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REVIEW ARTICLE

Cisplatin: Process and Future

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Summary

One of the most important anticancer agents is cisplatin (CDDP). Numerous studies with a CDDP-based combination have been reported over the last 30 years. The use of CDDP in the 1980s and 1990s showed responses in advanced stage non-small-cell lung cancer (NSCLC). Over the years it was found that the side effects of this agent (particularly nephrotoxicity) were a common problem. Agents such as carboplatin, taxanes, gemcitabine, irinotecan and pemetrexed proved to be effective in NSCLC with reduced or no nephrotoxicity. The administration of these newer agents improved several side effects, but without improving efficacy. When prophylactic (adjuvant) treatment for NSCLC was introduced, CDDP was the agent selected, which indicated the value of the drug.

Recently, a novel formulation of CDDP, liposomal cisplatin, which has shown very low toxicity, no nephrotoxicity and equal effectiveness was produced; its importance is its higher effectiveness than standard CDDP in lung adenocarcinoma.

Key words: *cisplatin, lipoplatin, lung adenocarcinoma, non small cell lung cancer, novel formulation, toxicity*

Introduction

CDDP has been shown to be an active agent. The response rate in NSCLC was increased when CDDP was combined with other cytotoxic agents. Numerous studies with a CDDP-based combination have been performed over the last 30 years. The outcome of chemotherapy trials before CDDP involvement was considered to be more toxic than effective [1-4] and the introduction of CDDP in clinical practice produced some flare of hope. The use of CDDP in the 1980s and 1990s showed responses in advanced-stage (IIIB and IV) NSCLC [5-8]. The percentage of responses increased, indicating that there was sensitivity to CDDP in NSCLC. It also led to the assumption that when chemotherapy is applied before surgery and/or radiation therapy, the tumor response is 2 or 3-fold higher than after radio-surgery. Response rates of 50-60% were reported [9-14].

During the last 20 years, taking into account the fact that CDDP was nephrotoxic, clinical trials tried new non-nephrotoxic agents. The new agents were tested as monotherapy or in combination with CDDP. The objective of these trials was to increase effectiveness, response rate and survival, plus to reduce the adverse reactions. Some of the new agents proved to be effective and could be used as front-line chemotherapy and administered even without CDDP. These agents included taxanes (paclitaxel, docetaxel), gemcitabine, irinotecan, vinorelbine and pemetrexed. The median and overall survival rates using CDDP, either combined with previously tested agents (etoposide, vinblastine, vindesine, doxorubicin, mitomycin-C, ifosfamide) or with the newer agents, were similar [15-19] and no improvement in effectiveness was detected. The same results were reported when the cytotoxic drug combinations were tested without CDDP. The results, although effective, were not better than CDDP-based chemotherapy [20-25]. All of these new agents also produced adverse reactions but no nephrotoxicity.

Until the last decade, all of the aforementioned data suggested that CDDP-based chemotherapy should be a standard first-line treatment for advanced NSCLC [26]. These data led to the use of CDDP as adjuvant chemotherapy in patients who

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had lung tumor resection. The CDDP-based combination has been selected for the prophylactic treatment of NSCLC.

Recurrence of NSCLC after tumor resection does happen in a high percentage of patients, ranging from 30 to 70% [27]. It is interesting to know that lung cancer is one of the most frequent cancers worldwide [28], with NSCLC representing more than 80% of all lung tumors. In early-stage disease, surgery is the treatment with curative intent; disease recurrence led to postsurgical prophylactic (adjuvant) treatment. Adjuvant radiotherapy is not recommended after surgery because it may produce a deleterious effect on long-term survival at least in I and II disease stages [29].

Adjuvant chemotherapy, when administered, has shown that CDDP-based chemotherapy could yield an overall survival (OS) advantage of 5% at 5 years [8], but the difference in OS (hazard ratio [HR]=0.87) was not significant (p = 0.8).

The need for NSCLC prophylactic treatment after tumor resection requires continued investigation.

A published review presented several trials which included 4584 patients. A significant OS benefit from postoperative CDDP-based chemotherapy in patients with NSCLC was shown. The median follow-up time was 5.2 years, the overall HR of death was 0.89 (95% CI, 0.82-0.96) and the p value 0.005. The benefit varied with disease stage [29].

The combination of CDDP with several other agents for the treatment of inoperable NSCLC and the reasonably good results led to the choice of at least one of these combinations for adjuvant treatment. Initially, CDDP was combined with both older and newer agents. Over time, CDDP analogues were produced; carboplatin, a cisplatin analogue, was often substituted for CDDP. After 1990, new agents, having been proven to be effective were used in combination with CDDP or with carboplatin. There are also trials not using cisplatin or carboplatin: cyclophosphamide, ifosfamide, doxorubicin (or epirubicin), nitrosoureas, mitomycin C, vinblastine or vindesine and etoposide used prior to the 1990s were replaced by the newly produced drugs [6,7,17-19]. Taxanes (paclitaxel or docetaxel) were the most common drugs selected [8,14]. The combination of taxanes with other new agents such as gemcitabine, irinotecan, vinorelbine and pemetrexed, without CDDP, became part of clinical trials [20-25].

Paclitaxel, one of the eligible agents having been effective, was and still is, one of the first-line drug treatments in NSCLC [30,31]. Docetaxel, the second taxane, has been another agent used as first-line treatment in NSCLC [32]. Data has shown the use of docetaxel in combination with or without CDDP [31,33-35]. The results of all the aforementioned studies and of others indicate that controversies are common with regard to the results of the different trials. These controversies in NSCLC might be due to the non-homogeneous patient cohorts. In NSCLC patients, at least three different histological types of cancer are incorporated and two or three different disease stages. This lack of homogeneity might be the reason for these controversial results.

No trial using new agents showed such agents to be better than CDDP. Of course, there are effective agents without nephrotoxicity but other adverse reactions (in particular, myelotoxicity) are common with the use of the majority of non-CDDP agents. A meta-analysis of 52 trials in NSCL patients, the majority of which used CDDP in combination with other agents, showed an improvement in overall survival with a 20% reduction in the risk of death, prolongation of survival and an improvement in the quality of life [8]. Ten years ago it was accepted that CDDP-based chemotherapy should be a standard first-line treatment for advanced NSCLC [26]. The trials have failed to find a substitute for CDDP with better safety and efficacy [26].

The research continues. New drugs are under investigation. It is worth mentioning a new CDDP formulation, liposomal cisplatin (lipoplatin), which over recent years has been used in trials and the data has indicated that there is no nephrotoxicity and no other serious adverse reactions. It is important that its effectiveness is equal to CDDP in NSCLC. This new agent is more effective than CDDP in adenocarcinoma of the lung.

Liposomal cisplatin has been tested in animals and in humans. Phase I, II and III studies have recently been published.

Lipoplatin is a new liposomal formulation formed from CDDP and liposomes composed of dipalmitoyl phosphatidyl glycerol (DPPG), soyphosphatidyl choline (SPS-3) cholesterol, and methoxypolythylene glycol – distearoyl phosphatidylethanolamine (m-PEG 2000-DSPE). It was developed to reduce the toxicity rendered by CDDP and to improve the targeting of the drug to the primary tumor and to metastases by enhancing the half-life circulation time in body fluids and tissues [36].

Preclinical studies have shown lipoplatin's lower toxicity in rats, in comparison to CDDP [37,38].

The lipoplatin maximum tolerated dosage (MTD) was determined (200mg/m^2) in a phase I study [39]. The half life of lipoplatin is 60-117 h, depending on the dose. Excretion in the urine reaches about 40% of the infused dose in 3 days. The formulation and technology of liposomal cisplatin are as follows: about 15 extrusions are performed to give to the nanoparticles their final size of 110nm, using a thermobarrel, extruder and membranes of 0.2, 0.1, 0.08, and 0.025μm pore size under ultra pure nitrogen pressure. The nanoparticles, 110nm in diameter, have the ability to target tumors and metastasis following intravenous administration using the compromised endothelium of the tumor vasculature sprouted during neoangiogenesis [40]. Lipoplatin has shown an amazing concentration in tumors and metastases at levels up to 200-fold higher compared to the adjacent normal tissue in surgical specimens from patients [36].

It is important to mention resistance to tumor cells to CDDP and a role for lipoplatin. The resistance of tumor cells to CDDP is attributed to at least four different mechanisms: i) decreased levels of cisplatin entrance to the cytoplasm or increased efflux through the cell membrane; ii) increased levels of glutathione; iii) modulation of signaling pathways; and iv) enhanced levels of DNA repair.

However, additional pathways have been found for establishing the CDDP- resistant phenotype [41]. The direct fusion of lipoplatin nanoparticles with the membrane of the tumor cell suggests that lipoplatin can have applications after the failure of CDDP front-line chemotherapy and the development of CDDP resistance at the cell membrane level.

A phase II trial in inoperable pancreatic cancer with lipoplatin combined with gemcitabine showed effectiveness and produced a response in patients not responding to gemcitabine administered alone [42]. A good response was observed with the administration of lipoplatin combined with 5-fluorouracil and leucovorin, given weekly along with radiotherapy, in patients with advanced gastric cancer [43]. Another phase II trial was done in metastatic breast cancer, where combination of lipoplatin with vinorelbine was administered. The objective response rate of this combination was 64% and side effects were acceptable [44].

One phase II and two phase III trials in NSCLC have been recently completed and published. In these studies, lipoplatin was combined with a second agent in comparison with CDDP also combined with the same second agent and the objectives were to determine the side effects and efficacy. In the phase II study the second agent was gemcitabine. The response rate of the group of patients treated with lipoplatin was 31.7% and of the CDDP group it was 25.6%. Toxicity was much lower in the lipoplatin-treated patients [45].

The other two phase III trials showed the value of lipoplatin vs CDDP in NSCLC; Arm A patients were randomly allocated to receive lipoplatin 200mg/m^2 combined with paclitaxel 135 mg/m^2 and Arm B, to receive CDDP 75 mg/m^2 combined with paclitaxel (as above). The treatment was administered on day 1 every 2 weeks. Arm A patients showed statistically significant lower nephrotoxicity than that of Arm B. Leucopenia, nausea/vomiting and asthenia were also significantly lower in Arm A. There was no statistically significant difference in median and overall survival, although the response rate of the lipoplatin Arm was 58.8% and of the CDDP Arm 47% [46]. In the latter two studies [45,46] it was observed that liposomal cisplatin seemed to produce a higher response rate than CDDP in adenocarcinoma of the lung.

This observation led to the next trial which included non-squamous cell NSCLC patients. The majority of the patients in both Arms had adenocarcinoma and also undifferentiated carcinoma. The treatment was lipoplatin plus paclitaxel (Arm A) vs CDDP plus paclitaxel (Arm B). A partial response was achieved by 59.22% of Arm A patients and 42.42% of Arm B patients (p= 0.036). The median survival time in months was 10 for Arm A and 8 for Arm B (p=0.1551). After 18 months, the number of surviving patients was double for Arm A compared to Arm B [47].

The data of the last two studies indicate that liposomal cisplatin exerts very low toxicity (no nephrotoxicity, in particular) and it is the only new agent which is not only non-toxic but also better in efficacy compared with CDDP in adenocarcinoma of the lung.

Conclusion: CDDP has remained one of the best anticancer agents, used for over 30 years in a broad spectrum of malignancies. The effort to find a substitute for CDDP with the use of new anticancer drugs mainly without nephrotoxicity and with at least equal efficacy, continues. Liposomal cisplatin seems to be the only new agent without serious side effects which also produces a statisti-

cally significant response rate in lung adenocarcinoma compared to CDDP.

Executive summary

The present review describes the process of one of the most important and effective drugs in cancer treatment. CDDP has been administered in several malignancies, such as head and neck cancer, ovarian cancer, testicular cancer and in particular, lung cancer. Several studies have shown its efficacy, but the main side-effect of nephrotoxicity has been a problem. Hydration proved to be helpful, but efficacy was still limited in a good percentage of patients. Trials with new agents, mainly carboplatin, taxanes, gemcitabine, irinotecan and pemetrexed have been tested as substitutes for CDDP, but none was shown to be more effective.

Recently the new CDDP formulation, liposomal cisplatin (lipoplatin), has been shown to be a good substitute for CDDP due to its lower toxicity and equal efficacy.

Future perspectives

Current new agents such as pemetrexed or abraxane may be used in the future as substitutes of previous effective drugs as they may show a statistically significant higher effectiveness. Over the last 10 years, research has been directed to targeted therapies. Several tyrosine kinase pathways exposing certain genes that, when mutated they affect tumor development, have been studied. Tyrosine kinase inhibitors (TKI) including for example, imatinib, were successfully used for chronic myeloid leukemia and gastrointestinal stromal tumors. Epidermal growth factor receptor (EGFR) tyrosine kinases have also been successfully targeted by monoclonal antibodies at the cell surface. Several other monoclonal antibodies have been produced for additional different malignancies [48]. Gefitinib and erlotinib have been used for adenocarcinoma of the lung when the tumor harbors EGFR mutations [49,50]. Alk activity can be efficiently targeted by the TKI crizotinib. Effective uses of P13K and MEK inhibitors to treat mutant K-ras in lung cancer are currently in development [51].

In this light, the progression of research and an understanding of the role of chromatin in the control of gene expression, genetic alterations and other mechanisms are being investigated as avenues to target cancer. It is appreciated that epigenetic abnormalities cooperate with genetic alterations to cause dysfunction of key regulatory pathways [52]. Such abnormalities have led to novel therapeutic approaches which target some of the most well-characterized genetic aberrations; these include the use of inhibitors of DNA methylation and histone deacetylates [53].

Similarly, the ubiquitin-proteasome pathway has been targeted. Here, the targeting agents include epoxomicin, TMC-95A lactacystin and carfilzomid, which target the proteasome and induce cell death through selective inhibition of the chromotrypsin-like activity of the proteasome. A number of other drugs are under investigation [54].

In addition, many research efforts are taking place in order to discover new targeting agents which could circumvent resistance to existing drug treatments.

It would appear that during the next 5-10 years, the production of targeting treatments for cancer should once again blossom.

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