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Anti-Tumour Treatment

Cisplatin in the modern era: The backbone of first-line chemotherapy for non-small cell lung cancer

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ABSTRACT

The treatment of advanced non-small cell lung cancer (NSCLC) may be changing, but the cisplatin-based doublet remains the foundation of treatment for the majority of patients with advanced NSCLC. In this respect, changes in practice to various aspects of cisplatin use, such as administration schedules and the choice of methods and frequency of monitoring for toxicities, have contributed to an incremental improvement in patient management and experience. Chemoresistance, however, limits the clinical utility of this drug in patients with advanced NSCLC. Better understanding of the molecular mechanisms of cisplatin resistance, identification of predictive markers and the development of newer, more effective and less toxic platinum agents is required. In addition to maximising potential benefits from advances in molecular biology and associated therapeutics, modification of existing cisplatin-based treatments can still lead to improvements in patient outcomes and experiences.

Introduction

Lung cancer is the most common cancer worldwide [1]. It is the leading cause of cancer-related death [1] and is seen most frequently in developing countries [2]. It is also the most common cancer in men worldwide with 1.2 million cases, accounting for 16.7% of the total cancer burden [2]. Most cases are non-small cell lung cancer (NSCLC) related to tobacco-driven carcinogenesis [2]. Early stage lung cancer can be treated with curative intent, largely surgery [3]. However, the majority of patients present with incurable advanced NSCLC stage IIIB or IV [4], or relapse after curative intent surgery, which reflects the aggressive nature of the disease and poor prognosis [4]. The economic impact falls not only on the health service but on society, because premature deaths, time off work and unpaid care by family and friends also contribute to cancer costs [5].

The genetic heterogeneity of advanced NSCLC has become more apparent over the last decade [6]. Current classification of advanced NSCLC includes histological and molecular subtypes, and classification of NSCLC using these characteristics now influences therapeutic decisions [7]. In addition, genetic drivers that are key oncogenic events have been identified in NSCLC. The incidence of epidermal growth factor receptor (EGFR) mutations in the Caucasian population is approximately 10%, but it is higher in never-smokers, patients with adenocarcinomas, those who are women and those who are East-Asian [8]. The EML4-ALK fusion gene is present in approximately 4% of lung cancers and is encountered more frequently in never-smokers, younger patients and those with adenocarcinomas [8–10]. Thus, only a small proportion of the total population of patients with advanced NSCLC are presently candidates for molecular-targeted therapies.

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For patients with NSCLC who do not have drug-targetable driver mutations (approximately 85–90%), platinum-based chemotherapy remains the unchallenged standard of care. Furthermore, cisplatin is the more active platinum agent for patients with advanced NSCLC and for patients with early-stage disease requiring induction/adjuvant therapy [11]. This review examines the evidence for the use of cisplatin in first-line combination regimens for NSCLC, the issues surrounding the use of cisplatin in this context and the advances that are being made in attempts to optimise therapy. Other platinum agents are mentioned where relevant.

Discovery and initial clinical use of cisplatin

The compound *cis*-[$Pt(NH_3)_2(Cl)_2$] was first described by Michele Peyrone [12] in the 1840s and was originally known as Peyrone's salt (Table 1). In 1965, Rosenberg et al. [13] described electrolysis of platinum electrodes generating a soluble platinum complex, which inhibited binary fission in *Escherichia coli*. In 1968, *cis*-diamminedichloroplatinum (II) (cisplatin) was administered intraperitoneally to mice bearing a standard murine transplantable tumour of the day, sarcoma-180, and was shown to cause marked tumour regression [14]. The antitumour activity of cisplatin was later confirmed, particularly during the 1970s, first in testicular cancer [15], followed by ovarian cancer [16] and then NSCLC [17]. Cisplatin and its second-generation derivative, carboplatin, are alkylating agents that induce DNA damage and interfere with DNA repair. The mechanism of action of cisplatin is shown in Fig. 1 [18]. Three main toxicity problems were identified with cisplatin: emesis, nephrotoxicity and neuropathy/ototoxicity. Overcoming these treatment-limiting events has been one of the main themes of clinical trials. Approval by the US Food and Drug Administration (FDA) was granted in 1978 [19] once cisplatin-related nephrotoxicity was attenuated by hydration [20].

For current regimens, cisplatin is usually administered in combination with third-generation cytotoxic agents at a cumulative dosage of 50–100 mg/m^2 every 3 weeks [21].

Evolution of cisplatin-based chemotherapy in advanced NSCLC

There has been a concerted effort over the years to define, and refine, the use of cisplatin in the treatment of NSCLC (Table 1; also reviewed elsewhere [22,23]). In 1995, a meta-analysis of 11 randomised trials first identified the benefit of cisplatin in patients with advanced NSCLC [24]. Cisplatin-based chemotherapy reduced the risk of death by 27%, improved 1-year survival by 10% and increased median survival by 1.5 months compared with supportive care. However, this meta-analysis included only 416 patients treated with a wide variety of regimens, and thus larger randomised controlled trials of cisplatin-based chemotherapy versus supportive care were needed.

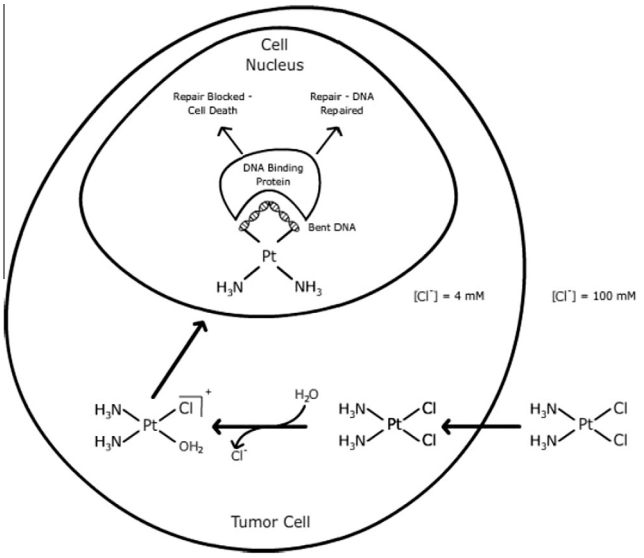

Fig. 1. Mechanism of action for cisplatin (Adapted from Ref. [18]). Following entry into the tumour cell, cisplatin is aqueated before entering the nucleus where it forms DNA adducts resulting in cell death.

In subsequent randomised trials that compared mitomycin/ifosfamide/cisplatin (MIC) [25], mitomycin/cisplatin/vinblastine, ifosfamide/epirubicin/cisplatin [26] or etoposide/carboplatin [27] to supportive care, chemotherapy was again associated with significantly improved survival. The MIC trial [25] showed for the first time that in advanced NSCLC, cisplatin-based chemotherapy improved quality of life. This trial used the relatively low dose of cisplatin 50 mg/m^2 every 3 weeks.

Of the more recent pivotal studies (Table 1), the Eastern Cooperative Oncology Group (ECOG) 1594 trial [28] is worthy of note, because this was one of the largest trials of advanced NSCLC, recruiting more than 1200 patients with ECOG performance status (PS) 0–1 and evaluating survival for four platinum-based doublet combination regimens (cisplatin/paclitaxel as reference regimen

Table 1
Chronology of cisplatin events in relation to evolution of treatment of advanced non-small cell lung cancer (NSCLC) with corresponding reference.

Year	Discovery/findings	Reference
1844	Discovery of cisplatin by Peyrone (Peyrone's salt)	[12]
1965	Cisplatin formation after electrolysis of saline solution with platinum electrodes kills *E. coli* around the electrode	[13]
1969	Cisplatin demonstrates dramatic clinical activity, especially in testicular tumours	[15–17]
1977	Discovery that cisplatin nephrotoxicity is attenuated by saline pre-hydration	[20]
1978	FDA approval	[19]
1986–1991	Cisplatin/etoposide or cisplatin/vinca alkaloids/mitomycin become "standards"	[98–100]
1990	Introduction of 5HT-3 receptor antagonists to control emesis	[101]
1995	Cisplatin regimens versus best supportive care show 1.5-month survival benefit in meta analysis of 416 patients in 11 randomised trials	[24]
1996	Cisplatin/paclitaxel better than cisplatin/etoposide (>2-fold increase in RR)	[102]
1999	Tumour-related symptoms and thus quality of life improved by chemotherapy	[25]
2002	ECOG 1594 trial in 1207 patients shows overall RR 19% and median survival 8.0 months in 4 cisplatin or carboplatin treatment arms	[28]
2007	Cisplatin better than carboplatin for RR, especially with second-generation doublet partners, in a meta analysis of 2968 patients	[11]
2008	In nonsquamous NSCLC, cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 day 1 better for OS than cisplatin 75 mg/m^2 plus gemcitabine 1250 mg/m^2 days 1 and 8, both regimens given every 3 weeks	[29]
2011	In combination with gemcitabine 1250 mg/m^2, cisplatin in a higher dose of 80 mg/m^2 was better for OS than cisplatin 50 mg/m^2 and was non-inferior to carboplatin AUC 6, all regimens given every 3 weeks	[30]

Paclitaxel 135 mg/m^2 day 1 + cisplatin 75 mg/m^2 day 2 every 3 weeks; cisplatin 100 mg/m^2 day 1 + gemcitabine 1000 mg/m^2 days 1, 8, 15 every 4 weeks; cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 day 1 every 3 weeks; carboplatin AUC 6 + paclitaxel 225 mg/m^2 day 1 every 3 weeks.
ECOG = Eastern Cooperative Oncology Group; *E. coli* = *Escherichia coli*; NSCLC = non-small cell lung cancer, OS = overall survival; RR = response rate.