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Review Article

Current Concepts in the Use of Cisplatin: A Historical Perspective and Its Recent Advances in the Treatment of Non-Small Cell Lung Cancer

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Abstract

Cisplatin is a first generation chemotherapy agent whose anticancer activity was discovered through serendipity. The accidental discovery of its anticancer properties in the 1970s represents a major landmark in the history of successful anticancer agents. Cisplatin is an effective anticancer agent that has been successfully utilized in the treatment of a wide range of cancers including lung, head and neck, testicular, bladder, cervical, and ovarian cancers. Cisplatin exerts its cytotoxic effects by forming DNA adducts and subsequently inhibiting DNA replication. However, its dose-limiting adverse toxicity profile, the low biological availability and the development of resistance to cisplatin treatment in certain tumors has led to the development of other platinum (II) analog s such as carboplatin, oxaliplatin, etc., as potential anticancer drugs. Alternatively, to minimize the tumor resistance and improve its clinical effectiveness, cisplatin was combined successfully with other cytotoxic drugs. Currently, cisplatin combination regimens are the premier form of combination therapy for a variety of tumors including lung, head and neck, bladder, cervical, ovarian and other solid tumors. In this review article, we provide an overview of the current state of knowledge and clinical experience of cisplatin specifically highlighting its historical background, mechanism of action, development of tumor resistance and strategies to overcome its resistance in the treatment of cancer. In addition, we analyzed the current use of platinum-based combination therapies with novel cytotoxic drugs, and new targeted and immunotherapeutic agents in the treatment of non-small lung cancer.

INTRODUCTION

Cisplatin is a first generation chemotherapy agent whose anticancer activity was discovered through serendipity by Barnet Rosenberg in 1965 [1]. Based on its promising activity in preclinical models, cisplatin entered phase I clinical trials in 1971 for the treatment of cancer [2]. The first evidence of substantial anti-tumor activity of this single agent chemotherapy was seen in 1974 for both testicular and ovarian cancers [3,4]. In 1978, the Food and Drug Administration granted its approval for use under the name of Platinol® (Bristol-Myers Squibb) for the treatment of metastatic testicular, bladder, and ovarian cancer in combination with other drugs. The antitumor effects of the platinum compounds and their clinical application in the late 1970s was a milestone in the development of successful systemic anti-cancer chemotherapeutic agents [5].

Cisplatin is one of the most potent chemotherapy agents that is used in a wide variety of cancer therapies. Specifically, cisplatin-based chemotherapy has been successfully employed in the management of malignancies that include gynecological, lung, head and neck, bladder, germ cell, lymphoma, osteosarcoma, and melanoma as well as neuroblastomas [6,7]. Although cisplatin proved to be effective against many cancers, its toxicities such as renal damage, neurotoxicity, emesis, and ototoxicty has limited its long-term use in the treatment of cancer [6,7]. The dose-limiting side effects for cisplatin is nephrotoxicity and neurotoxicity [8]. In addition to its adverse toxicity profile, the low biological availability restricts its therapeutic applications. Moreover, it is ineffective for other cancers and may lead to the development of a drug resistance in some cancers. To overcome these limitations, a search began for cisplatin analogues that were more potent and effective against a larger range of tumors, but less toxic, and would have fewer side effects, and were not subject to the development of drug resistance. This led to the introduction of the other platinum (II) analog compounds such as carboplatin, oxaliplatin, etc., as potential anticancer drugs (Figure 1).

HISTORICAL PERSPECTIVE

Cisplatin is a small molecule with an interesting history. It is a metallic coordination of complexes of a platinum compound with a square planar geometry and called as cis-diamminedichloroplatinum (II) or cisplatinum. It was first synthesized by Michael Peyrone in 1844 [9] in Turin, Italy and was historically known as Peyron's chloride. The sterical configuration of the cisplatin molecule was originally elucidated by the Zurich's scientist, Alfred Werner in 1893 [10]. It played

a vital role in the establishment of Alfred Werner's theory of coordination chemistry when he correctly proposed its square planar configuration and distinguished between the cis and trans isomers: cisplatin and transplatin. Cisplatin is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in organic solvents such as dimethylprimanide and dimethylformamide. Although cisplatin was synthesized in 1844, it did not undergo much scientific investigations until Barnet Rosenberg's accidental discovery of its antitumor activities in the1960s [1].

MECHANISM OF ACTION OF CISPLATIN

Cisplatin-based chemotherapy exerts its cytotoxic effect by forming DNA adducts and subsequently inhibiting DNA replication [2,6,11,12]. The mechanism of action of cisplatin is shown in Figure 2. In its cis configuration where two ammine ligands are on one side and other two chloro ligands are on the other side of the same square creates the planar geometry around the platinum (II) ion which makes cisplatin to bind DNA covalently leading to the destruction of tumor cells. However, in its trans configuration (transplatin) where the two ligands are on both sides of the square plane, it cannot bind to the two strands of DNA to induce any DNA damage and thus it is ineffective against cancer cells [2,6,11,12].

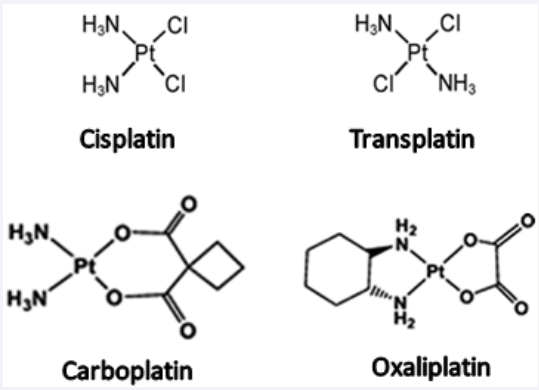

Figure 1 Molecular structure of platinum compounds.

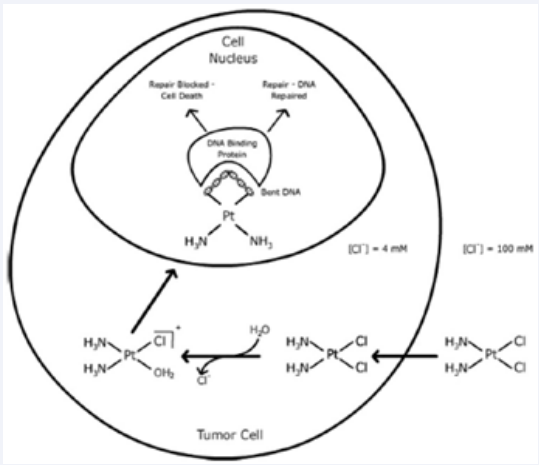

Figure 2 Mechanism of action of cisplatin.

Following its administration, a majority (over 90%) of the cisplatin binds to plasma proteins and is excreted through the renal system [2,13]. The unbound or intact cisplatin molecules are transported through the blood in an unaltered form. Since the blood supply to tumor cells is much higher than that of normal cells, a higher amount of the drug is delivered to malignant tumor cells. After passive transport of the unbound cisplatin through the cell membranes, it is hydrolyzed due to the lower chloride concentration in the intracellular regions. During its hydrolysis, the chloride ligand on the cisplatin becomes an aqua ligand by displacing the chloride molecule with a water molecule forming a reactive, positively charged [cis-Pt (NH_3) 2Cl (H_2O)]+ species that cannot readily leave the cell [14]. The positively charged species readily allows the cisplatin to coordinate with the negatively charged DNA and form a crosslinked adduct. Thus, the hydrolysis reaction of cisplatin is the rate-determining step for DNA binding.

Cisplatin binds to the DNA in many different ways. Specifically, it can bind to the nucleotide bases such as guanine, or cytosine, or adenine. However, its binding to guanine is more favored due to a higher nucleophylicity [12]. Nevertheless, crosslinked adducts that were formed when cisplatin binds with nucleotide bases of the DNA, actively interferes with cell division through mitosis [15]. The damaged DNA elicits DNA repair mechanisms, which in turn activate apoptosis when the repair proves to be impossible. The crosslinked adducts de-stacks the nucleotide bases making a kink in the DNA helix which blocks the DNA repair mechanisms leading to apoptosis and programmed cell death [12]. In addition, cisplatin induces tumor cell death by the induction of apoptosis which is mediated by the activation of various signal transduction pathways, including calcium signaling, death receptor signaling, and the activation of mitochondrial pathways [16]. Moreover, cisplatin also interferes with the transcription and DNA replication mechanisms in the cell leading to cytotoxicity depending on the cell type and the concentration of the drug molecule. In addition to DNA damage, cisplatin is capable of inducing an oxidative stress, which is one of the most important mechanisms leading to its cytotoxic effects on tumor cells. Cisplatin causes oxidative stress by increasing the level of reactive oxygen species also known as oxygen free radicals and reducing antioxidant defense mechanisms [17-19]. Under oxidative stress condition, excessive reactive oxygen species such as super oxide anions and hydroxyl radicals can damage cellular proteins, lipids and DNA leading to tumor cell death.

Cisplatin toxicity

Although cisplatin is a highly effective anticancer agent, its full potential is limited by its dose-limiting toxicity such as nephrotoxicity and neurotoxicity [20-23]. It is believed that cisplatin-induced nephrotoxicity is mediated through its transport into the renal epithelial cells, which subsequently causes injury to the nuclear and mitochondrial DNA, activation of cell apoptosis and necrosis, and the stimulation of inflammatory responses. The production of a reactive oxygen species by the cisplatin molecule has also been implicated in the development of its nephrotoxicity. However, novel strategies are being explored to overcome the cisplatin-induced nephrotoxicity while protecting its clinical activity [24-26]. Among those strategies, magnesium supplementation has been shown to be effective

in protecting against cisplatin-induced nephrotoxicity [27,28]. Similarly, cisplatin-induced nephrotoxicity has been shown to be prevented with the glutathione supplementation in ovarian cancer patients [29]. Cisplatin induced other common side effects include ototoxicity, hepatotoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia [8,23].

Cisplatin resistance

Although cisplatin plays a major role in the treatment of a variety of malignancies, its clinical use is limited by either acquired or intrinsic tumor cell resistance or its adverse side effects [30-34]. Most of our understanding about the tumor cells' resistance after cisplatin exposure is derived from preclinical models. It appears that the development of cisplatin resistance is multifactorial [30]. After formation of the cisplatin linked DNA adducts, the development of tumor drug resistance can occur either by DNA repair or removal of these adducts, or by the development of tolerance mechanisms [30-34]. It is possible that tumor cells can elude the cytotoxic potential of cisplatin before it binds to the cytoplasmic targets and DNA. Reduced intracellular concentrations due to decreased cisplatin uptake or elevated reflux and increased inactivation by sulfhydryl molecules such as glutathione can also cause resistance to cisplatin. In addition, increased excision of the platinum adducts from DNA by cellular repair pathways or increased lesion bypass can also result in its resistance [30-34]. Differential capacity to repair cisplatin-DNA adducts may also be responsible for the variability of the clinical effectiveness of cisplatin-based therapy. Moreover, altered expression of regulatory proteins involved in signal transduction pathways that control the apoptosis can also affect the tumor sensitivity to the drug. A better understanding of the tumor resistance mechanisms is needed for the development of different therapeutic strategies aimed at circumventing cellular resistance to cisplatin and for improving cancer therapy [30-34].

Carboplatin or Cis diammine (1,1-cyclobutanecarboxylato) is a second-generation platinum (II) complex chemotherapeutic drug used for the treatment of various cancers (Figure 1). It was approved in the United Kingdom and Canada in 1985 and shortly thereafter in the United States [6,16,35]. The molecular structure of the carboplatin differs from cisplatin in that it has a bidentate dicarboxylate ligand in place of the two chloride ligands, which are the leaving groups in cisplatin. The mechanism of action of carboplatin is very similar to that of cisplatin as it binds with DNA and affects replication. However, the carboxyl ester groups in this platinum complex of carboplatin are less easily displaced so that it exhibits lower reactivity, slower DNA binding kinetics, and a more favorable adverse effects profile as compared to cisplatin. In some tumors, Carboplatin appears to be better tolerated and may have less potent cytotoxic activity than cisplatin, whereas both drugs seem to have comparable efficacy in lung and ovarian cancers [36,37].

Cisplatin combined with other antitumor agents

The major obstacle concerning the efficacy of cisplatin is the development of tumor cell resistance [16,30]. To overcome this cellular resistance and improve clinical effectiveness, cisplatin is commonly used in combination with other cytotoxic agents [38]. It is believed that combining cisplatin with other different antitumor agents either delays the development of tumor resistance or completely overcomes drug resistance. Conventionally, etoposide, bleomycin and less commonly vinblastine are combined with cisplatin-based chemotherapy for the treatment of certain tumors. Such combinations have been shown to be effective in increasing the remission rates and reducing the side effects of the cisplatin [6,39]. Following the success of cisplatin combination, many trials have assessed the clinical effectiveness of novel therapeutic combinations with cisplatin for the treatment of advanced non small cell lung cancer (NSCLC). Currently, the most commonly used cisplatin based chemotherapy agents for NSCLC include docetaxel, paclitaxel, gemcitabine, pemetrexed, irinotecan, and vinorelbine [40].

Cisplatin in the treatment of advanced NSCLC

NSCLC accounts for up to 85% of all lung cancer cases [41,42], and roughly more than 70% of patients present with locally advanced or disseminated disease at the time of diagnosis and are not appropriate candidates for surgery [43]. Most NSCLC patients present with locally advanced inoperable or metastatic disease, which in the past made their cancer incurable, and almost all of these patients died from their disease.

Cisplatin or carboplatin containing doublets in advanced NSCLC

Despite significant treatment advances, cisplatin or carboplatin based doublet regimens are still the mainstay of most of the combination regimens used in the treatment of the patients with advanced NSCLC. For several decades, there has been a concerted effort to define and refine the use of the platinum agents in the management of advanced NSCLC. A meta-analysis of 16 clinical trials comparing platinum-based regimens to non-platinum agents showed statistically significant higher response rates with an improved one-year survival favoring the use of the cisplatin for the treatment of metastatic NSCLC [44]. In addition, a number of randomized controlled trials have shown that cisplatin or carboplatin based chemotherapy is associated with an improvement in the overall survival and the patients' quality of life compared to best supportive care alone in patients with advanced NSCLC [45-47]. A number of randomized phase III trials have evaluated the clinical effectiveness of platinum-based doublet regimens successfully in advanced non-small cell lung cancer (Table 1) [48-63]

The Eastern Cooperative Oncology Group's (ECOG) 1594 four-arm randomized phase III trial compared the clinical effectiveness and toxicity profile of platinum based doublet chemotherapy in patients with advanced NSCLC [49]. The platinum-based doublet chemotherapy included cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus paclitaxel, or a reference regimen of cisplatin plus paclitaxel. The rationale for conducting such a trial was to gain an insight into the efficacy of the new, at that time, platinum-based doublet combinations. The ECOG study demonstrated no difference in response rate, median survival time, or one-year survival rate among the four platinum-based doublet regimens. However, cisplatin plus gemcitabine did confer a longer time to tumor progression. Similar outcomes were reported in the Southwest Oncology Group 9509 study

Table 1: Clinical outcomes of the selected randomized phase III trials of platinum-based doublet chemotherapy in advanced non-small cell lung cancer.

Regimen	Patients (N)	Selection of Patients	Median PFS or TTP Months	Median OS Months	Reference
Cisplatin plus irinotecan vs Cisplatin plus gemcitabine or Cisplatin plus vinorelbine or Carboplatin plus paclitaxel	145 146 145 145	Unselected	4.7 4 4.1 4.5	13.9 14 11.4 12.3	[48]
Cisplatin plus gemcitabine vs. Cisplatin plus docetaxel or Carboplatin plus paclitaxel or Cisplatin plus paclitaxel	288 289 290 288	Unselected	4.2** 3.7 3.1 3.4	8.1 7.4 8.1 7.8	[49]
Carboplatin plus pemetrexed vs. carboplatin plus gemcitabine	219 217	Unselected	NR	7.3 7	[50]
Cisplatin plus capecitabine vs. cisplatin plus 5-fluorouracil	139 137	Unselected	5.6 5	10.5 9.3	[51]
Cisplatin plus gemcitabine vs. Cisplatin plus pemetrexed	488 512	Nonsquamous	4.7 5.3	10.4* 11.8	[52]
Cisplatin plus docetaxel or Carboplatin plus docetaxel vs. Cisplatin plus vinorelbine	408 406 404	Unselected	NR	11.3* 10.1 9.4	[53]
Cisplatin plus etoposide versus Carboplatin plus paclitaxel	178 188	Unselected	3.7 4	9.1 7.8	[54]
Cisplatin plus vinorelbine vs. Docetaxel plus gemcitabine	197 192	Unselected	NR	9.7 9	[55]
Cisplatin plus docetaxel vs. Cisplatin plus vindesine	156 155	Unselected	NR	11.3 9.6	[56]
Cisplatin based doublets vs. Gemcitabine plus vinorelbine	252 251	Unselected	5.8 4.3	9.5 8	[57]
Cisplatin plus paclitaxel vs. Cisplatin plus gemcitabine or Paclitaxel plus gemcitabine	159 160 161	Unselected	4.2 5.1 3.5	8.1 8.9 6.7	[58]
Cisplatin plus gemcitabine vs. Gemcitabine plus epirubicin	119 121	Unselected	6.5 5.8	10.8 9	[59]
Cisplatin plus paclitaxel vs. Carboplatin plus paclitaxel	302 306	Unselected	3.3 2.9	9.8 8.5	[60]
Cisplatin plus vinorelbine vs. Carboplatin plus paclitaxel	197 203	Unselected	NR	8.1 8.6	[61]
Cisplatin plus gemcitabine vs. Cisplatin alone	260 262	Unselected	5.6** 3.7	9.7** 7.6	[62]
Cisplatin plus gemcitabine vs. Cisplatin plus etoposide	69 66	Unselected	6.9** 4.3	8.7 7.2	[63]

*P < 0.05; **P < 0.01; PFS: Progression free survival; TTP: time to tumor progression; OS: Overall survival NR: Not reported

and other randomized studies that compared various two-drug platinum based combinations [53,54,61].

Irinotecan, a cytotoxic alkaloid has been extensively evaluated in combination with cisplatin in patients with advanced NSCLC in Japan. A four-arm randomized clinical phase III trial compared the efficacy of cisplatin plus Irinotecan versus cisplatin plus gemcitabine or cisplatin plus paclitaxel or cisplatin plus vinorelbine in advanced NSCLC patients [48]. Similar to the findings observed in ECOG 1594 trial [49], the study demonstrated comparable efficacies among the four regimens. Importantly, the platinum-based doublet regimens have demonstrated a clinical effectiveness and acceptable safety profile in elderly patients and in patients with a poor performance status [64,65]. To assess the clinical role of platinum-based chemotherapy, several phase III trials assessed the clinical activity of the platinum-based versus platinum-free doublets in patients with advanced NSCLC (Table 1). Although these trials demonstrated similar results for platinum-based and platinum-free doublets, the platinum-based treatment revealed higher response rates with a trend towards better survivals [55,57,58]. However, the superiority of platinum-based treatment was not confirmed in all of the studies [66-68]. The platinum doublets that are currently preferred for advanced NSCLC include the combinations of cisplatin or carboplatin with one of the third-generation non-platinum based chemotherapy agents.

Cisplatin or carboplatin containing triplets in advanced NSCLC

Given that platinum-based doublets are associated with superior clinical outcomes than with those of the single agents in advanced NSCLC patients, could better survival outcomes be seen if another cytotoxic drug was added to the cisplatin-based doublets. In this regard, several randomized clinical trials have assessed the clinical effectiveness and safety of these triplet

regimens by adding an active cytotoxic drug to the platinum based doublets in an attempt to further improve treatment outcomes in patients with advanced NSCLC (Table 2) [69-77].

Numerous phase III randomized trials have studied the role of platinum-based triplets in treatment of advanced NSCLC [69,70,73,76]. Although three-drug platinum based regimens achieved significantly higher response rates in patients with advanced NSCLC, the triplet regimens failed to demonstrate clinical benefit in terms of progression free survival and overall survival, and were associated with significantly higher toxicity. The clinical effectiveness of triplet regimens was further addressed in two meta-analyses [78,79] that were consistent in demonstrating that the triplet regimens improved response rates, but those improvements did not lead to any significant survival prolongation. In addition, the triplet combination therapy had higher toxicities. Based on these findings, the 2009 American Society of Clinical Oncology (ASCO) guidelines recommend against the use of triplet cytotoxic drug combinations in the treatment of advanced NSCLC [80].

Cisplatin or carboplatin combined with molecular targeted agents in advanced NSCLC

The treatment of patients with advanced NSCLC has continued to improve due to the continued evolution of novel chemotherapy drugs and the introduction of novel targeted agents. In addition, an increased understanding of the biological mechanisms of lung tumor growth and different histologic and molecular subtypes have allowed the identification of certain molecular targets such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and program death-ligand 1 (PD-L1) for novel targeted therapies [81-83]. A number of clinical trials have been dedicated to try to improve the treatment survival outcomes by combining novel drugs to standard platinum-based doublets, but most were not successful (Tables 3) [84-91].

Platinum-based chemotherapy in combination with EGFR inhibitors such as gefitinib and erlotinib in advanced NSCLC patients have shown mixed results in randomized clinical trials. A recent phase III open label (NEJ009) trial [84] recently assessed the clinical effectiveness of combining gefitinib with platinum based chemotherapy in previously untreated patients with advanced NSCLC harboring EGFR-activating mutations. The trial demonstrated that the patients who were treated with platinum-based chemotherapy plus gefitinib had superior survival outcomes than those received gefitinib alone. Similarly, the Iressa Mutation-Positive Multicenter Treatment Beyond ProgRESsion Study (IMPRESS) [86] compared the continuation of gefitinib plus chemotherapy with a placebo plus chemotherapy in patients who progressed after gefitinib therapy and had a EGFR mutation positive advanced NSCLC. The study did not show any survival benefit with the combination therapy and the findings were sufficient to warn against the continuation of treatment with first-generation EGFR tyrosine kinase inhibitors beyond radiologic disease progression when chemotherapy was initiated.

A phase III FASTACT-2 trial [88] has shown that an Intercalated combination of platinum based chemotherapy plus erlotinib significantly improved the overall survival of patients with advanced NSCLC. A meta-analysis that included randomized controlled trials concluded that the combination of erlotinib plus platinum-based chemotherapy did not show a significant survival benefit in patients with advanced NSCLC [92]. However, this meta-analysis showed that platinum-based chemotherapy with erlotinib was a viable treatment option for patients with NSCLC, especially for those who never smoked and patients who had EGFR mutation-positive disease.

Table 2: Clinical outcomes of the selected randomized phase III trials of platinum-based triplet regimens (triplets versus triplets or doublets) in advanced non-small cell lung cancer.

Regimen	Patients (N)	Selection of Patients	Median PFS or TTP Months	Median OS Months	Reference
Triplets with or without platinum vs. Doublets with or without platinum	214 203	Unselected	5.7 5.6	103 10.4	[69]
Cisplatin plus vinorelbine and bexarotene vs. Cisplatin plus vinorelbine	311 312	Unselected	NR	12.3 9.9	[70]
Cisplatin plus gemcitabine and vinorelbine or cisplatin plus gemcitabine and paclitaxel vs. Gemcitabine and vinorelbine or Gemcitabine and paclitaxel	216 217	Unselected	6.1 5.5	10.7 10.5	[71]
Cisplatin plus gemcitabine and paclitaxel gemcitabine versus Gemcitabine and paclitaxel	165 159	Unselected	7.6* 5.1	10.8* 8.3	[72]
Cisplatin plus gemcitabine and vinorelbine vs. Cisplatin plus gemcitabine	188 182	Unselected	6.7 6.3	8.2 9.3	[73]
Cisplatin plus vinorelbine and ifosfamide vs. Cisplatin plus vinorelbine	126 133	Unselected	4.4 5	8.2 10	[74]
Cisplatin plus vindesine and mitomycin C vs. Cisplatin plus vinorelbine	58 55	Unselected	4.5 4.2	8 7	[75]
Cisplatin plus gemcitabine and vinorelbine vs. Cisplatin and gemcitabine or Cisplatin and vinorelbine	60 60 60	Unselected	NR	12.8** 10.5 8.8	[76]
Cisplatin plus mitomycin and vinorelbine versus Cisplatin plus mitomycin and vindesine	114 113	Unselected	NR	8.4 8.6	[77]

*P < 0.05; **P < 0.001; PFS: Progression free survival; TTP: time to tumor progression; OS: Overall survival; NR: Not reported

Table 3: Clinical outcomes of the selected randomized phase III trials of platinum-based doublet regimens with molecularly targeted agents in advanced non-small cell lung cancer.

Regimen	Patients (N)	Selection of patients	Median PFS Months	Median OS Months	Reference
Carboplatin plus pemetrexed and gefitinib vs. Gefitinib alone	172 172	EGFR Mutation positive	20.9** 11.2	52.2** 38.8	[84]
Carboplatin plus paclitaxel vs. Gefitinib alone	609 608	Adeno-carcinoma	5.8 5.7	17.3 18.6	[85]
Cisplatin plus pemetrexed and gefitinib vs. Cisplatin plus pemetrexed	132 132	EGFR mutation positive	NR	13.4 19.5	[86]
Cisplatin plus pemetrexed and gefitinib vs. Cisplatin plus pemetrexed	133 132	EGFR mutation positive, relapsed on gefitinib	5.4 5.4	NR	[87]
Cisplatin/carboplatin plus gemcitabine and erlotinib vs. Cisplatin/carboplatin plus gemcitabine	49 48	EGFR mutation positive	7.6** 6	18.3* 15.2	[88]
Cisplatin/carboplatin plus gemcitabine and erlotinib vs. Cisplatin/carboplatin plus gemcitabine	226 225	Unselected	16.8** 6.9	31.4** 20.6	[88]
Cisplatin plus gemcitabine and erlotinib vs. Cisplatin plus gemcitabine	580 579	Unselected	5.9 6.2	10.8 11	[89]
Cisplatin plus paclitaxel and erlotinib vs. Cisplatin plus paclitaxel	526 533	Unselected	10.6 10.5	5.1 4.9	[90]
Cisplatin plus gemcitabine and gefitinib (250 mg) vs. Cisplatin plus gemcitabine and gefitinib (500 mg) or Cisplatin plus gemcitabine and placebo	365 365 363	Unselected	5.8 5.5 6	9.9 9.9 10.9	[91]

*P < 0.05; **P < 0.001 ; PFS: Progression free survival; TTP: time to tumor progression; OS: Overall survival; EGFR: Epidermal growth factor receptor; NR: Not reported

Cisplatin or carboplatin combined with molecular targeted antibodies in advanced NSCLC

Several clinical randomized phase III trials have evaluated the clinical effectiveness and safety of combining cisplatin or carboplatin based chemotherapy with molecular targeted antibodies that target EGFR or VEGF pathways in patients with advanced NSCLC. However, many of these trials failed to demonstrate any survival benefit in those patients. Cetuximab is a recombinant human-mouse chimeric monoclonal antibody that that binds to EGFR and competitively inhibits ligand (EGF) binding. In a multinational randomized phase III FLEX (First-Line ErbituX in lung cancer) trial [93] the clinical effectiveness of the addition of cetuximab to platinum-based chemotherapy was evaluated in patients with EGFR-expressing advanced NSCLC. The FLEX trial demonstrated that the patients' overall survival was prolonged with the EGFR targeted antibody cetuximab added to the platinum-based chemotherapy in patients with advanced NSCLC across all histological subtypes. However, the BMS-099 phase III trial [94] showed no survival benefit when cetuximab was added to the platinum based chemotherapy in the treatment of advanced NSCLC patients. The list of selected randomized phase III trials that evaluated clinical effectiveness of the combination of platinum-based chemotherapy with molecularly targeted antibodies is provided in Table 4 [95-100]

Increased VEGF expression is known to be associated with adverse clinical outcomes in patients who have advanced NSCLC. VEGF promotes tumor angiogenesis, which is critical for tumor progression [101]. Bevacizumab is a recombinant, humanized, monoclonal antibody against VEGF that has been assessed for its clinical effectiveness in patients with advanced NSCLC. A large randomized phase III trial by the Eastern Cooperative Oncology Group (ECOG 4599)100 evaluated the addition of bevacizumab to platinum -based chemotherapy agents used to treat patients with advanced non-squamous NSCLC. The study excluded patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or performance status ECOG >1. The trial demonstrated a significantly longer overall survival and progression free survival in patients treated with bevacizumab plus chemotherapy than those treated with chemotherapy alone.

The Avastin in Lung (AVAiL) trial [99] also assessed the clinical effectiveness of cisplatin-based chemotherapy regimens with gemcitabine and with or without bevacizumab in patients with advanced NSCLC. This study showed a significant improvement in the primary end-point of progression free survival with the addition of bevacizumab compared with chemotherapy alone. A recent French Cohort Study102 demonstrated the survival benefits of chemotherapy combinations with bevacizumab in advanced NSCLC patients. Similar outcomes were reported in other randomized studies that compared platinum-based doublet chemotherapy regimens with or without the addition of bevacizumab in patients with advanced NSCLC. Based on the data from ECOG 4599 trial [100-102], the use of bevacizumab with platinum-based chemotherapy regimen has been approved by the Food and Drug Administration for the treatment of patients with advanced NSCLC.

Cisplatin or carboplatin combined with immune checkpoint inhibitors in advanced NSCLC

Immune checkpoint inhibitors (ICIs) are an emerging class of immunotherapy agents that stimulate lymphocytes against tumor cells [103,104] The most studied immune checkpoint inhibitors in the treatment of advanced NSCLC is anti-PD1/anti-PD-L1 agents. In the recent past, several phase III randomized trial have evaluated the clinical effectiveness of the combination of

platinum based with a novel immunotherapy agents in advanced NSCLC (Table 5) [105-109].

The expression of programmed death ligand 1 (PD-L1) is considered a predictive biomarker of anti-programmed death 1 (PD-1)/PD-L1 cancer therapies [111,112]. Immune checkpoint inhibitors targeting the PD-1 receptor and its ligand PD-L1 have recently emerged as a new therapeutic approach for patients with NSCLC. In particular, monoclonal antibodies targeting PD-1 or its ligand PD-L1 have been shown to be active against NSCLC. Pembrolizumab is a fully humanized antibody that disrupts the engagement of PD-1 with its ligands PD-L1 and impedes inhibitory signals and enhances the potential immunogenic effects of cytotoxic chemotherapy [113].

The recent global, double blind, placebo-controlled, phase III KEYNOTE-189 trial [105] assessed the clinical effectiveness of a combination of the cisplatin or carboplatin based chemotherapy with either pembrolizumab or a placebo in patients with non-squamous NSCLC. The trial demonstrated that the addition of pembrolizumab to pemetrexed and a platinum-based chemotherapy resulted in significantly longer overall and progression-free survivals than chemotherapy alone. Based on this data, the Food and Drug Administration approved the use of pembrolizumab in combination with platinum-based chemotherapy for patients with metastatic non-squamous NSCLC. Similarly, another double blind, placebo-controlled, phase III KEYNOTE-407 trial [106] evaluated the clinical activity of the addition of the platinum-based chemotherapy in combination with in patients with advanced squamous NSCLC. The trial showed that the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.

Another recent open-label, randomized IMpower 150 phase III trial [108] evaluated atezolizumab plus bevacizumab plus chemotherapy in patients with metastatic non-squamous NSCLC. This trial showed that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status. The phase III CheckMate 227 trial [109] also recently evaluated the clinical activity of the combination of the cisplatin or carboplatin based chemotherapy with nivolumab versus chemotherapy in patients with non-squamous NSCLC who harbor <1% tumor PD-L1 expression. The findings of the trial are encouraging and the PFS favors platinum-based chemotherapy in combination with nivolumab. The overall survival results are currently pending from this trial. Although the combination of platinum based chemotherapy with immune therapy agents that target targeting PD-1 or its ligand PD-L1, its combination with ipilimumab, a cytotoxic T-cell lymphocyte antigen-4 (CTLA4) inhibitor, has failed to demonstrate a survival benefit, as compared with platinum-based chemotherapy alone, in patients with metastatic squamous NSCLC [110].

Several trials are currently underway investigating platinum-based chemotherapy in combination with checkpoint inhibitors and combinations of PD-1 or PD-L1 agents in patients with advanced NSCLC. The data of the clinical outcome of some of these trials is still evolving but should be available in the near future. The findings of these trials will be important in defining those patient populations who can derive additional benefits from platinum-based combination therapy in the clinical landscape of NSCLC.

As with the rapidly evolving treatment landscape of advanced NSCLC, major innovations in radiation therapy techniques have occurred for the treatment of malignant tumors including NSCLC. An important advance in radiation therapy is the introduction

Table 4: Clinical outcomes of the selected randomized phase III trials of platinum-based doublets with molecularly targeted antibodies in advanced non-small cell lung cancer.

Regimen	Patients (N)	Selection of NSCLC	Median PFS Months	Median OS Months	Reference
Carboplatin plus pemetrexed and bevacizumab vs. Carboplatin plus pemetrexed	144 152	Nonsquamous	5.5 4.4	11.7 10.5	[95]
Cisplatin plus pemetrexed and bevacizumab induction If response or stable disease bevacizumab plus pemetrexed vs. Bevacizumab	376 128 125	Nonsquamous	7.4** 3.7	19.8 15.9	[96]
Carboplatin plus pemetrexed and bevacizumab vs. Carboplatin plus paclitaxel and bevacizumab	472 467	Nonsquamous	6 5.6	17.7 17.7	[97]
Platinum doublet plus bevacizumab induction then bevacizumab vs. Bevacizumab plus pemetrexed	373 370	Unselected	3.7 4.8**	13.3 14.4	[98]
Carboplatin plus taxane and cetuximab vs. Carboplatin plus taxane	338 338	Unselected	4.4 4.2	9.7 8.4	[94]
Cisplatin plus vinorelbine and cetuximab vs. Cisplatin plus vinorelbine	557 568	Unselected	4.8 4.8	11.3 10.1	[93]
Cisplatin plus gemcitabine and bevacizumab (7.5 mg) vs. Cisplatin plus gemcitabine and bevacizumab (7.5 mg) vs. Cisplatin plus gemcitabine and placebo	345 351 347	Nonsquamous	6.7* 6.5* 6.1	NR	[99]
Carboplatin plus paclitaxel and bevacizumab vs. Carboplatin plus paclitaxel	444 434	Unselected	6.2** 4.5	12.3** 10.3	[100]

*P < 0.05; **P < 0.01; PFS: Progression free survival; TTP: time to tumor progression; OS: Overall survival; PD-L1: Program death-ligand 1; HR: Hazard ratio; NR: Not reported

Table 5: Clinical outcomes of the selected randomized phase III trials of platinum-based doublets with immune checkpoint inhibitors in advanced non-small cell lung cancer.

Regimen	Patients (N)	Selection of NSCLC	Median PFS Months	Median OS Months	Reference
Cisplatin/carboplatin plus pemetrexed and pembrolizumab vs. Cisplatin/ carboplatin plus pemetrexed and placebo	405 202	Nonsquamous	8.8** 4.9	Not Reached 11.3	[105]
Carboplatin plus paclitaxel and pembrolizumab vs. Carboplatin plus paclitaxel and placebo	278 281	Squamous	6.4** 4.8	15.9** 11.3	[106]
Carboplatin plus paclitaxel and atezolizumab vs. Carboplatin plus paclitaxel	718 343	Squamous	6.3 5.6	14.0$ 13.9	[107]
Platinum doublet plus atezolizumab and bevacizumab vs. Platinum doublet plus bevacizumab	400 400	Nonsquamous	8.3** 6.3	19.2* 14.7	[108]
Platinum doublet plus nivolumab vs. Platinum doublet	177 186	< 1% tumor PD-L1 expression	HR = 0.74	NR	[109]
Carboplatin plus paclitaxel and ipilimumab vs. Carboplatin plus paclitaxel and placebo	388 361	Squamous	5.6 5.6	13.4 12.4	[110]

*P < 0.05; **P < 0.001; PFS: Progression free survival; TTP: time to tumor progression; OS: Overall survival; PD-L1: Program death-ligand 1; HR: Hazardratio; NR: Not reported; $: Overall survival data not matured

of highly advanced three dimensional conformal radiation therapeutic devices and treatment planning systems for the treatment of complex and irregularly shaped tumors. Specifically, intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have transformed the delivery of radiation to the tumor and has broadened the range of the applications of radiation therapy [114]. A number of randomized clinical trials and meta-analyses have evaluated the clinical effectiveness of radiation therapy with platinum-based chemotherapy in patients with surgically unresectable stage III NSCL [115-124]. These studies support the conclusion that combined modality approaches using radiation therapy combined with cisplatin-based chemotherapy improves the survival compared with radiotherapy alone in patients with surgically unresectable stage III disease. Currently, the combination of platinum based chemotherapy and radiotherapy is the standard treatment approach for unresectable stage III NSCLC patients with a good performance status , Concomitant platinum based chemoradiation therapy, although associated with a potentially increased toxicity, has demonstrated to be a better strategy over that of sequential chemoradiation therapy, and it is to be considered the standard treatment approach in unresectable stage III NSCLC patients with a good performance status [119-121].

CONCLUSION

Cisplatin is a first-generation platinum-based antitumor agent. The introduction of cisplatin-based chemotherapy represented a major landmark and breakthrough in the history of anticancer therapies. Cisplatin has proven to be one of the more potent chemotherapeutic agents and is widely used in the treatment of a variety of malignant tumors. However, because of some severe safety issues associated with cisplatin therapy, especially nephrotoxicity, the development of second generation platinum agents such as carboplatin, which are equally as effective as cisplatin, but have a less toxic profile were developed. Further understanding of the mechanisms of action of these platinum agents and mechanisms of acquired tumor resistance has led to resurgence in use of platinum agents in cancer treatment. By developing strategies to circumvent tumor resistance and improve clinical effectiveness, platinum agents have been combined successfully with the other cytotoxic agents, molecularly targeted agents, immunotherapeutic agents and radiotherapy for the treatment of cancer.

An increased understanding of the biological mechanisms of tumor growth and the discovery of histologic and molecular subtypes of NSCLC have allowed identification of certain molecular targets such as EGFR, VEGF, and PD-L1 genes for novel targeted and immunotherapeutic agents. The novel targeted agents include gefitinib, erlotinib, cetuximab, bevacizumab, and immunotherapeutic agents include pembrolizumab, atezolizumab and nivolumab. The addition of these targeted or immunotherapies therapies with platinum-based chemotherapy agents has yielded mixed results in randomized clinical trials of patients with advanced NSCLC. In an effort to improve overall clinical outcomes, several randomized phase III trials are currently evaluating the clinical effectiveness of novel molecular targeted drugs and immunotherapeutic agents in combination with platinum-based chemotherapy in patients with advanced NSCLC. The clinical outcomes of these trials will be important to help define what possible additional clinical benefits of adding targeted and immunotherapies will be seen when combined with platinum-based chemotherapy.

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