomerular filtration rate [5,3]. Better understanding of the mechanism of cisplatin nephrotoxicity could lead to novel renoprotective interventions that would not reduce its anti-tumoral effects.

Multiple cytotoxic mechanisms contribute to renal damage following exposure to cisplatin. The most known mechanism is the alteration of the synthesis and repair of DNA that entails the arrest of the cell cycle; is also involved in the dysfunction of cytoplasmic organelles such as endoplasmic reticulum and mitochondria which play a key role in the cisplatin nephrotoxicity; other effects are inhibition of p53 tumour suppressor protein and generation of reactive oxygen species by activating apoptosis pathways and producing oxidative stress and inflammation [5,15]. Extensive research has found that cisplatin entry into a cell through two transport proteins: Human Copper Transport Protein 1 (Ctr1) and the Organic Cation Transporter 2 (OCT2) both expressed in renal tubular cells. The cellular transport plays an important role in the nephrotoxicity. Other platinum derivatives do not appear to have the same affinity for these transporters: carboplatin seems not to be transported by OCT2 and although Oxaliplatin if transported by it, is rapidly expelled out of the renal tubule [16,17]. Several factors can potentiate renal dysfunction and contribute to the nephrotoxic potential of cisplatin (Table 1). These factors should be considered by the treating oncologist before initiating treatment in order to minimize the risk of excessive toxicity. These factors include intravascular volume depletion, the concomitant use of non-chemotherapeutic nephrotoxic drugs (eg: Aminoglycoside Antibiotics, Nonsteroidal Antiinflammatory Drugs) or radiographic ionic contrast in patients with or without pre-existing renal dysfunction, tumor-related urinary tract obstruction, and intrinsic renal disease, related to other comorbidities, or to the cancer itself [18]. Cisplatin kidney injury is dose-duration-frequency dependent [19]. Higher peak plasma concentrations from higher doses per treatment result in greater injury [20]. A higher cumulative dose has also been shown to increase risk for future kidney injury [21]. In the other hand, certain factors related to the patient increase their susceptibility to renal damage: patients with significant comorbid illness, advanced age and baseline poor were at a higher risk as demonstrated by Ignard-Bagnis et al [22]. Patients with lower albumin are presumed to have a higher unbound

fraction of cisplatin resulting in greater peak plasma concentrations and greater risk [15,19-22]. Cisplatin and platinum-based agents can affect the different parts of the nephron, producing a variety of renal complications such as acute renal failure, chronic kidney disease, nephrotic syndrome and hydroelectrolytic disorders, with clinical manifestations that range from an asymptomatic elevation of serum creatinine to renal impairment requiring dialysis [18].

Thus, cisplatin nephropathy not only presents clinically as a renal impairment, although it is the most well-known and expected manifestation. Acute kidney injury is seen in 20–30% of the patients. Prior to the use of renoprotective measures such as intensive hydration regimens, its incidence was practically one hundred percent of the patients [23]. The more common kidney manifestation is hypomagnesaemia due to urinary magnesium wasting with a prevalence ranging from forty to one hundred percent; at the same time, hypomagnesaemia may exacerbate cisplatin toxicity [24,25]. A fractional magnesium excretion above 2.5 % would be indicative of a magnesium wasting component. When cisplatin associates with bleomycin or gemcitabine may produce thrombotic microangiopathy apparently related to direct vascular damage and secondary platelet activation. The clinical manifestations of this disorder are similar to haemolytic-uremic syndrome or thrombotic thrombocytopenic purpura and its presentation may be acute or appear months after the end of treatment. Its presentation may be acute or appear months after the end of the. In its late form, the diagnosis of presumption would be due to the coexistence of haemolytic anaemia and thrombopenia [26]; cisplatin often causes anaemia due mainly to its myelosuppressive effect, but in addition, through renal tubular damage, there is a deficiency of erythropoietin, which in turn contributes to the anaemia [27]. Other manifestations such as salt wasting [28], distal renal tubular acidosis [29] and Fanconi-like syndrome [30,31] have been described (Table 2). Cisplatin nephrotoxicity may be present with different histopathological patterns and grades with greater involvement of the tubulinterstitial compartment and predominance in the proximal tubular portions as well as minimal glomerular degeneration described by Tanaka H et al. in their rat and human autopsy studies [32]. A routine renal biopsy is not necessary unless the clinical situation requires clarification that may alter the patient’s management. During the course of investigation of cisplatin nephrotoxicity, several strategies have been studied to reduce toxicity of treatment: use of less intensive treatment, avoid bolus administration, less toxic analogues such as carboplatin, the administration of protective agents before and after treatment are some of the strategies carried out. The incidence and severity of nephrotoxicity increases with successive cycles of treatment and

Table 2: Clinical presentation of cisplatin nephrotoxicity.

Acute kidney injury
Hypomagnesemia
Thrombotic microangiopathy
Anemia (myelosuppressive effect, renal tubular damage with deficiency of erythropoietin)
Salt wasting
Distal renal tubular acidosis
Fanconi-like syndrome

Table 3: Measures of treatment and prevention of nephrotoxicity by cisplatin.

Hydration
Short-duration, low-volume, outpatient hydration regimens
Magnesium supplementation
Forced diuresis with Mannitol for high-dose cisplatin and/or patients with preexisting hypertension
Use limited to patients with a creatinine clearance (CrCl) >60 mL/min
Limit dosing and/or dose intensity
Frequent monitoring of renal function

may become irreversible. Discontinuing treatment with cisplatin is indicated when progressive renal failure develops. There are many options for preventing cisplatin-induced renal damage. The biggest challenge is to protect the kidney without reducing cytotoxic effects. The most well-known and used strategy is hydration and forced diuresis with diuretics such as mannitol [15].

Evidence-based recommendations on hydration regimens are limited. A recent systematic review by Crona DJ et al. evaluates hydration and supplementation strategies to prevent nephrotoxicity induced by cisplatin. Hydration is essential in all patients, low volume and short duration hydration in outpatients is beneficial even when high doses of cisplatin are used; administration of mannitol should be considered in patients receiving high doses of cisplatin and / or pre-existing hypertension; magnesium supplements (8-16 milliequivalents) may limit such nephrotoxicity. These findings represent the best current clinical practice for safe treatment with cisplatin [33] (Table 3). We have chosen this clinical case because metastatic choriocarcinoma is a disease for which platinum-based chemotherapy is the best therapeutic option. It can also be observed that not only has cisplatin nephrotoxicity consequences for the kidney, but it can also worsen the vital prognosis of patients due to delays in treatment cycles and other complications that derive from this, even in the long term. Platinum-based chemotherapy is the cornerstone of treatment of many tumours. For this reason, this case report and bibliographic review intend to guarantee the quality of life of oncologic patients by generalizing the measures of kidney function monitoring, early diagnosis and treatment. The clinician must be aware of available prevention strategies. These aspects are the keys for an effective approach of cancer patients eligible for cisplatin chemotherapy.

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