Anti-Tumour Treatment

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


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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\textsubscript{3})\textsubscript{2}(Cl)\textsubscript{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-diaminedichloroplatinum (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\textsuperscript{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.

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\textsuperscript{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.

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

Paclitaxel 135 mg/m\textsuperscript{2} day 1 + cisplatin 75 mg/m\textsuperscript{2} day 2 every 3 weeks; cisplatin 100 mg/m\textsuperscript{2} day 1 + gemcitabine 1000 mg/m\textsuperscript{2} days 1, 8, 15 every 4 weeks; cisplatin 75 mg/m\textsuperscript{2} + docetaxel 75 mg/m\textsuperscript{2} day 1 every 3 weeks; carboplatin AUC 6 + paclitaxel 225 mg/m\textsuperscript{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.
versus cisplatin/gemcitabine, cisplatin/docetaxel and carboplatin/-paclitaxel). There were no significant differences between the regimens in response rates (RRs) (17–22%), median survival (7.4–8.1 months) or 1-year survival (31–36%). Time to progression was significantly improved in the gemcitabine/cisplatin arm compared with cisplatin/paclitaxel (4.2 months vs 3.4 months, *P* = 0.001), but at a higher risk of grades 3–5 renal toxicity (9% vs 3%). Together, the results of this and other pivotal studies (Table 1) led to a number of platinum-based doublets being accepted as standard of care.

The first phase III study in NSCLC to prospectively report survival differences between cisplatin doublets according to histology was published by Scagliotti and colleagues [29] in 2008. This randomised noninferiority study compared cisplatin/gemcitabine with cisplatin/pemetrexed in chemotherapy-naive patients with advanced NSCLC. A pre-specified subgroup analysis confirmed that pemetrexed-containing chemotherapy had different effects on survival in patients with nonsquamous NSCLC compared to those with squamous cell carcinoma. Overall survival (OS) was significantly improved for pemetrexed-based therapy over gemcitabine-based therapy in patients with adenocarcinoma (12.6 months versus 10.9 months; hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.71, 0.99; *P* = 0.03) and large-cell carcinoma (10.4 months versus 6.7 months; HR 0.67; 95% CI 0.48, 0.96; *P* = 0.03). In patients with squamous cell carcinoma, OS was higher with cisplatin/gemcitabine (10.8 months versus 9.4 months; HR 1.23; 95% CI 1.00, 1.51; *P* = 0.05). Finally, in the recent British Thoracic Oncology Group 2 (BTOG2) trial (NCT00112710) comparing platinum-based regimens plus gemcitabine, OS for cisplatin in a higher dose of 80 mg/m² was superior to lower-dose cisplatin 50 mg/m² (9.5 months versus 8.3 months) and similar to that for carboplatin AUC 6 (10.0 months) [30].

Acceptible third-generation agents for combination with cisplatin include docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed and vinorelbine [8,31]. The most commonly used platinum doublet regimens are cisplatin plus gemcitabine, pemetrexed or vinorelbine, and carboplatin plus paclitaxel. Given that cisplatin plus pemetrexed showed a significant OS advantage over cisplatin plus gemcitabine in patients with adenocarcinoma and large-cell carcinoma [29], this combination is regarded as a standard of care for patients with nonsquamous tumour histology [8]. For patients with more advanced disease and PS 2, the best choice of first-line chemotherapy is unclear. Low-dose cisplatin combinations, carboplatin combinations or single-agent therapy with gemcitabine, vinorelbine or taxanes are options [8,32]. Although single-agent chemotherapy has been evaluated [8,31,32], platinum-based combinations may be superior. Indeed, first-line carboplatin plus paclitaxel was associated with a significantly higher RR and longer time to progression than gemcitabine or vinorelbine in PS 2 patients in a combined analysis of two identical trials [33]. More recently, carboplatin plus pemetrexed has shown a notable significant survival advantage in PS 2 patients with mainly nonsquamous histology when compared to pemetrexed alone in this setting (9.3 months versus 5.3 months, *P* = 0.0001) [34].

Platinum-based chemotherapy regimens are also the preferred option for elderly patients with a PS 0–1 or those with a PS 2 with adequate organ function [8]. Indeed, carboplatin plus paclitaxel showed a survival advantage compared to monotherapy with gemcitabine or vinorelbine in the iFTCT–0501 trial [35]. However, single-agent chemotherapy may remain the recommended treatment for elderly patients who are unfit or have co-morbidities [8]. Patients with a poor PS (3–4) and no targetable mutation should be offered best supportive care [8].

In terms of patient profile, the ideal candidate for cisplatin-based regimens has a PS of 0–1 and no limited co-morbidities. Patients who receive carboplatin, on the other hand, are generally older, with more co-morbidities and greater weight loss prior to treatment [36]. Based on the clinical evidence previously detailed, cisplatin is usually administered in combination regimens at a dosage of 75–80 mg/kg² every 3 weeks for up to 4–6 cycles. However, recent evidence indicates that 6 cycles do not provide any added benefit [37].

### Avoiding nephrotoxicity

The first step in avoiding platinum-associated nephrotoxicity is to select patients with an appropriate glomerular filtration rate (GFR) of >60 ml/min. Numerous methods can be used to estimate GFR, the detailed evaluation of which is beyond the scope of this review. The gold standard is chromium-51 labelled ethylenediamine-tetra-acetic acid (51Cr-EDTA) clearance, but because this is a threshold measurement, if Cockcroft–Gault is >60 ml/min then many physicians would accept this as a measure of acceptable renal function. However, the Cockcroft–Gault method has pitfalls, and the so-called Wright equation is now widely used and gives results close to that of 51Cr-EDTA.

Previously, prolonged hydration schedules of up to 13 h were used for cisplatin (Table 2). Much shorter hydration schedules of, for example, 3 to 5 h, have been investigated and shown to be feasible [38,39]. Indeed, the BTOG2 study (NCT00112710) showed that a shortened hydration schedule could even be used in patients with mild nephrotoxicity [30]. This has made outpatient administration of cisplatin feasible and routine, especially because severe emesis (which may require hospitalisation) is now rarely a problem. However, it should be borne in mind that the patients in the BTOG2 study had a GFR of >60 ml/min selected by application of the Wright equation, and the summary of product characteristics of cisplatin has not been modified to reflect the shorter hydration times.

Replacement of branded cisplatin with a generic version of this agent in Japan has been associated with slightly more severe renal toxicity (as determined by elevated serum creatinine levels) in one study [40], although two other investigations did not concur with this finding [41,42]. The generic version of cisplatin was also associated with a greater incidence of hyponatraemia when compared with branded cisplatin [42].

### Avoiding emesis

To manage the potentially dose-limiting toxicity of emesis, clinicians have traditionally relied upon serotonin receptor-3 (5-HT3) antagonists and corticosteroids [43,44]. Since the introduction of the oral neurokinin-1 (NK-1) receptor antagonist aprepitant in 2003 for highly emetogenic chemotherapy [45], this agent has been part of the standard of care for patients receiving cisplatin. When used in combination with a 5-HT3 receptor antagonist and dexamethasone, it increases the rate of complete control of emesis (no vomiting and no use of rescue medications) from approximately 50% to 75% [45]. A powerful effect is particularly seen on delayed emesis [45]. The European Society of Medical Oncology and the Multinational Association of Supportive Care in Cancer (ESMO/MASCC) guidelines on nausea and vomiting were updated in 2010 to include these findings [46]. Interestingly, in a more recent noninferiority study, the intravenously administered NK-1 receptor antagonist fosaprepitant given as a single dose of 115 mg was not inferior to the 3-day aprepitant regimen involving once-daily dosing at 125 mg on day 1 and 80 mg on days 2 and 3 [47]. During cisplatin therapy, the use of an NK-1 receptor antagonist plus a 5-HT3 antagonist and dexamethasone should be regarded as standard care.
Avoiding neurotoxicity

Peripheral neurotoxicity is the most common dose-limiting problem associated with cisplatin therapy [48]. Cisplatin neurotoxicity is first characterised by paraesthesias and numbness, which typically occur during the first few drug cycles. Loss of vibration sense, paraesthesia and ataxia can become apparent after several treatment cycles. Peripheral neuropathic changes may begin after completion of the chemotherapy course and progress for 2.5–5.5 months after stopping cisplatin [49]. Ototoxicity caused by cisplatin is cumulative and can be irreversible, therefore, monitoring audiograms should be considered [48]. Ototoxicity has been shown early promise (e.g. glutathione, vitamin E, calcium/magnesium infusions and the use of anticoagulants) [52,53]. Nevertheless, clinical trial reporting of National Cancer Institute Common Toxicity Criteria (CTC) adverse event grade has been shown to under-report ototoxicity and minimises the clinical significance of hearing loss [51].

Despite efforts to find specific agents that can prevent or minimise neurotoxicity caused by platinum drugs, there is currently no effective standard treatment, although some approaches have shown early promise (e.g. glutathione, vitamin E, calcium/magnesium infusions and the use of anticoagulants) [52,53]. Nevertheless, translational genomics has recently been cited as an approach that may help develop preventative and interventional strategies for cisplatin-induced peripheral neurotoxicity [54].

Major vascular events

Venous and arterial thromboembolic events (TEE) are increased by 4.1-fold in cancer patients, and the use of chemotherapy heightens this risk to 6.5-fold [55]. In patients with NSCLC treated with cisplatin, the incidence of TEE is even higher (up to 17.6%) [56]. In these studies, deep venous thrombosis and pulmonary emboli were the most common events; however, arterial events including limb ischaemia, myocardial infarction and cerebrovascular accidents account for a substantial proportion of TEE and result in significant morbidity and mortality.

The aetiologic mechanisms of cisplatin-associated vascular toxicity have not been clearly elucidated, but may involve increased von Willebrand factor levels [57], hypomagnesaemia, activation of platelets, alteration of thromboxane prostacyclin homeostasis [58] and damage to endothelial cells by thrombin generation via procoagulant endothelial microparticles [59]. Some authors have suggested that, due to the high incidence of TEE, all patients receiving cisplatin-based chemotherapy may benefit from TEE prophylaxis and that prospective studies are warranted [60].

New drugs in randomised trials in the new millennium

One way to improve outcomes for patients treated with cisplatin doublets in the first-line setting is to add a new biological therapy. The non-selective application of EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib has not proven to be effective. Indeed more than 14,000 patients have been entered into studies with these and other targeted agents without measurable gain in OS (Table 3). All the trials had scientific rationales, for example, targeting cell surface receptors such as EGFR, immunomodulators such as interleukin-2, or toll-like 9 receptors, addition of cyclooxygenase-2 inhibitors, and antisense approaches against protein kinase C-alpha. Despite this, the high failure rate of these trials should motivate researchers to improve the quality of translational research and thereby increase the probability of clinical success and patient benefit.

Cisplatin resistance

Platinum-based chemotherapy for advanced NSCLC is not curative, and in neo-adjuvant chemotherapy trials pathological complete RRs are approximately 10% [61]. This reflects either de novo
or acquired resistance to chemotherapy and represents one of the most significant barriers to improving long-term outcomes [62]. Most of the studies to elucidate mechanisms of resistance to platinum agents have been conducted in cell lines [63]. Multiple mechanisms seem to be at play, and these studies have provided valuable insights that have formed the basis of several rational approaches to circumvent resistance in patients [63].

**Table 3**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Trials (n)</th>
<th>Patients (n)</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>2</td>
<td>2130</td>
<td>[104,105]</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>3</td>
<td>2405</td>
<td>[106–108]</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>1</td>
<td>676</td>
<td>[109]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Unknown, angiogenesis</td>
<td>1</td>
<td>722</td>
<td>[110]</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>VEGFR2 and EGFR</td>
<td>1</td>
<td>181</td>
<td>[111]</td>
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<tr>
<td>Sorafenib</td>
<td>VEGFR2, RAF</td>
<td>2</td>
<td>1830</td>
<td>[112,113]</td>
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<tr>
<td>Prinomastat</td>
<td>MMP</td>
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<td>[114]</td>
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<td>Rebinostat</td>
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<td>Retinoid X-receptor</td>
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<td>623</td>
<td>[125]</td>
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</table>

Table populated based on PubMed searches, 13 Aug 2014, using the search string ‘NSCLC OR “Non small cell lung cancer” AND (OS OR “overall survival”) AND <<name of drug>>’ and the filters ‘Clinical Trial, Phase II’ and ‘Clinical Trial, Phase III’. Results were manually filtered to include only first-line treatment, platinum doublets and trials showing no overall survival advantage.

The total number of patients (all regimens) enrolled in the trial(s).

**Fig. 2.** Major mechanisms of tumour resistance to cisplatin. For further explanation refer to the text. BRCA1, breast cancer 1 early onset; cAMP, cyclic adenosine monophosphate; CTR1, Copper TRansport1 (high affinity copper transporter of the plasma membrane); ERCC, excision repair cross compliment; SIRT1, sirtuin (silent mating type information regulation 2 homolog) 1 (Saccharomyces cerevisiae).

**Transport and enhanced DNA repair and cisplatin resistance**

Mechanisms of tumour resistance to cisplatin mediated by inadequate levels of platinum reaching target DNA are shown in Fig. 2. Cisplatin enters cells either by transporters, such as the copper transporter CTR1, or by passive diffusion [64]. A loss of CTR1 results in less platinum entering the cells and, therefore, in resistance. Enzymatic inactivation of cisplatin by metallothioneins and glutathione-related metabolism enzymes, such as glutathione transferase, have also been described in some platinum-resistant cancer cells.

There are four main DNA-repair pathways: nucleotide-excision repair (NER), base-excision repair (BER), mismatch repair (MMR) and double-strand-break repair (Fig. 2). BRCA1 is a tumour suppressor involved in DNA repair, in both NER and homologous repair pathways, which repairs double-strand breaks. BRCA1 mediates resistance to cisplatin in multiple cancers, including NSCLC [65,66]. In the absence of functional BRCA1, 53 binding protein 1 (53BP1) can mediate DNA repair via error-prone non-homologous end joining (NHEJ), whilst being able to block homologous repair [67]. Accordingly, in NSCLCs with low levels of BRCA1, high levels of 53BP1 are predictive for shorter survival compared with low levels of the tumour suppressor 53BP1 [68].

Excision repair cross-complementation group 1 (ERCC1) is also involved in regulation of the NER pathway. Increased ERCC1 expression is correlated with cisplatin resistance in cells harbouring this mutation [69]. Indeed, adjuvant cisplatin-based therapy improved survival in patients with ERCC1-negative NSCLC [65,66]. In the absence of functional BRCA1, 53 binding protein 1 (53BP1) can mediate DNA repair via error-prone non-homologous end joining (NHEJ), whilst being able to block homologous repair [67]. Accordingly, in NSCLCs with low levels of BRCA1, high levels of 53BP1 are predictive for shorter survival compared with low levels of the tumour suppressor 53BP1 [68].

Excision repair cross-complementation group 1 (ERCC1) is also involved in regulation of the NER pathway. Increased ERCC1 expression is correlated with cisplatin resistance in cells harbouring this mutation [69]. Indeed, adjuvant cisplatin-based therapy improved survival in patients with ERCC1-negative NSCLC (HR 0.65, P = 0.002), but not in those patients with ERCC1-positive NSCLC (adjusted HR for death 1.14, P = 0.4) [70]. However, subsequent analysis of this cohort and also a validation set from the JBR10 and CALGB 9633 trials were unable to verify these original results with 16 commercially available antibodies, questioning the usefulness of evaluating NER ERCC1 expression in therapeutic decision-making due to lack of epitope specificity [71].

In contrast to somatic mutations, germline genetic polymorphisms may regulate sensitivity to platinum. Accordingly, in an analysis of 229 patients with NSCLC receiving front-line...
chemotherapy, 25 functional polymorphisms in 16 genes involved in cisplatin metabolism were analysed. As the number of unfavourable NER genotypes increased (of a possible 12 polymorphisms), a progressively increased hazard of death was observed, suggesting that multiple NER genetic variants have a cumulative effect [72].

Defective DNA repair pathways and cisplatin resistance

Cells defective in DNA MMR are known to be highly resistant to cisplatin [73]. The putative DNA MMR gene and candidate tumour suppressor NPR12 encoded at 3p21.3 have been correlated with cisplatin response [74]; somatic mutation in this region has been found to be associated with smoking [75]. Additionally, promoter methylation of the MMR gene hMLH1 occurred in 55.8% of NSCLCs in one analysis [76] and was associated with poor prognosis in another [77]. Aurora kinase A is a regulator of DNA damage-induced apoptotic response, and its encoding gene AURKA is significantly amplified in cancer. Elevated aurora kinase A mediates cisplatin resistance through phosphorylation of p73 [78].

Poly adenosine diphosphate (ADP)-ribose polymerase (PARP)1 overexpression and constitutive hyperactivation has been associated with cisplatin resistance [79]. Targeting PARP repair of platinum-induced DNA adducts is one resistance mechanism that may show promise in future clinical trials [80].

Survival pathway activation and platinum resistance

Hypoxia is a common feature of solid tumours, including NSCLC, that mediates platinum resistance through inactivation of a tumour suppressor pathway regulated by the nicotinamide adenine dinucleotide (NAD)^+−dependent protein deacetylase, sirtuin 1 (SIRT1) [81], both in vitro and in vivo. Hypoxia leads to downregulation of SIRT1 with consequent inhibition of AMP-activated protein kinase (AMPK) leading to attenuation of apoptosis. Overexpression of paxillin, a protein that mediates extracellular signal-regulated kinase (ERK) activation, has also been implicated in cisplatin resistance [82]. Phosphorylation of paxillin via the SRC pathway increased ERK activation, which activates BCL2 transcription, thereby increasing BCL2 levels and cisplatin resistance.

Matrix remodelling and cisplatin resistance

Molecular profiling has revealed frequent upregulation of extracellular matrix proteins in platinum-resistant cells. The gene COL1A2, which encodes collagen VI, is sufficient to confer resistance to cisplatin in vitro (when cells are cultured in its presence), and in vivo expression is increased in the extracellular matrix adjacent to the tumour, suggesting that cancers may remodel the extracellular matrix to mediate cisplatin resistance [83]. Collagen VI alpha-3 mediates cisplatin resistance through its cleavage product endotrophin, which induces epithelial-mesenchymal transition and has been identified as a possible target for therapy, as it can be inhibited by thiazolidinediones [84].

Stemness and platinum resistance

A subset of primary NSCLC cells express CD133, a surface glycoprotein associated with cancer-initiating cells. These cells exhibit high tumorigenic potential in severe combined immunodeficiency (SCID) mice with expression of genes involved in drug efflux and stemness, and they also exhibit resistance to cisplatin. Furthermore, these cells are enriched after platinum treatment, reflecting a putative population of cisplatin-activated chemoresistant cells [85]. Selection for cisplatin resistance in vitro following repeated exposure enriches a cell population [86].

Golgi response and resistance to DNA damage

The cytoplasmic response to DNA damage has recently been shown to involve dramatic reorganisation of the golgi, resulting in golgiprophosphoprotein 3 (GOLPH3)-dependent cytoplasmic dispersal [87]. GOLPH3 is phosphorylated following DNA damage by DNA-dependent protein kinase leading to an increased interaction with myosin 18A (myo18A), which tethers golgi via F-actin. Importantly, this process appears to be linked to the survival of cells following DNA damage, and as such, overexpression of GOLPH3, which is a significantly focally amplified gene in solid cancers, confers resistance to DNA damage-inducing agents.

The DNA damage “responder phenotype” and platinum rechallenge

A recent pooled analysis showed that NSCLC patients who had relapsed after first-line platinum-based chemotherapy obtained an RR of 27% after platinum rechallenge with pemetrexed or taxanes [88]. Another approach has been to explore molecular determinants of homologous recombinant repair deficits [89]. Indeed, there is a potential link between BRCA1 expression and platinum sensitivity [90,91], and PARP inhibition has been shown to induce synthetic lethality in BRCA1-deficient NSCLC cell lines [92]. Together these findings suggest that exploitation of homologous repair deficiency could be achieved by rechallenge with platinum-based regimens or by the use of a PARP inhibitor. Furthermore, an ongoing trial (CRUK PIN) is exploring PARP inhibitor maintenance in DNA damage-sensitive patients after treatment with cisplatin (ClinicalTrials.gov Identifier NCT01788332). Conversely, recent evidence from preclinical studies of cisplatin-resistant cell lines has shown that PARP1 overexpression may be associated with sensitivity to PARP inhibition but resistance to cisplatin. If this biology extends to the clinical scenario, one implication may be that a subset of platinum-refractory NSCLCs may exhibit sensitivity to PARP inhibition.

The future: new platinums on the horizon

The limitations of cisplatin have led to the development of newer agents with the aims of reducing toxicity and overcoming resistance [93]. By the 1990s, cisplatin and carboplatin were established marketed agents. Although many other new platinum agents had entered development, fewer than 1% of the great number of platinum complexes tested preclinically reached clinical trials [93] and none (until recently) provided the significant benefit that cisplatin or carboplatin offered [63] in NSCLC. Further understanding of the mechanisms of action of these agents and mechanisms of acquired tumour resistance led to a resurgence in platinum development and usage [94]. Strategies included greater delivery of platinum to the tumour by, for example, using liposomal preparations, combining platinum agents with targeted therapies such as bevacizumab, and the development of newer agents that circumvent resistance [63]. The most notable agents to undergo development in this respect are oxaliplatin, satraplatin (an oral alternative to carboplatin) [63], picoplatin (which confers a reduction in inactivation by the thiol-containing compounds glutathione [95] and metallothionein [96]). However, none of these agents has shown promise in the treatment of NSCLC. Against this background, one newer platinum agent that has shown some promise is nedaplatin. In a recent Phase III study of Japanese patients with squamous cell NSCLC, a significant improvement in OS was noted for those treated with nedaplatin plus docetaxel (13.6 vs 11.4 months; HR 0.81, 95% CI 0.65, 1.02; p = 0.037) [97].
Conclusions

For those patients with NSCLC who do not have a drug-targetable driver (approximately 85–90%), platinum-based chemotherapy remains the first-line treatment, which confers the most clinical benefit for patients with advanced NSCLC. Platinum-based therapy is also the principal approach following targeted therapy. Within the group of chemotherapeutic options available, cisplatin-based doublet therapy at a cisplatin dose of 75–80 mg/m² every 3 weeks for up to 4–6 cycles remains the mainstay of first-line treatment (although recent evidence suggests that 6 cycles do not provide additional benefit). For this reason, research activity has mainly focussed on improving delivery of cisplatin and managing the well-established toxicity profile.

Further research regarding sensitivity and resistance to cisplatin is ongoing and may one day lead to a stratified approach to NSCLC patient selection for this agent.

Conflicts of interest statement

M. Das, F. Maxwell, C. Visseren-Grul and D. Ferry are employees of Eli Lilly & Company. J. Cadranel is a primary investigator of several Lilly trials (without financial compensation), participates as an expert in French and international Lilly Advisory Boards (with financial compensation) and has received fees from Eli Lilly to give talks in different academic meetings. T. Benejal, D. Christoph, D. Fennell, R. Lal and Y. Summers have declared no conflicts of interest.

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