Evolution of high-dose cisplatin

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Summary

High-dose cisplatin therapy, defined as 200 mg/m²/course, is currently undergoing extensive clinical trials in a variety of solid tumors. The reduction of the incidence and severity of cisplatin-induced nephrotoxicity has led to clinical trials of higher doses of cisplatin. By maintaining nephrotoxicity to acceptable levels, dose response relationships have shown increased efficacy of cisplatin therapy. However, new dose-limiting toxicities, primarily severe neurotoxicity and myelosuppression, have prevented further dosing increases. The following review will trace the evolution and the current status of high-dose cisplatin therapy. In addition, a summary of the dose-limiting non-renal toxicities and their relationship to pharmacokinetics and dosing schedules will be discussed.

Introduction

Cisplatin is an eleven atom inorganic cis complex of platinum with a broad spectrum of antitumor activity. Cisplatin was first used clinically in the early 1970’s for the treatment of refractory cancers. Currently, cisplatin containing regimens have become the treatment of choice for a variety of malignancies including a number of solid tumors, such as ovarian, testicular, non-small cell lung, and head and neck cancers. Early Phase I and II studies examining the dose response relationship of cisplatin show that the therapeutic benefits of cisplatin were minimized by a dose limiting nephrotoxicity [1]. Attempts to utilize higher doses of cisplatin lead to significant increases in cisplatin associated toxicities [2]. Based on the results of these studies, most clinical trials have used cisplatin in doses ranging from 30 to 120 mg/m² per course of therapy, which is now considered conventional cisplatin dosing.

The use of “high-dose” cisplatin, defined as a total dose of 200 mg/m² per course (HDCP), has evolved primarily due to methods which minimize the dose-limiting nephrotoxicity. Numerous techniques for reducing the incidence and severity of nephrotoxicity have been reported, including dosing schedule modifications, pre- and post-hydration, hypertonic saline, and mannitol or furosemide administration [2–14]. Clinical investigations of the steep dose response relationship of cisplatin have now become possible due to the development and refinement of these techniques.

Hypertonic saline

Early animal studies have shown that an increased therapeutic index was achieved using prehydration and osmotic diuresis as prophylaxis against cisplatin induced nephrotoxicity [5]. More recent studies have shown that the activity of cisplatin is related
to the specific platinum species present at the extracellular and intracellular levels [15,16]. In high chloride environments, such as the extracellular space, the aquation equilibrium favors the neutral dichlorodiaminoplatinum structure [16,17]. Low chloride environments, such as intracellularly, favor the formation of a positively charged platinum molecule which appears to possess antitumor and toxic activity [18]. Thus, the delivery of cisplatin in a high chloride solution apparently favors the less toxic platinum complex.

Litterst demonstrated that the administration of cisplatin in hypertonic saline (4.5% NaCl) significantly protected animals against nephrotoxicity when compared to a control group administered cisplatin in D5W [19]. Litterst also showed that hypertonic saline administration had no deliterious effects on cisplatin cytotoxicity. In contrast with these findings, Aamdal et al. utilized a variety of mouse tumor model systems to demonstrate that increasing concentrations of saline in the vehicle of administration leads to a corresponding decrease in cisplatin antitumor activity [20]. In agreement with Litterst, Mannel et al. found no difference in antitumor activity with various concentrations of saline when cisplatin was administered intraperitoneally in a mouse tumor model [21].

Ozols et al. designed a clinical study based on Litterst’s observations and demonstrated that the dose-limiting nephrotoxicity of high-dose cisplatin (HDCP) therapy was reduced when cisplatin was administered in 3% saline [22,23]. Seventeen previously untreated patients with poor prognosis non-seminomatous testicular cancer were treated with HDCP [23]. In addition, six patients with relapsed ovarian cancer previously treated with standard dose cisplatin were treated with HDCP. The dosing regimen consisted of cisplatin 40 mg/m² per day by a 30 minute intravenous infusion for five consecutive days administered in hypertonic saline (3%) with extensive pre- and post-hydration. Objective responses were seen in 88% of the previously untreated testicular cancer patients, with 50% of patients with refractory ovarian cancer demonstrating partial responses. Transient elevations in serum creatinine occurred in the majority of patients, but only two patients obtained levels above 2.0 mg/dl. The study also showed a high incidence of non-renal toxicities, particularly severe myelosuppression and neurotoxicity. Six of the 17 testicular patients and four of the six refractory ovarian patients developed transient peripheral neuropathies, while high tone hearing loss occurred in all patients receiving more than three cycles of HDCP. Severe leukopenia (WBC's < 1000/mm³) and thrombocytopenia (platelets < 20,000/mm³) occurred in all patients. Although the use of hypertonic saline resulted in acceptable levels of renal toxicity, non-renal toxicities were significant and dose-limiting.

Ozols et al. further examined single agent HDCP in 19 patients with refractory ovarian cancer [24]. Seventeen of the patients had previously received cisplatin therapy. Although objective responses were achieved in six of 19 patients, non-renal toxicities were substantial. Myelosuppression was severe, with 26% of patients having WBC below 1000/mm³, and 89% having platelet counts less than 20,000/mm³. Peripheral neuropathies developed in all patients that received more than two cycles of HDCP, with 37% of patients having severe paresthesias or ataxia. The study suggests that hypertonic saline and intensive hydration minimized renal toxicity, while non-renal toxicities remained dose-limiting.

### Clinical trials of HDCP

Numerous clinical trials have reported a variety of results with the five day high-dose cisplatin regimen used as single agent or as part of combination therapy. The following section will review the significant findings of these trials. Table 1 shows the treatment responses of these studies, while Table 2 summarizes the clinical toxicities.

Legha and Dimery reported that renal toxicity of HDCP can be reduced without the use of hypertonic saline [7]. The results show that intravenous hydration alone (4–5 l/day) reduced the incidence of renal toxicity in 13 patients treated with the five day HDCP regimen. The dose limiting toxicities were acute myelosuppression and chronic severe peripheral neuropathies. These authors concluded that HDCP (40 mg/m²/d × 5d) is fraught with se-