Oxaliplatin: a review in the era of molecularly targeted therapy

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ABSTRACT

Objective

To review preclinical and clinical data for oxaliplatin in the current context of molecularly targeted therapy.

Methods of Study Selection

We searched the PubMed and PubChem databases by combining the search terms "oxaliplatin" or "platinum" or both, with "clinical trials," "pharmacokinetics," and "pharmacodynamics."

Data Extraction and Synthesis

Oxaliplatin has a complicated pharmacokinetic profile, with activity against digestive cancers in particular. It has several mechanisms of action, but cancer cells can develop resistance. Real or potential synergism has been observed when oxaliplatin is combined with other cytotoxic agents or molecularly targeted agents. Peripheral neuropathy is a prominent toxic effect.

Conclusions

Oxaliplatin lends itself to further clinical research in combination with molecularly targeted therapy.

KEY WORDS

Oxaliplatin, targeted therapy, chemotherapy, mechanism of action

1. INTRODUCTION

The advent of molecularly targeted anticancer therapy could cause a certain lack of interest in the development of novel conventional cytotoxic drugs. However, molecularly targeted agents have not shown any curative properties when administered as monotherapy. In that regard, there is hope in combining molecularly targeted anticancer therapy with conventional cytotoxic chemotherapy. Such combinations can come about only through rational design of clinical trials, taking into account the pharmacology and clinical development of the drugs involved. It is therefore worthwhile revisiting classical chemotherapy agents, because this renewed knowledge could provide a foundation for future trials.

Oxaliplatin is the newest platinum derivative in standard chemotherapy. Here, we review oxaliplatin from the pharmacologic and drug development perspectives, and we comment on possible associations of this drug with molecularly targeted therapy.

2. CHEMICAL AND PHYSICAL PROPERTIES AND BIOTRANSFORMATION

Oxaliplatin differs from cisplatin in that the amine groups of cisplatin are replaced by diaminocyclohexane (DACH). The molecular weight of oxaliplatin is 397.3. It is slightly soluble in water, less so in methanol, and almost insoluble in ethanol and acetone [1]. Its full chemical name, oxalato(trans-L-1,2-diaminocyclohexane)platinum, refers to the presence of an oxalate "leaving group" and the DACH carrier ligand, which are responsible, at least in part, for its unique properties [2,3]. For example, unlike cisplatin, oxaliplatin in plasma rapidly undergoes non-enzymatic transformation into reactive compounds because of displacement of the oxalate group, a process that complicates its pharmacokinetic profile. Most of the compounds appear to be pharmacologically inactive, but dichloro(DACH) platinum complexes enter the cell, where they have cytotoxic properties.

3. MECHANISMS OF ACTION

Various mechanisms of action are ascribed to oxaliplatin. Like other platinum-based compounds, oxaliplatin exerts its cytotoxic effect mostly through DNA damage. Apoptosis of cancer cells can be caused by formation of DNA lesions, arrest of DNA synthesis,

inhibition of RNA synthesis, and triggering of immunologic reactions. Oxaliplatin also exhibits synergism with other cytotoxic drugs, but the underlying mechanisms of those effects are less well understood.

3.1 DNA Lesions

At intracellular physiological concentrations of HCO_3^- and $H_2PO_4^-$, and after aquation, dichloro(DACH)platinum compounds, once formed in plasma, enter the cell nucleus, where, with a peculiar tropism for GC-rich sites, they bind a nitrogen atom (N7) of guanine, forming DNA monoadducts, then diadducts [4]. Although the effect of oxaliplatin is mostly on genomic DNA, adducts are also formed in nucleosomes.

Oxaliplatin can induce 3 types of crosslinks:

- DNA intra-strand crosslinks
- DNA inter-strand crosslinks
- DNA–protein crosslinks

Intra-strand crosslinks seem to be the predominant mechanism of action in the induction of DNA lesions, with binding of two Gs [4], or less frequently, a G–A base pair.

Inter-strand crosslinks are believed to significantly contribute to the cytotoxicity of cisplatin [5], but seem less important in the mechanism of action of oxaliplatin. A study by Woynarowski *et al.* confirms both their presence at a low rate and their lethal properties [6].

As to DNA–protein crosslinks, despite their denaturating effect on enzymes and other important intracellular proteins, most studies have not proven that they cause cell death [5].

Monoadducts are devoid of significant cytotoxic action. Lethal DNA biadducts inhibit both DNA replication and transcription, causing apoptosis after cell cycle arrest [7] unless nucleotide excision repair has occurred. Formation of these DNA adducts is greater and more rapid with cisplatin than with oxaliplatin. Yet, oxaliplatin is, overall, more cytotoxic than cisplatin. The therapeutic effects of oxaliplatin therefore clearly do not depend only on the alkylating–intercalating effects of the platinum moiety [7].

The apoptotic pathway of colon cancer cells after exposure to oxaliplatin involves caspase 3 activation, translocation of Bax in the mitochondria, and release of cytochrome C in the cytosol [8].

Some aspects of the DNA lesions are relatively specific to oxaliplatin. For example, the conformation of oxaliplatin adducts, as compared with those of cisplatin or carboplatin adducts, makes binding with the mismatch repair (MMR) protein complex more difficult, presumably resulting in greater irreversibility of the lesions. In addition, the bulky DACH compound is postulated to more effectively prevent DNA synthesis than does the *cis*-diamine carrier ligand of cisplatin [2].

3.2 Arrest of DNA Synthesis

Experiments looking at the mechanism of synergism between oxaliplatin and 5-fluorouracil (5FU) have uncovered a direct inhibitory effect of oxaliplatin on thymidylate synthase, preventing the incorporation of thymidine in nucleic acid synthesis [9]. This antimetabolite-like effect results in arrest of the mitotic process. Because oxaliplatin is usually combined with 5FU, itself a thymidylate synthase inhibitor, it is unclear whether this mechanism of action of oxaliplatin plays an important role *in vivo* of its own.

3.3 Inhibition of Messenger RNA Synthesis

Inhibition of DNA replication is not always sufficient to cause cell death. Inhibition of transcription at the initiation and elongation phases also plays a key role. Three main mechanisms of transcription inhibition are postulated for oxaliplatin [10]:

- ***Binding of transcription factors:*** At the initiation stage, platinum–DNA adducts can serve as binding sites for transcription factors, especially when those factors have a strong chemical affinity for platinum. Thus, natural binding of the transcription factors to their promoter sites is prevented.
- ***Inhibition of RNA polymerases:*** This inhibition is established for cisplatin, but is presumably also true of oxaliplatin. The bases of platinum–DNA adducts are not able to enter the active site of an enzyme such as pol II.
- ***Role of nucleosomal DNA adducts:*** These adducts have the potential to block access by the RNA polymerase to the DNA template.

3.4 Immunologic Mechanisms

It has recently been discovered that oxaliplatin can cause the immunogenic death of colon cancer cells in murine and human cell lines [11]. After exposure to oxaliplatin, colon cancer cells emit several immunogenic signals on their surface before undergoing apoptosis. These signals trigger the production of interferon γ by T cells and also interact with the toll-like receptor 4 of dendritic cells, the whole process resulting in a sort of tumour vaccine. A particularly convincing argument of the importance of this mechanism is that humans carrying a mutant allele of the *TLR4* gene resulting in loss of function were found to experience a lesser benefit from oxaliplatin chemotherapy in the metastatic setting, with a statistically significant shorter progression-free and overall survival.

3.5 Mechanism of Action in Oxaliplatin-Based Combinations

Because single-agent oxaliplatin has low activity in many tumours, it is often combined with other chemotherapeutic agents, 5FU being the most common.

The exact mechanism of synergism between 5FU and oxaliplatin is complex, but experimental observations suggest that oxaliplatin can downregulate or inhibit dihydropyrimidine dehydrogenase, slowing the catabolism of 5FU [9].

Oxaliplatin has been combined with other cytotoxic therapeutic agents with varying degrees of success. The mechanism of action of these combinations is less well documented and beyond the scope of this article.

Relatively few data document the potential for synergism of oxaliplatin-based combinations with molecularly targeted therapy. *In vitro* experiments show enhanced cytotoxicity to cisplatin in cells pretreated with rapamycin, after suppression of DNA repair mechanisms by the latter agent [12]. Combinations of oxaliplatin with inhibitors of the mammalian target of rapamycin should be evaluated in the clinical setting.

3.6 Resistance to Oxaliplatin

Despite initial sensitivity to oxaliplatin, most cancer cells will eventually develop resistance. Many mechanisms of resistance have been described or hypothesized because of similarity between oxaliplatin and cisplatin [13,14]. The intracellular fate of the drug can be affected by decreased uptake (resulting in lower intracellular concentration) or inactivation by structural or spatial changes (conjugation with glutathione or sequestration with metallothionein). However, the most important mechanisms seem to be related to DNA repair: MMR, or nucleotide excision repair (NER). Cells that overexpress ERCC1, an excision repair enzyme, are resistant to oxaliplatin [15].

The combination of oxaliplatin with other antineoplastic drugs may prevent resistance—or even reverse it. For instance, *in vitro* assays show that cetuximab reduces the expression of components of NER pathways, used by the cell to remove platinum–DNA adducts [16]. A potential area of research would be the combination of oxaliplatin with inhibitors of Aurora kinases and of poly–adenosine diphosphate ribose polymerase [17].

3.7 Drug Interactions

Recent data show that oxaliplatin has little to no effect on cytochrome P450, one of the main enzymes involved in drug biotransformation [18]. That finding suggests that, when necessary, oxaliplatin may be safe to use in co-administration with other commonly used drugs.

4. TOXICITY PROFILE

Oxaliplatin causes adverse reactions that narrow its therapeutic index. The target organs are mainly the hematopoietic system, the peripheral nerves, and the gastrointestinal (GI) system.

4.1 The Hematopoietic System

Oxaliplatin is moderately myelotoxic, more so than cisplatin. The severity of myelotoxicity is proportional to the dose, typically 85–135 mg/m^2 intravenously. Grades 3 and 4 neutropenia are common, but with only a 4% incidence of neutropenic fever [19]. Anemia and thrombocytopenia are usually not severe.

Like many other cytotoxic drugs, oxaliplatin presumably affects progenitor cells in the bone marrow. It also enters peripheral blood cells: DNA adducts are present in leukocytes after oxaliplatin administration [20]. Whether this action contributes to hematologic toxicity is uncertain, but the number of platinum–DNA adducts in the blood cells of patients treated with cisplatin correlates with the degree of leucopenia and thrombocytopenia [21].

Other, less frequent, mechanisms of hematologic toxicity have been described. For instance, hypersensitivity reactions after repeated infusions of oxaliplatin can cause hemolytic anemia and secondary immune thrombocytopenia [22]. In addition, rare cases of secondary acute leukemia have also been reported, as with other alkylating agents [23].

4.2 The Peripheral Nerves

Peripheral neuropathy is extremely common in oxaliplatin-treated subjects. It exists in an acute and a chronic form, believed to result from distinct, but overlapping, pathophysiologic mechanisms.

Acute peripheral neuropathy is characterized by paresthesia, dysethesia, or allodynia affecting the extremities, the lips, and the oropharyngolaryngeal area during or shortly after oxaliplatin infusion. It is often triggered by exposure to cold. It usually subsides within a few hours or days [24]. Experimental data suggest that oxaliplatin affects voltage-gated sodium channels in complex pathways involving calcium. Calcium itself is chelated by oxalate, a metabolite of oxaliplatin [25].

Chronic oxaliplatin-induced peripheral neuropathy results from cumulative exposure to the drug. The incidence of grades 3 and 4 neuropathy is about 15% [26] in patients who have received a cumulative dose of about 800 mg/m^2. It essentially involves the extremities. Although described initially as a degenerative process of the axons, in which the previously mentioned sodium ion channels play a role, it is now thought as well to be a state secondary to accumulation of platinum compounds in the dorsal root ganglia cells, causing atrophy and mitochondrial

dysfunction [27]. It is irreversible in fewer than 5% of cases. Most of the time, peripheral neuropathy manifests itself as decreased distal sensations and proprioception. As with the acute form, involvement of motor fibres is rare.

An understanding of the mechanism of peripheral neuropathy induced by oxaliplatin is crucial for the prevention and treatment of this phenomenon [28,29]. Many drugs for that purpose (for example, xaliproden, gabapentin) have been unsuccessfully tested. However, despite a previous controversy, the results of a retrospective study [30] and of an incompletely accrued randomized controlled trial [31] indicate a benefit with infusions of calcium gluconate and magnesium sulphate before and after oxaliplatin administration. The benefit consists of a significant reduction in the incidence of chronic peripheral neuropathy symptoms secondary to oxaliplatin. Although initially described, the improvement of acute neurotoxicity by this intervention has not been confirmed. There is no evidence to suggest a decrease in the anticancer effects of oxaliplatin when calcium and magnesium infusions are administered.

An additional research question is whether oxaliplatin can safely be combined with anti-neoplastics that have a different mechanism of neurotoxicity. Few studies in that regard have been performed, but uncontrolled trials suggest no increase in the incidence of severe peripheral neuropathy when oxaliplatin is associated with vinca alkaloids [32], taxanes [33], and proteasome inhibitors [34].

4.3 The GI System

The GI side effects attributed to oxaliplatin consist mainly of nausea, vomiting, and diarrhea [35]. Usually mild to moderate in intensity, they are considered to be nonspecific toxic effects of the drug on the rapidly dividing cells of the GI tract.

5. PHARMACOKINETICS

5.1 Generalities

Oxaliplatin is often administered concomitantly with 5FU. Phase I trials have shown no alteration of oxaliplatin pharmacokinetics when 5FU is administered concomitantly [36]. In addition, most papers do not address the pharmacokinetics of oxaliplatin *per se,* but of the platinum content. In fact, shortly after infusion, oxaliplatin forms many different platinum compounds that bind to blood or cell proteins. These molecules are thought to be of no pharmacologic interest [37]. Therefore, in most experiments, only the ultrafilterable platinum component is measured, which complicates interpretation of the pharmacologic data. Platinum derived from oxaliplatin is described as having a "tri-exponential" pattern of elimination, the half-lives being successively 0.28 hour, 16.3 hours, and 273 hours.

One paper reported the pharmacokinetics of oxaliplatin itself rather than of platinum after oxaliplatin infusion [38]. The half-life ($t_{1/2}$) of oxaliplatin is 14.1 minutes. Another half-life of 45 minutes is related to *in vivo* degradation in blood rather than to elimination. Also, "a significant correlation between the clearance and the *in vivo* degradation rate constants" was found, suggesting that there could be a physiologic link between those two processes.

5.2 Impaired Kidney Function

In a study examining the pharmacokinetics of oxaliplatin in the setting of renal function impairment [39], 34 patients were stratified according to creatinine clearance and received oxaliplatin at various dose levels.

The area under the curve (AUC) increased with lower creatinine clearance, supporting the understanding that the clearance of oxaliplatin occurs largely through renal mechanisms. However, no increased toxicity was observed, even with an increased AUC secondary to renal dysfunction.

5.3 Impaired Liver Function

Similarly, 60 cancer patients with liver dysfunction were stratified according to the results of liver function tests (total bilirubin, aspartate aminotransferase, and alkaline phosphatase) or their status as liver transplant recipients [40]. They received oxaliplatin 60–130 mg/m^2 according to a dose-escalation protocol.

Unlike renal insufficiency, liver dysfunction does not seem to affect oxaliplatin clearance and AUC, except in the group with the most severe abnormalities. No increased side effects were seen in the patients tested.

5.4 Long-Term Retention of Oxaliplatin Derivatives

Given that the 3rd half-life of oxaliplatin is in the order of hundreds of hours, accumulation of the drug in tissues may presumably be expected. In this regard, a study examined long-term retention of platinum 8–75 months after treatment with cisplatin and oxaliplatin [41].

The results showed that the plasma concentration of platinum in individuals previously exposed to oxaliplatin or cisplatin is larger by a factor of 30 than that in unexposed controls. The metal is found in both whole and ultrafilterable plasma. Risk factors for persistent high levels are decreased glomerular function and high cumulative dose. The authors demonstrated that the platinum found is still reactive, capable of forming platinum–DNA adducts *in vitro*. Although the physiologic significance of this reactivity is unknown, the findings are of concern with regard to long-term toxic effects such as secondary malignancies.

6. CLINICAL DEVELOPMENT OF OXALIPLATIN

6.1 Early Studies

The development of oxaliplatin was born of the need to find an alternative to cisplatin, an effective agent in various cancers, but substantially toxic. A recognized limitation of cisplatin was also its lack of activity against colorectal cancer, one of the most common human malignancies.

The phase I studies evaluated activity and safety for a range of doses. Unlike the usual classical studies, in which patient cohorts are given progressively higher doses of the studied drug, Mathé *et al.* used a different design: Doses were escalated in each study patient until the maximally efficient dose range, defined as between 45 mg/m^2 and 67 mg/m^2 administered intravenously, was reached [42]. An absence of nephrotoxicity, setting oxaliplatin apart from cisplatin, was observed. Hints of activity against lung cancer, breast cancer, melanoma, and hepatoma were noted.

In a more conventional phase I trial [43], dose escalation reached 200 mg/m^2 delivered intravenously. At that dose level, the characteristic peripheral neuropathy was recognized, leading to the recommendation, now accepted, that the maximum dose to be used in clinic be 135 mg/m^2 administered intravenously. Activity was also seen in various tumours, including some that had been pretreated with cisplatin.

Pharmacokinetic studies in that early period were also conducted. Although synergism between oxaliplatin and 5FU was rapidly recognized, relatively few pharmacodynamic studies were performed, possibly because of an assumption that oxaliplatin and cisplatin shared the same mechanism of action. However, interest in unmasking specific aspects of oxaliplatin arose when it was discovered that oxaliplatin and cisplatin are not cross-resistant.

6.2 Oxaliplatin in Colorectal Cancer

The modest activity (10%) of single-agent oxaliplatin in 5FU-refractory colorectal cancer was recognized early [44]. This activity rate is about 20% in untreated cases, according to a paper published in 1998 [45]. In both articles, the authors concluded that oxaliplatin combinations should be explored to improve outcomes. In fact, an uncontrolled study had already suggested synergy of 5FU and oxaliplatin, with reported response rates as high as 58% in a heterogeneous cohort of untreated and previously treated colorectal cancer patients [46].

The high activity of 5FU–leucovorin–oxaliplatin in 5FU-refractory colorectal carcinoma was confirmed in later trials, and the combination was given the acronym FOLFOX [47]. Several versions of this regimen have been developed (from FOLFOX1 to FOLFOX7) to improve 5FU-related toxicity and patient convenience. There is no strong evidence that any of the FOLFOX variations is superior to the others in terms of efficacy.

The real value of oxaliplatin in metastatic colorectal cancer has been demonstrated in randomized trials. For example, a phase III study conducted by de Gramont [48] comparing 5FU–leucovorin with FOLFOX4 in previously untreated metastatic colorectal cancer, showed a significant improvement in response rate (50.7% vs. 22.3%) and progression-free survival (9 months vs. 6.2 months) in favour of FOLFOX. Similar results have been reported in trials in which capecitabine was substituted for 5FU and leucovorin, forming the XELOX or CAPOX regimen [49]. In addition, oxaliplatin in combination with fluoropyrimidines remains useful, even after progression on 5FU–irinotecan, another standard regimen for metastatic colorectal cancer [50].

Given the effectiveness of oxaliplatin-based chemotherapy in advanced colorectal carcinoma, there was obvious interest for studies in the adjuvant setting. In patients who have undergone surgery for stage III colon cancer, 5FU or capecitabine (compared with observation) significantly improves the cure rate. Those results are furthered by the addition of oxaliplatin to the 5FU backbone. A recent publication confirms that, as compared with 5FU, FOLFOX improves overall survival in stage III patients [51].

Molecularly targeted cancer therapy is also added to oxaliplatin-based chemotherapy for the purpose of synergism. For now, the agents that are routinely used in that context are monoclonal antibodies. Clinical trials of bevacizumab, the antibody against vascular endothelial growth factor, in combination with FOLFOX or XELOX for metastatic colorectal cancer have shown positive results in terms of response rate, progression-free survival, or overall survival, depending on the particular clinical setting [52,53]. Improved response rates and progression-free survival are seen when an antibody (cetuximab or panitumumab) against the epidermal growth factor receptor (EGFR) is added to FOLFOX or XELOX, although the benefit of those antibodies is limited to patients harbouring an unmutated *KRAS* gene in their colorectal tumour [54,55].

Disappointingly, adding both bevacizumab and an anti-EGFR antibody to FOLFOX or XELOX is ineffective and even deleterious [56]. In addition, neither bevacizumab nor cetuximab improves overall survival or disease-free survival when given in combination with oxaliplatin-based chemotherapy in the adjuvant setting [57,58]. Overall, these results show how little is understood about the interaction of oxaliplatin with antibodies, and how useful pharmacodynamic studies would be in that regard.

Even fewer data are available regarding potential combinations of oxaliplatin with anti-angiogenic small molecules and multikinase inhibitors. The occasional antagonistic effects encountered in some *in vitro* experiments [59] highlight the need for careful research.

6.3 Other Cancers

Given its success in colorectal cancer, oxaliplatin has been tested in other digestive cancers. Because of its less toxic profile, many research protocols substitute it for cisplatin. The present review considers only gastroesophageal and pancreatic cancers.

In a phase III trial, Cunningham *et al.* [60] randomized patients with advanced gastric or esophageal cancer to either epirubicin–cisplatin–5FU or epirubicin–oxaliplatin–capecitabine. Response rate and progression-free survival were similar in both groups, suggesting equivalency between cisplatin and oxaliplatin, and between 5FU and capecitabine respectively.

Oxaliplatin in combination with 5FU or gemcitabine shows promising results as a salvage regimen for metastatic pancreatic cancer after failure of gemcitabine [61], but no results of phase III trials have yet been published in definitive form.

7. FUTURE PERSPECTIVES

Although it belongs to the same class of drugs as cisplatin and carboplatin, oxaliplatin shows marked differences in its pharmacokinetic and pharmacodynamic profiles, as well as in its spectrum of antitumour activity and its toxicity.

The pharmacology of oxaliplatin has uncovered one of the most appealing characteristics of the drug: its lack of cross-resistance with cisplatin and carboplatin, which complements its manageable toxicity profile. Pharmacodynamic characterization of oxaliplatin has also helped in achieving an understanding of the pathogenesis of the accompanying peripheral neuropathy, which should result in more effective management of that complication.

The discovery of multiple mechanisms of action of oxaliplatin, coupled with increased knowledge of cellular mechanisms of resistance, should facilitate design of clinical trials with novel combinations. An obvious goal would be to improve the results of current chemotherapy regimens without excessive toxicity. In particular, future studies should focus on combinations of oxaliplatin with molecularly targeted agents, because those combinations present potential therapeutic complementarity, with little overlap in pharmacologic characteristics.

8. CONFLICT OF INTEREST DISCLOSURES

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