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Oxaliplatin

A Review of its Pharmacological Properties and Clinical Efficacy in Metastatic Colorectal Cancer and its Potential in Other Malignancies

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Data Selection

Sources: Medical literature published in any language since 1966 on oxaliplatin, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'oxaliplatin' or 'ACT-078' or 'L-OHP'. Medline search terms were 'oxaliplatin' or 'ACT-078' or 'L-OHP'. Searches were last updated 22 September 2000.

Selection: Studies in patients with cancer who received oxaliplatin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Oxaliplatin, cancer, colorectal, ovarian, tumour, platinum, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Oxaliplatin is a platinum compound that inhibits DNA synthesis, primarily by causing intrastrand cross-links in DNA. Oxaliplatin has a broad spectrum of antineoplastic activity and has demonstrated a lack of cross-resistance with other platinum compounds.

In patients with metastatic colorectal cancer, intravenous oxaliplatin has been trialled as a monotherapy and in combination with other agents. The highest response rates were achieved when oxaliplatin was used in combination with fluorouracil/folinic acid (leucovorin; calcium folinate), typically ≥50% in the first-line setting and 13 to 45% as a second-line therapy.

First-line triple therapy with oxaliplatin and fluorouracil/folinic acid achieved significantly higher response rates and longer median progression-free survival than fluorouracil/folinic acid therapy alone. However, no significant difference in the median duration of overall survival was found. This may be a consequence of the subsequent use of oxaliplatin and/or surgery after disease progression in patients who relapsed after fluorouracil/folinic acid therapy alone.

Neoadjuvant therapy with oxaliplatin/fluorouracil/folinic acid has proven beneficial in enabling surgical removal of previously unresectable liver metastases. In 2 studies, surgery with curative intent was performed in 16 and 51% of patients with initially unresectable liver metastases following oxaliplatin/fluorouracil/folinic acid therapy; the 5-year survival rates were 40 and 50%, respectively.

In patients with advanced ovarian cancer, first-line therapy with oxaliplatin/cyclophosphamide achieved an objective response rate which did not differ significantly from that of cisplatin/cyclophosphamide (33 *vs* 42%). In addition, oxaliplatin has shown efficacy in patients with platinum-pretreated ovarian cancer and achieved objective response rates similar to paclitaxel in this setting (16 *vs* 17%).

Promising results have also been found with oxaliplatin in patients with non-Hodgkin's lymphoma, breast cancer, mesothelioma and non-small cell lung cancer.

Reversible, cumulative, peripheral sensory neuropathy is the principle dose-limiting factor of oxaliplatin therapy. Haematological and gastrointestinal toxicities occur frequently but are generally mild to moderate in intensity.

Conclusion: Oxaliplatin in combination with fluorouracil/folinic acid is an

effective treatment option for patients with metastatic colorectal cancer, both as a first-line therapy and in patients refractory to previous chemotherapy. Although preliminary results failed to show any overall survival advantage of this regimen over fluorouracil/folinic acid alone, this may be a consequence of trial design and requires further examination. Additional clinical investigation of oxaliplatin in patients with other cancers is warranted given the promising results achieved in early trials, most notably in patients with platinum-pretreated ovarian cancer.

Overview of Pharmacodynamic Properties

Oxaliplatin is a diaminocyclohexane (DACH) carrier ligand-based platinum compound that inhibits DNA synthesis. The major cytotoxic lesions are intrastrand platinum-DNA adducts, formed by cross-linking between activated platinum species and specific base sequences. In addition, apoptosis may also contribute to the mechanism of action of this drug.

Oxaliplatin has shown *in vitro* antiproliferative activity against several human tumour cell lines and against tumour isolates from patients. Moreover, greater cytotoxic activity than cisplatin or carboplatin has been reported for oxaliplatin against some drug-resistant cancer cell lines.

Oxaliplatin has shown similar antitumour activity to cisplatin *in vivo* in a number of murine tumours, including colon carcinoma, melanoma, P388 and L40 AkR leukaemia models. Superior antineoplastic efficacy to cisplatin has been reported in murine tumour models of mammary carcinoma, sarcoma, L1210 leukaemia and LGC lymphoma, and efficacy is retained in some cisplatin-resistant strains.

Additive or synergistic effects of a number of oxaliplatin-based combinations have been reported in human colon cancer cell lines and in several *in vivo* tumour models, most notably oxaliplatin and fluorouracil.

Overview of Pharmacokinetic Properties

Oxaliplatin undergoes rapid nonenzymatic biotransformation to form a variety of reactive platinum intermediates and these species bind rapidly and extensively to plasma proteins and erythrocytes.

Maximum plasma concentrations (C_{max}) of platinum and area under the concentration-time curve values of 0.83 to 1.21 mg/L and 11.9 to 13.6 mg/L · h, respectively, have been reported in the pharmacologically active ultrafilterable plasma fraction following a 2-hour infusion of oxaliplatin 130 mg/m^2. Steady-state plasma ultrafiltrate platinum concentrations were achieved during the first cycle of treatment with oxaliplatin 130 mg/m^2, and accumulation was not reported after single or multiple dosing.

Platinum C_{max} was dependent on the time of peak oxaliplatin infusion during a chronomodulated treatment regimen. Ultrafilterable platinum C_{max} was significantly lower after peak delivery at 0100 hours compared with values at 0700 or 1600 hours.

Oxaliplatin-derived platinum has a volume of distribution from plasma ultrafiltrate of 582 to 812L and a clearance range of 9.3 to 10.1 L/h. Excretion of oxaliplatin biotransformation products is principally by the renal route.

Exposure to plasma platinum was increased in patients with moderate renal impairment compared with that in individuals with normal renal function. However, further deterioration of renal function was not reported and the toxicity of oxaliplatin was not increased in patients with renal impairment.

Reported pharmacokinetic interactions of oxaliplatin with fluorouracil or raltitrexed are inconsistent. There were no pharmacokinetic interactions between oxaliplatin and irinotecan or topotecan.

Clinical Efficacy

The majority of clinical trials have focused on the efficacy of oxaliplatin in metastatic colorectal cancer and, more recently, in patients with advanced ovarian cancer. Preliminary studies have also looked at oxaliplatin in the treatment of several other cancers including non-Hodgkin's lymphoma, non-small cell lung cancer, mesothelioma and breast cancer.

While oxaliplatin monotherapy has been investigated in some trials, the drug has been most widely used in combination with fluorouracil/folinic acid (leucovorin; calcium folinate). There is some evidence to suggest that chronomodulated delivery of these agents achieves a higher response rate than standard fixed-rate infusion; however, whether this translates into a survival benefit is unclear.

Metastatic Colorectal Cancer

In patients with metastatic colorectal cancer, the addition of oxaliplatin to first-line fluorouracil/folinic acid therapy significantly increased the objective response rate compared with fluorouracil/folinic acid therapy alone in 2 large randomised trials: the objective response rates were 53 *vs* 16% ($p < 0.001$) and 50.7 *vs* 22.3% ($p < 0.001$) in patients receiving fluorouracil/folinic acid with or without oxaliplatin, respectively. Median progression-free survival was also significantly longer for patients receiving oxaliplatin in both trials (≈9 *vs* 6 months), but there was no significant difference in the median duration of overall survival. This could be due to the fact that second-line oxaliplatin and/or irinotecan and/or surgery was allowed in patients initially randomised to receive only fluorouracil/folinic acid therapy.

In patients relapsing after fluorouracil-based therapy, oxaliplatin combined with fluorouracil/folinic acid produced objective response rates typically between 13 and 45%. Median progression-free survival typically ranged between 5 and 10 months and the median duration of survival was between 9 and 17 months. Initial reports indicate that oxaliplatin may also be effectively combined with irinotecan (second-line objective response rates of 28 to 44%) and raltitrexed (first-line objective response rate of 62%) in patients with metastatic colorectal cancer. These combinations have also been examined in combination with fluorouracil-based therapy.

As a monotherapy, oxaliplatin produced response rates of 20 and 24% as a first-line therapy and ≈10% as a second-line therapy in patients refractory to, or progressing after, fluorouracil-based therapy.

Chemotherapy with oxaliplatin/fluorouracil/folinic acid is useful in reducing metastases, such that a proportion of patients with previously unresectable disease can undergo surgery with curative intent. In 2 separate studies ($n = 330$ and 151), surgery with curative intent was performed in 16 and 51% of patients with initially unresectable liver metastases following oxaliplatin/fluorouracil/folinic acid therapy (complete resection was achieved in 87 and 75% of these patients); the 5-year survival rates were 40 and 50%. The latter, retrospective analysis included only patients with metastases confined to the liver; this study also reported 5-year survival rates for the total patient population (28%) and for patients achieving complete resection (estimated at 58%).

Advanced Ovarian Cancer

In patients with advanced ovarian cancer, first-line combination therapy with oxaliplatin/cyclophosphamide showed similar efficacy to cisplatin/cyclophosphamide. No significant differences were reported between the oxaliplatin and cis-

platin treatment arms for objective response rate (33 *vs* 42%), median progression-free survival (13 months) and median overall survival (36 *vs* 25 months).

Oxaliplatin also has shown efficacy as a second-line therapy in patients with platinum-pretreated advanced ovarian cancer, and had similar efficacy to paclitaxel in 1 trial (objective response rates 16 and 17%, respectively).

Other Cancers

The clinical efficacy of oxaliplatin has been studied in a range of other cancer types including non-Hodgkin's lymphoma, breast cancer, non-small cell lung cancer, squamous cell carcinoma of head and neck, malignant melanoma, mesothelioma and glioblastoma. In the largest of these trials, combined oxaliplatin/fluorouracil achieved an objective response rate of 25% in 53 patients with advanced breast cancer, and oxaliplatin/raltitrexed achieved a response rate of 26% in 58 patients with mesothelioma.

Tolerability

The main toxicities occurring with oxaliplatin can be generally divided into neurological, gastrointestinal and haematological.

A cumulative, but generally reversible, peripheral sensory neuropathy is the principle dose-limiting factor. Severe neurotoxicity with functional impairment has been estimated to occur in 10% of patients at a cumulative dose of 780 mg/m^2 (9 treatment cycles at 85 mg/m^2 once every 2 weeks or 6 treatment cycles at 130 mg/m^2 once every 3 weeks), and in 50% of patients at a cumulative dose of 1170 mg/m^2.

Gastrointestinal and haematological toxicities occur frequently but are generally mild to moderate in intensity. Unlike cisplatin, oxaliplatin is not associated with renal or auditory toxicity.

The adverse events occurring with oxaliplatin monotherapy increase predictably when used in combination with other chemotherapies. In a large meta-analysis (n = 682), patients receiving oxaliplatin in combination with fluorouracil/folinic acid appeared to have a higher incidence of grade 3 to 4 nausea/vomiting, diarrhoea, haematological events, peripheral neuropathy versus patients receiving oxaliplatin monotherapy.

Furthermore, combination therapy with oxaliplatin and fluorouracil/folinic acid was associated with significantly higher rates of nausea/vomiting, diarrhoea and peripheral neuropathy than fluorouracil/folinic acid therapy alone in 2 randomised phase III trials.

Chronomodulated delivery of combination oxaliplatin/fluorouracil/folinic acid chemotherapy may improve tolerability. This technique was associated with significantly lower rates of severe mucositis (13 *vs* 76%; $p < 0.0001$), peripheral neuropathy (16 *vs* 31%; $p = 0.01$), withdrawal because of adverse events (28 *vs* 51%; $p = 0.002$) and hospital admissions for severe adverse events (10 *vs* 31%; $p = 0.001$) than a fixed rate infusion schedule.

Oxaliplatin has also shown acceptable toxicity when used in combination with other chemotherapies including irinotecan, raltitrexed, paclitaxel, cisplatin and cyclophosphamide; however, data are still limited.

The tolerability of oxaliplatin compared equally or favourably with paclitaxel, irinotecan and cisplatin in initial comparative studies.

Dosage and Administration

Oxaliplatin is available in several countries in Europe, Asia and Latin America for use in combination with fluoropyrimidines as a first-line therapy for metastatic colorectal cancer. It is also available for use in combination with fluoro-

pyrimidines as a second-line therapy for colorectal cancer in some Asian and South American countries.

The recommended dosage of oxaliplatin in combination with fluoropyrimidines is 85 mg/m^2 once every 2 weeks as a first-line therapy and 130 mg/m^2 once every 3 weeks as a second-line therapy. The dosage should be administered as a 2- to 6-hour intravenous infusion and given before fluoropyrimidine therapy.

The dosage should be adjusted according to tolerability; gastrointestinal toxicity may be reduced with prophylactic and/or therapeutic antiemetic therapy.

Although oxaliplatin has also been investigated in combination with other agents (such as irinotecan and raltitrexed) and in other indications, formal dosage guidelines are not available for the use of oxaliplatin in these settings.

1. Introduction

Over the past 2 decades, several thousand platinum complexes have been synthesised and over 25 have entered clinical trial development in attempts to develop less toxic and non–cross-resistant analogues.[1,2]

Oxaliplatin, a diaminocyclohexane (DACH) carrier ligand-based platinum compound (fig. 1), possesses both of these attributes and demonstrates a wide spectrum of antineoplastic activity.

Unlike other platinum compounds, oxaliplatin has displayed efficacy in colorectal cancer; it has also shown promising results in the treatment of patients with advanced ovarian cancer (including those with tumours refractory to previous platinum-based therapy), and other cancers such as non-Hodgkin's lymphoma, breast cancer and non-small cell lung cancer.

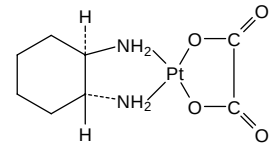
The aim of this article is to provide a review of clinical trials of intravenous oxaliplatin in patients with colorectal and other cancers, and to determine its efficacy and tolerability relative to those of other frequently used agents.

2. Overview of Pharmacodynamic Properties

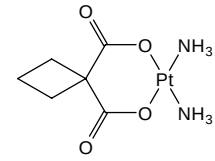
As the pharmacodynamic properties of this drug have recently been reviewed elsewhere,[3-5] this section provides an overview.

2.1 Mechanism of Action

Although the precise mechanism of action of oxaliplatin remains unclear, the cytotoxicity of platinum compounds is believed to result from inhibition of DNA synthesis. The major cytotoxic lesions are intrastrand platinum-DNA adducts, formed by cross-linking between activated platinum species and specific base sequences, notably 2 adjacent guanine residues or 2 adjacent guanine-



Oxaliplatin



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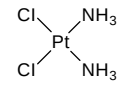

Cisplatin

Fig. 1. Chemical structures of oxaliplatin, carboplatin and cisplatin.

Table I. Summary of the preclinical antitumour effects of oxaliplatin (reviewed by Raymond et al.[4])

In vitro cell lines	Antiproliferative activity at least as effective as cisplatin in human neuroblastoma,[18] colon (HT29, HCT116),[15,19] breast (MCF-7),[20] ovarian (A2780)[7,19] and endometrial (HEC59)[15] carcinoma cells and in murine leukaemia cells (L1210, P388)[21]
	Cytotoxicity greater than cisplatin or carboplatin in human drug-resistant ovarian, germ and non-small cell lung cancer cells[22-24]
	Additive or synergistic effects in human colonic cancer cell lines with: • fluorouracil (HT29, HT-29-5-FU, CaCo2, COLO205, SW620, CAL14, WIDR)[25,26] • SN38 (HT29)[27] • gemcitabine (HCT116, Colo 320 DM)[28] • AG337 (HT29)[25]
Tumour CFU isolated from patients	Marked cytotoxic activity against colonic, gastric, ovarian and non-small cell lung cancer cells and against clones resistant to carboplatin, fluorouracil, irinotecan, paclitaxel or doxorubicin[29]
In vivo tumour models	Greater antineoplastic effects than cisplatin against mouse L1210 leukaemia, LGC lymphoma, MA16-C mammary carcinoma and M5076 sarcoma models[30,31]
	Comparable antineoplastic activity to cisplatin against mouse P388 leukaemia, L40 AkR leukaemia, C38 colon carcinoma and B16 melanoma tumour models[30-32]
	Efficacy in cisplatin-resistant mouse L1210 leukaemia and LGC lymphoma[30,31]
	Additive or synergistic effects with: • fluorouracil (mouse L1210 leukaemia and GR1 mammary tumour models, HT29 human colon xenografts)[25,31] • irinotecan (mouse GR1 mammary tumours)[33] • paclitaxel plus tirapazamine (MV-522 human lung carcinoma xenografts)[34] • carboplatin (mouse L1210 leukaemia model)[35] • cisplatin (mouse L1210 leukaemia model)[35]

AG337 = thymidylate synthase inhibitor; **CFU** = colony forming units; **SN38** = active metabolite of irinotecan.

adenine bases. Interstrand cross-links may also be formed, although they account for <5% of the total platinum-DNA adducts.[4,5]

The type and site of adducts formed by oxaliplatin appear to be the same as those formed with other platinum compounds. However, a greater degree of inhibition of DNA synthesis and cytotoxicity has been associated with the DACH-platinum adducts of oxaliplatin compared with the *cis*-diamine-platinum adducts formed by cisplatin and carboplatin.[4-7] The bulky DACH carrier ligand of oxaliplatin is thought to contribute to this enhanced activity as well as to the lack of cross-resistance between oxaliplatin and cisplatin.[4,5] The DACH ligand may also hinder DNA repair by preventing or reducing the binding of specific damage repair proteins such as the mismatch repair enzyme complex, thereby decreasing the replicative bypass of platinum-DNA adducts.[4,8,9]

As a result of these or other contributing factors, oxaliplatin was shown to affect DNA integrity and induce apoptosis, which may also contribute to the mechanism of action of this drug.[10,11]

Several mechanisms have been implicated in the development of tumour cell resistance to all platinum compounds. These include:[4,5,12-14]

- reduced cellular drug accumulation
- drug inactivation by conjugation with glutathione or sequestration involving metallothionine
- enhanced tolerance to platinum-DNA adducts
- increased excision-repair of platinum-DNA adducts.

Defects in mismatch repair and enhanced replicative bypass have also been reported as mechanisms of resistance to cisplatin or carboplatin but do not appear to contribute to oxaliplatin resistance.[4,15-17]

2.2 Antitumour Effects

2.2.1 In Vitro Studies

Oxaliplatin has shown *in vitro* antiproliferative efficacy against several human tumour cell lines and tumour isolates from patients (table I). Additionally, although oxaliplatin is not effective

against all cisplatin-resistant cell lines,[36,37] greater cytotoxic activity than cisplatin or carboplatin has been reported against some drug-resistant cancer cell lines.[22-24]

In a key study,[22] the sensitivity to oxaliplatin of ovarian and epithelial cisplatin-resistant cell lines of the US National Cancer Institute's Anticancer Drug Screen was evaluated. Mean concentrations of oxaliplatin required to inhibit cell proliferation by 50% (IC_{50}) were 0.12 and 0.39 μmol/L against cisplatin-sensitive strains of A2780 ovarian and KB-31 epithelial cells, respectively, compared with 0.21 and 0.75 μmol/L for cisplatin and 0.35 and 1.65 μmol/L for carboplatin. IC_{50} values for oxaliplatin were increased 4.7- and 2.7-fold, respectively, in the equivalent cisplatin-resistant clones. Respective values were 92- and 78-fold higher for cisplatin and 64- and 57-fold higher for carboplatin.[22]

2.2.2 In Vivo Studies

Oxaliplatin has shown antitumour activity in a number of murine tumour models (table I).[4] The efficacy of oxaliplatin was similar to that of cisplatin against colon carcinoma, melanoma, and P388 and L40 AkR leukaemia models.[30-32] Moreover, oxaliplatin showed superior antineoplastic efficacy to that of cisplatin in models of mammary carcinoma, sarcoma, L1210 leukaemia and LGC lymphoma.[30,31] At oxaliplatin dosages of 5 to 12.5 mg/kg, ≈1.4- to 3.6-fold increases in survival duration versus control animals (presumably receiving vehicle) were reported in mice grafted with solid tumours, whereas cisplatin 3.12 or 6.25 mg/kg was associated with 1.5- to 3.2-fold improvements.[3,4] Values for haematological tumours were 1.8- to 3.1-fold and 1.1- to 2.5-fold for oxaliplatin and cisplatin, respectively.

The efficacy of oxaliplatin was maintained in cisplatin-resistant strains of 2 haematological malignancies.[30,31] In a murine model of cisplatin-resistant L1210 leukaemia, oxaliplatin 6.25 mg/kg produced a >7-fold increase in survival duration compared with the same dosage of cisplatin.[30] Moreover, >50% cure was effected by oxaliplatin 5 mg/kg in mice with LGC lymphoma, whereas cisplatin was inactive in the same model.[31] However, neither oxaliplatin nor cisplatin showed activity against grafts of glioma 26, B16 melanoma, Lewis lung carcinoma or MA16-C mammary adenocarcinoma in this study.[31]

2.3 In Combination with Other Agents

A number of *in vitro* and *in vivo* studies have shown additive or synergistic effects of some oxaliplatin-based combinations against certain cancer cell lines (table I). For example, in *in vitro* studies in human colon cancer cell lines, oxaliplatin appeared to have additive or synergistic effects with fluorouracil,[25,26] gemcitabine,[28] AG337[25] and with the active metabolite of irinotecan, SN38.[27] However, antagonistic or less than additive effects of oxaliplatin plus SN38 have been reported in other colon cancer cell lines. The additive effects of oxaliplatin and fluorouracil have been confirmed *in vivo* in a murine HT29 xenograft model.[25]

3. Overview of Pharmacokinetic Properties

This section provides an overview of the pharmacokinetic properties of intravenous oxaliplatin in patients with various malignancies. These have recently been reviewed in detail elsewhere.[3,38,39]

Oxaliplatin undergoes rapid nonenzymatic biotransformation to a variety of reactive intermediates,[19,38] and evaluation of platinum pharmacokinetics rather than those of the parent compound is generally employed for routine pharmacokinetic studies.[38] Antitumour and toxic properties are thought to reside in platinum species present in the ultrafilterable plasma fraction (nonprotein bound drug and biotransformation species), whereas platinum bound to plasma proteins or erythrocytes is considered to be pharmacologically inactive. Indeed, in an *in vitro* study, maximal uptake (37%) of platinum into erythrocytes occurred within 2 hours of exposure and was not exchangeable into plasma. Thus, intra-erythrocyte platinum does not act as a drug reservoir.[19]

Oxaliplatin-derived platinum binds rapidly and extensively to plasma proteins. In patients with cancer, the extent of platinum-plasma protein binding after a 2-hour infusion of oxaliplatin 130 mg/m^2 increased from 70% at 2 hours to 95% 5 days after the infusion.[40] This dose schedule produced maximum plasma concentrations (C_{max}) of platinum of 0.83 to 1.21 and 2.96 to 3.22 mg/L in plasma ultrafiltrate and total plasma, respectively (table II).[38] Area under the concentration-time curve from zero to infinity (AUC_∞) values were 11.9 to 13.6 and 207 to 290 mg/L · h for ultrafiltrate and total plasma, respectively.

Steady-state plasma ultrafiltrate platinum concentrations were achieved during the first cycle of treatment with oxaliplatin 130 mg/m^2, and accumulation was not reported after single or multiple dosing (with or without fluorouracil/folinic acid).[41,42] However, a progressive accumulation of platinum in erythrocytes has been reported.[41,42]

Platinum C_{max} was dependent on the time of peak oxaliplatin infusion during a chronomodulated treatment regimen (see section 4.1). Patients (n = 36) with metastatic colorectal cancer were treated with oxaliplatin 25, fluorouracil 800 and folinic acid 150 mg/m^2/day for 4 days. Total platinum and ultrafilterable (free) C_{max} values were significantly lower after peak oxaliplatin delivery at 0100 hours than at 0700 or 1600 hours (0.7 *vs* 1.2 or 1.0 mg/L, p = 0.001 for total platinum and 0.12 *vs* 0.24 or 0.19, p = 0.003 for free platinum).[43]

Oxaliplatin-derived platinum has a large volume of distribution from plasma ultrafiltrate (582 to 812L) and a triexponential half-life decline with short initial α and β distribution phases (≈0.2 to 0.3 hours and ≈15 to 16 hours, respectively) and a long terminal γ phase (252 to 273 hours).[38] The clearance of ultrafilterable platinum ranges from 9.3 to 10.1 L/h (table II).

Excretion of oxaliplatin biotransformation products occurs principally by the renal route.[40,44] Urinary platinum accounted for ≈50% of the administered oxaliplatin 130 mg/m^2 dosage within 72 hours and 57% was recovered by day 11.[40] Faecal platinum excretion accounted for only 2.1% of the administered dosage after 5 days.[44]

Table II. Summary of mean platinum pharmacokinetics (measured using ICPMS) in patients with various malignancies after a single 2-hour infusion of oxaliplatin 130 mg/m^2 as monotherapy (reviewed by Graham et al.[38])

Parameter	Total plasma platinum	Ultrafilterable plasma platinum
C_{max} (mg/L)	2.96-3.22	0.83-1.21[a]
AUC_∞ (mg/L • h)	207-290	11.9-13.6
$t_{½\alpha}$ (h)		0.21-0.28
$t_{½\beta}$ (h)		15.1-16.3
$t_{½\gamma}$ (h)	189-239	252-273
V_{ss} (L)		582-812
CL (L/h)		9.3-10.1

a Value calculated on cycle 5 of treatment (each cycle defined as one 2-hour infusion of oxaliplatin every 3 weeks).

AUC_∞ = area under the plasma concentration-time curve from zero to infinity; **CL** = total clearance; **C_{max}** = peak plasma concentration; **ICPMS** = inductively coupled plasma mass spectrometry; **$t_{½\alpha}$** = distribution half-life; **$t_{½\beta}$** = elimination half-life; **$t_{½\gamma}$** = terminal elimination half-life; **V_{ss}** = volume of distribution at steady state.

Exposure to plasma platinum was increased in patients with moderate renal impairment compared with that in individuals with normal renal function. Although ultrafilterable platinum C_{max} did not differ between groups, higher AUC (9.16 *vs* 5.21 mg/L · h, p = 0.004) and lower systemic clearance values (14.23 *vs* 25.70 L/h, p = 0.005) were reported among patients with renal impairment [creatinine clearance 27 to 57 ml/min (1.62 to 3.42 L/h)] compared with individuals with normal renal function.[45] However, further deterioration of renal function was not reported and the toxicity of oxaliplatin was not increased in patients with impaired renal function.[46] Total body platinum clearance was independent of age, gender and hepatic function.[47]

3.1 Drug Interactions

The effects of oxaliplatin on the pharmacokinetics of fluorouracil (in the presence of folinic acid) are inconsistent. While a 2-hour infusion of oxaliplatin 85 mg/m^2 did not affect the pharmacokinetic parameters of fluorouracil,[48] another study reported significantly increased plasma levels of

fluorouracil when oxaliplatin 130 mg/m^2 was added to the regimen.[49] A third study reported that the linear elimination rate was increased and the AUC of fluorouracil decreased ($p = 0.05$, both parameters) in the presence of oxaliplatin.[50] The pharmacokinetic properties of oxaliplatin were not affected by fluorouracil.[48]

There were no pharmacokinetic interactions between oxaliplatin 85 or 110 mg/m^2 and irinotecan 150 to 250 mg/m^2 during coadministration.[51] Similarly, the pharmacokinetics of oxaliplatin 85 mg/m^2 and topotecan 0.5 mg/m^2 were unaffected when these agents were administered in combination.[52]

Increasing dosages of raltitrexed (3 to 3.75 mg/m^2) did not appear to affect the pharmacokinetic properties of oxaliplatin 130 mg/m^2.[53] However, in another study, oxaliplatin clearance appeared to increase and terminal half-life decreased by approximately 87 and 36%, respectively, during raltitrexed coadministration.[54]

4. Clinical Efficacy

The clinical focus of oxaliplatin therapy has largely been on its role in the treatment of metastatic colorectal cancer. However, oxaliplatin has also been trialled both as a first- and second-line therapy for the treatment of advanced ovarian cancer, and initial reports have investigated the activity of this agent in other malignancies including non-Hodgkin's lymphoma, breast cancer, non-small cell lung cancer, mesothelioma and squamous cell carcinoma of the head and neck.

The primary efficacy end-point in oxaliplatin trials was the objective response rate, i.e. complete plus partial response rate. Secondary end-points included the duration of response, time to disease progression (or treatment failure), duration of progression-free survival and median duration of survival. The incidence of disease stabilisation was also reported by most investigators.

Tumour responses were evaluated according to WHO criteria:[55]

- complete response: total disappearance of all measurable and assessable lesions documented at 2 observations 4 weeks apart with no new lesions appearing
- partial response: ≥50% decrease in tumour area (sum of the products of the greatest length and the maximum perpendicular width of all measurable lesions) with no new lesions appearing and no increase in size in any previous lesions
- stable disease: <25% increase in indicator lesions with no new lesions appearing
- progressive disease: ≥25% increase in one or more lesions or the appearance of new lesions.

Treatment was continued until disease progression or the occurrence of intolerable adverse events.

4.1 Metastatic Colorectal Cancer

In patients with colorectal cancer, most data pertain to the use of oxaliplatin in combination with fluorouracil-based therapy; however, phase II trials have studied oxaliplatin monotherapy, and recent trials have investigated combination therapy with oxaliplatin and irinotecan (topoisomerase I inhibitor) or raltitrexed (thymidylate synthase inhibitor).

Several regimens of oxaliplatin/fluorouracil/folinic acid have been used (tables III and IV), which varied in dosage, duration of infusion and frequency of administration. Both standard (fixed rate) and chronomodulated infusion schedules have been investigated. Chronomodulation is based on circadian rhythm, with peak delivery of fluorouracil and folinic acid at 0400 hours and/or peak delivery of oxaliplatin at 1600 hours. Some investigators believe that chronomodulated delivery of antineoplastic agents optimises clinical efficacy. Indeed, in 2 multicentre trials, objective response rates were significantly higher with chronomodulated versus fixed rate infusion schedules (table III).[56,57] Median progression-free survival also appeared higher with the chronomodulated regimen, however, whether there is any benefit in terms of long term survival remains unclear.[56-58]

Patients enrolled in clinical trials of oxaliplatin were aged 18 to 75 years and were generally required to have biopsy-proven adenocarcinoma,

measurable recurrent or metastatic disease, a WHO performance status ≤2 and a life expectancy >1 to 3 months. In studies of oxaliplatin as first-line therapy, previous chemotherapy for metastatic disease was not allowed. However, patients who had received prior adjuvant or neoadjuvant chemotherapy and/or radiotherapy were eligible for the study if they had had a disease-free period of ≥6 months after treatment completion. Tables III and IV summarise the results from trials with the largest populations (n > 25) and most complete data.

4.1.1 First-Line Therapy

Combination Therapy

This section will focus on combination therapy with oxaliplatin and fluorouracil/folinic acid as this regimen has been the most widely studied. However, promising results have been achieved with oxaliplatin combined with the raltitrexed (objective response rate 62% in a phase II trial, n = 63; table III)[61] indicating that this regimen warrants further investigation.

The addition of oxaliplatin to first-line fluorouracil/folinic acid therapy significantly increased objective response rates compared with fluorouracil/folinic acid therapy alone in 2 large phase III, randomised trials.[59,60] Each study utilised a slightly different regimen (see table III) but, in both studies, the coadministration of oxaliplatin more than doubled the objective response rate compared with fluorouracil/folinic acid therapy alone. The objective response rates were 53 *vs* 16% ($p < 0.001$) for patients receiving chronomodulated schedules[60] and 50.7 *vs* 22.3% ($p < 0.001$) for patients receiving fixed-rate infusion schedules[59] with or without oxaliplatin, respectively.

Progression-free survival was also significantly longer in patients receiving the oxaliplatin combination (8.7 *vs* 6.1 months[60] and 9.0 *vs* 6.2 months[59]). However, there was no significant difference in overall survival between the treatment groups in either trial. Indeed, the median overall survival durations observed for patients receiving fluorouracil-based chemotherapy were long (19.9 and 14.7 months) in both these trials compared with those obtained in previous studies (usually between 8 and 16.2 months with a median of approximately 12 months).[60]

The unusually long survival in these trials may be accounted for by the fact that post-study chemotherapy was allowed after disease progression. In fact, second-line oxaliplatin and/or irinotecan therapy was administered to 57 and 37% of patients initially randomised to receive fluorouracil/folinic acid therapy alone in the chronomodulated and fixed rate infusion studies, respectively. Of the 57 patients (57%) receiving oxaliplatin after failing chronomodulated fluorouracil/folinic acid therapy, 42 (74%) showed a further response (10 had partial responses and 32 had stable disease), including 16 of 21 patients (76%) who were refractory to fluorouracil.[60,87] In the other randomised trial,[59] the median survival in the oxaliplatin/fluorouracil/folinic acid arm was 14.8 months versus 12.2 months in patients not receiving oxaliplatin ($p = 0.04$ by the log rank test) when post-study chemotherapy with oxaliplatin and/or irinotecan was excluded from the analysis.[59]

Another reason for the long survival duration could be the fact that patients were able to undergo secondary liver resection. In patients receiving chronomodulated combination therapy,[60] resection of liver metastases was performed in 32% of patients treated with oxaliplatin combination therapy and 21% of patients receiving combination therapy without oxaliplatin as first-line therapy. A further 10 patients in the control arm underwent second-line surgery after crossing over to oxaliplatin therapy. The value of oxaliplatin chemotherapy combined with surgery is discussed in section 4.1.3.

Monotherapy

The efficacy of oxaliplatin monotherapy in chemotherapy-naive patients with advanced colorectal cancer has been evaluated in 2 small phase II trials.[64,65] Oxaliplatin (130 mg/m^2 infused over 2 hours once every 3 weeks) produced objective response rates of 20[65] and 24%;[64] the median times to disease progression were 6 and 7.2 months and the median durations of survival were 14.5 and 13.2 months.[64,65] While no direct comparisons are

Table III. Efficacy of intravenous oxaliplatin (OXA) as first-line therapy in patients with metastatic colorectal cancer

Reference (study design)	No. of evaluable pts	Treatment regimen (mg/m^2/day) [frequency]	Objective response rate (% pts) [CR + PR]	Disease stabilisation (% pts)	Median time to disease progression (mo)	Median duration of progression-free survival (mo)	Median duration of survival (mo)
Combination therapy (comparative studies)							
de Gramont et al. [59](mc, r)	207	OXA 85 2h inf d1 + FA 200 2h inf + 5-FU 400 B then 5-FU 600 CI d1-2 [q2wk]	50.7*** [1.4 + 48.6]	31.9	NR	9.0***	16.2
	206	FA 200 2h inf + 5-FU 400 B then 5-FU 600 CI d1-2 [q2wk]	22.3 [0.5 + 21.4]	51.0	NR	6.2	14.7
Giacchetti et al.[60](mc, r)	100	OXA 125 6h inf d1 + FA 300/5-FU 700 CM d1-5 [q3wk]	53[a]*** [3 + 50]	24	NR	8.7*	19.4
	100	FA 300/5-FU 700 CM d1-5 [q3wk]	16[a] [0 + 16]	45	NR	6.1	19.9
Combination therapy (noncomparative studies)							
Douillard et al.[61]	63	OXA 130 2h inf + RTX 3 15min inf [q3wk]	62 [2 + 60]	28.5	6.3	NR	≥13[b]
Lévi et al.[62][c]	46	OXA 25 CM + FA 300/5-FU 700 CM d1-5 [q3wk]	59 [11 + 48]	30	NR	11	15
Lévi et al.[63]	90	OXA 25 CM + FA 300/5-FU 700-1100 CM d1-5 [q2wk[d]]	66 [0 + 66]	21	NR	8.4	18.5
Chronomodulated versus continuous OXA infusion + 5-FU/FA							
Lévi et al.[57] (mc, r)	45 (6% had AC)	OXA 20-25 CM + FA 300/5-FU 600-700 CM d1-5 [q3wk]	53* [6 + 47]	36	NR	11	19*
	47 (11% had AC)	OXA 20-25 CI + FA 300/5-FU 600-700 CI d1-5 [q3wk]	32 [4 + 28]	46	NR	8	14.9
Lévi et al.[56] (mc, r)	93 (14% had AC)	OXA 20-25 CM + FA 300/5-FU 600-700 CM d1-5 [q3wk]	50** [5 + 45]	NR	6.4[e]*	9.8	15.9
	93 (13% had AC)	OXA 20-25 CI + FA 300/5-FU 600-700 CI d1-5 [q3wk]	29 [3 + 26]	NR	4.9[e]	7.9	16.9
OXA monotherapy (noncomparative studies)							
Bécouarn et al.[64]	38	OXA 130 2h inf d1 [q3wk]	24 [0 + 24]	41	7.2	4.2	13.2
Díaz-Rubio et al.[65]	25	OXA 130 2h inf d1 [q3wk]	20[f] [4 + 16]	32	6	4.0	14.5

a According to an independent radiology assessment. According to the investigators, the objective response rates were 59 *vs* 23 ($p < 0.001$).

b Median survival not yet reached.

c This study also included 46 previously treated patients (see table IV).

d Intrapatient dosage escalation of 5-FU was performed if toxicity was less than WHO grade 2. (100 mg/m^2/day after first course, and 50 mg/m^2/day after subsequent courses).

e Median time to treatment failure.

f According to investigators. An independent expert committee reported an objective response rate of 12%.

5-FU = fluorouracil; **AC** = adjuvant chemotherapy; **B** = bolus; **CI** = continuous infusion; **CM** = chronomodulated delivery rate (12-hour infusion of OXA with peak delivery at 1600 hours followed by 12-hour infusion of 5-FU/FA with peak delivery at 0400 hours); **CR** = complete response (defined in section 4); **d** = days; **FA** = folinic acid; **inf** = intravenous infusion; **mc** = multicentre; **mo** = months; **NR** = not reported; **PR** = partial response (defined in section 4); **pts** = patients; **q** = every; **r** = randomised; **RTX** = raltitrexed; **wk** = weeks. * $p < 0.05$; ** $p < 0.005$; *** $p < 0.001$ *vs* comparator.

available, these results are comparable with those seen in patients receiving first-line fluorouracil/folinic acid therapy (table III).[59,60]

4.1.2 Second-Line Therapy

Combination Therapy

In patients progressing after treatment with fluorouracil, subsequent combination therapy with oxaliplatin and fluorouracil/folinic acid typically produced objective response rates of between 13 and 45% in most phase II trials. Median progression-free survival in these patients ranged from about 5 to 10 months and the median duration of survival was between 9 and 17 months (table IV).[62,66-69,71-75]

This combination has also shown efficacy in a population of patients who had become refractory or who had progressed following irinotecan treatment.[70] Objective responses were observed in 7 of 41 patients (17%) given second-line oxaliplatin/fluorouracil/folinic acid.[70] The median time to disease progression and median overall survival was 11 and 12 months, respectively, in these patients (table IV).

A variety of different treatment regimens were used in these trials which differed in dosage, duration of infusion and frequency of administration of oxaliplatin and of fluorouracil-based chemotherapy. Although there is no internationally accepted gold standard fluorouracil/folinic acid regimen, 2-weekly high-dose continuous infusion schedules have proved superior to bolus schedules in terms of response rate and progression-free survival.[80] The addition of oxaliplatin to the high-dose 2-weekly regimen was examined in a number of trials.[71-75]

Oxaliplatin has also shown promise in combination with irinotecan and raltitrexed for the second-line treatment of metastatic colorectal cancer.

Initial investigations into the efficacy of oxaliplatin combined with irinotecan revealed this combination to be active, with objective responses of 28 to 44% in patients receiving this 2-drug regimen,[77-79] and 16[79] and 58%[76] in patients receiving oxaliplatin, irinotecan and fluorouracil based therapy (table IV).

Oxaliplatin also showed good activity when combined with raltitrexed (table IV).[83] In a dose-finding trial, the overall objective response was 37%, however, in the 17 patients receiving the recommended dosage (raltitrexed 3 mg/m^2/day followed by oxaliplatin 130 mg/m^2/day), an objective response was acheieved in 8 patients (47%) and 9 (53%) had stable disease. Raltitrexed and oxaliplatin were also used in combination with fluorouracil/folinic acid therapy,[82] with 26% of patients acheiving an objective response and a further 17% displaying a minor response (>25% reduction in tumour magnitude).

Monotherapy

Single-agent oxaliplatin achieved objective response rates of ≈10% in patients with metastatic colorectal cancer refractory to, or relapsing after, fluorouracil-based therapy in phase II studies (table IV). Fixed rate infusion schedules (130 mg/m^2 every 3 weeks)[86] and chronomodulated 5-day continuous infusion schedules (30 to 40 mg/m^2/day with peak delivery at 1600 hours)[85] produced comparable results; the median time to disease progression ranged from 4.5 to 6 months and median duration of survival was 8.2 and 10 months in 2 studies.[85,86]

4.1.3 Use in Patients with Unresectable Liver Metastases

Surgery is the only potentially curative treatment for colorectal cancer; however, approximately 50% of patients present with metastatic disease, and surgery is only possible in 10 to 20% of patients with liver metastases.[88] The overall 5-year survival rates in patients who are able to undergo primary liver resection is 30 to 40%.[89] Palliative chemotherapy remains the only option for patients with unresectable metastases and their prognosis is poor, however, these patients may be re-evaluated for surgery if they achieve an adequate response to chemotherapy.

Two studies[88,90] have evaluated the impact of oxaliplatin/fluorouracil/folinic acid therapy combined with surgery on the survival of patients with initially unresectable liver metastases.

Table IV. Efficacy of intravenous oxaliplatin (OXA) as second-line therapy in patients with metastatic colorectal cancer

Reference	No. of pts (previous treatment for advanced disease)	Treatment regimen (mg/m^2/day) [frequency]	Objective response rate (% pts) [CR + PR]	Disease stabilisation (% pts)	Median time to disease progression (mo)	Median progression-free survival (mo)	Median duration of survival (mo)
Combination therapy							
OXA + 5-FU/FA (noncomparative studies)							
Bertheault-Cvitkovic et al.[66]	37 (5-FU based)	OXA 25 CM + FA 300/5-FU 700-1100 CM d1-4 [q2wk][a]	40 [3 + 37]	51	NR	9.3	16.9
Brienza et al.[67]	98 (5-FU refractory)	OXA 80-100 q2wk or 100-130 q3wk 2-6h inf + 5-FU±FA (NR)	25.5 [NR]	31.6	4.1	NR	9.6
Gerard et al.[68]	36 (5-FU based)	OXA 130 2h inf d1 [q3wk] + FA 500 1h inf/5-FU 2600 CI d1,d8,d29,d43	28 [0 + 28]	17	10	NR	10
Janinis et al.[69]	32 (5-FU and/or IRIN)	OXA 50 2h inf + FA 500/5-FU 2500 CI [q1wk]	13 [0 + 13]	38	3	NR	9[b]
Kouroussis et al.[70]	41 (IRIN + 5-FU based)	OXA 100 d1 2h inf + FA 500/5-FU 1750 22h inf d1-2 [q3wk]	17 [2.5 + 14.5]	39	11	NR	12
Lévi et al.[62]	46[c] (NR)	OXA 25 CM + FA 300/5-FU 700 CM d1-5 [q3wk]	57 [2 + 55]	40	NR	10	13
OXA + 5-FU/FA (2-weekly studies)							
de Gramont et al.[71,72] André et al.[73]	13 (5-FU based)	OXA 130 [q4wk] + FA 500 2h inf/5-FU 1500-2000 22h inf d1-2 [q2wk]	31 [0 + 31]	38	NR	NR	11
	60 (5-FU based)	OXA 100 + FA 500 2h inf/5-FU 1500-2000 22h inf d1-2 [q2wk]	37 [2 + 35]	35	NR	NR	15
	46[72] (5-FU based)	OXA 100 + FA 500 2h inf/5-FU 1500-2000 22h inf d1-2 [q2wk]	46 [2.2 + 43.5]	46	NR	7	17
	40 (5-FU based)	OXA 85 + FA 500 2h inf/5-FU 1500-2000 22h inf d1-2 [q2wk]	16 [0 + 16]	53	NR	NR	10
	30[73] (5-FU based)	OXA 85 + FA 500 2h inf/5-FU 1500-2000 22h inf d1-2 [q2wk]	20 [NR]	50	NR	26wk	57wk
André et al.[74]	38[d] (5-FU based)	OXA 85 + FA 500 2h inf/5-FU 1500 22h inf d1-2 [q2wk]	18.4[e] [NR]	29	NR	4.6	10.6
	51 (5-FU based)	OXA 85 + FA 200 2h inf/5-FU 400 B + 5-FU 600 22h inf d1-2 [q2wk]	23.5[f] [NR]	31.4	NR	5.1	11.1
Maindrault-Goebel et al.[75]	60 (5-FU based)	OXA 100 + FA 400 2h inf/5-FU 400 B + 2400-3000 46h inf d1-2 [q2wk]	27 [0 +27]	45	NR	5.3	10.8
OXA + IRIN ± 5-FU/FA							
Calvo et al.[76][g]	33 (NR)	OXA 120 d1 + IRIN 250-300 d1 [q4wk] + FA 500/5-FU 2500 inf d1-4 or 5-FU 2600 d1,d15	58 [9 + 49]	21	8[h]	NR	NR[i]
Scheithauer et al.[77]	36 (5-FU based)	OXA 85 2h inf d1, d15 + IRIN 80 30 min inf d1, d8, d15 [q4wk][j]	42 [6 + 36]	36	7.5[h]	NR	NR[k]
Wasserman et al.[78][g,l]	34 (5-FU based)	OXA 85-110 + IRIN 100-250 [q2 or 3wk]	44 [3 + 41]	35	7.5	NR	NR

Contd on next page

Yves et al.[79]g	24 (5-FU based)	IRIN 180 d1 + (FA 200/5-FU 400 B + 5-FU 600 22h CI d1-2)[80] then OXA 85 d15 + (FA 200/5-FU 400 B + 5-FU 600 22h CI d15-16) [q4wk]	16 [0 + 16]	62	8	NR	10
	29 (5-FU based)	OXA 85 + IRIN 200 d1 [q3wk]	28 [0 + 28]	45	10	NR	12
OXA vs IRIN							
Ulrich-Pur et al.[81]g	27 (5-FU based)	OXA 85 d1,d15 + MMC 8 d1 [q4wk]	18.5[m] [NR]	NR	NR	NR	NR
	30 (5-FU based)	IRIN 120 d1,d15 + MMC 8 d1 [q4wk]	23.3[m] [NR]	NR	NR	NR	NR
OXA + raltitrexed (RTX) ± 5-FU							
Comella et al.[82]l	46 (5-FU ± IRIN)	OXA 85-130 2h inf + RTX 2.5-3 15min inf d1 + 5-FU 750-1200 B + FA 250 d2 [q2wk]	26[n] [2 + 24]	33	3.6[h]	NR	12
Kornek et al.[83]l	38 (NR)	OXA 85-140 + RTX 3 [q3wk]	37 (NR)	47	NR	NR	NR
Monotherapy							
Chacon. et al.[84]g	32 (5-FU based)	OXA 130 2-6h inf [q3wk]	9 [3 + 6]	19	NR	NR	NR
Lévi et al.[85]	29 (86% 5-FU based)	OXA 30-40 CM d1-5 [q3wk]	10 [0 + 10]	24	NR	5	10
Machover et al.[86]o	55 (5-FU based)	OXA 130 2h inf d1 [q3wk]	11 [0 + 11]	42	6	NR	8.2
Machover et al.[86]o	51 (5-FU based)	OXA 130 2h inf d1 [q3wk]	10 [0 + 10]	31	4.5	NR	NR

a Intrapatient dosage escalation of 5-FU (100 mg/m^2/day) was performed if toxicity was less than WHO grade 2.

b Taken from start of therapy.

c 42 patients (91%) had received previous chemotherapy with/without radiation therapy; 5 (11%) had received previous radiation therapy alone; this study also included 46 previously untreated patients (see table III).

d Oxaliplatin added to the same regimen under which the patient had progressed.

e Not including 7.9% unconfirmed responses.

f Not including 2% unconfirmed responses.

g Abstract report.

h Median time to treatment failure.

i Median survival duration not yet reached. After a median follow-up of 18 months, 18 (54.5%) patients are still alive.

j Granulocyte colony-stimulating factor (5 μg/kg/day subcutaneously on 5 consecutive days) was given to 31 of 36 patients with an absolute neutrophil count of 1000 to 2000/μL on day of scheduled drug administration.

k Median survival duration not yet reached. After a median follow-up of 14 months, 19 (53%) patients are still alive.

l Dose-finding study.

m No between-treatment statistical analysis was reported: 95% confidence intervals were 6.3 to 38.1% and 9.9 to 42.3% in OXA and IRIN arms, respectively.

n Not including 17% who showed a minor response to therapy (reduction >25%).

o Independent studies.

5-FU = fluorouracil; **B** = bolus; **CI** = continuous infusion; **CM** = chronomodulated delivery rate (12-hour infusion of OXA with peak delivery at 1600 hours followed by 12-hour infusion of 5-FU/FA with peak delivery at 0400 hours); **CR** = complete response (defined in section 4); **d** = days; **FA** = folinic acid; **inf** = intravenous infusion; **IRIN** = irinotecan; **MMC** = mitomycin C; **mo** = months; **NR** = not reported; **PR** = partial response (defined in section 4); **pts** = patients; **q** = every; **wk** = weeks.

In a prospective analysis,[88] the size of liver metastases shrank to a surgically manageable size in 53 of 330 patients (16%) with previously unresectable disease following combined oxaliplatin/fluorouracil/folinic acid chronotherapy. 37 patients underwent major hepatic metastasectomies and 16 had minor resection; 46 (87%) first hepatic metastasectomies were macroscopically curative. The cumulative 3- and 5-year survival rates for patients undergoing surgery were 54 and 40%, respectively. Survival rates varied according to the type of lesion: 5-year survival rates were 48% for ill-located lesions, 62% for large lesions, 40% for multinodular lesions and 14% for extrahepatic lesions.[88]

Based on these results, the subsequent study limited the patient population to those with unresectable liver metastases confined to the liver.[90] In this retrospective analysis, 89 of 151 patients (59%) receiving chronomodulated oxaliplatin/fluorouracil/folinic acid therapy[56,57,63,66,91] achieved a reduction of ≥50% in the size of previously unresectable liver metastases. Consequently, a total of 77 patients (51%) underwent liver surgery with curative intent and 58 of these patients (75%) achieved a complete resection. The overall median survival duration for all 151 patients was 24 months and the 5-year survival rate was 28%. In the 77 patients who underwent surgery, the overall survival duration was 48 months, and the estimated survival rate at 5 years was 50%. The median overall survival of the 58 patients with complete resection had not been reached, but the estimated 5-year survival rate was 58%.[90]

4.2 Advanced Ovarian Cancer

In patients with advanced ovarian cancer, oxaliplatin has been trialled both as monotherapy and in combination with cyclophosphamide, cisplatin and/or paclitaxel. The majority of trials have been in patients relapsing after platinum-based chemotherapy, with 1 trial investigating oxaliplatin as a first-line therapy.

Table V summarises the results from all available studies of oxaliplatin in this population, a number of which are ongoing. Patients enrolled in clinical trials of oxaliplatin were aged 25 to 82 years and were generally required to have biopsy-proven epithelial ovarian carcinoma, measurable recurrent or metastatic disease, a WHO performance status ≤2 and a life expectancy >1 to 3 months.

Patients with disease recurrence after previous platinum-based therapy were classified into 2 groups according to Markman's criteria:[99]

- platinum-sensitive: patients who have a complete response to primary chemotherapy and subsequent recurrence more than 6 months after discontinuation of treatment
- platinum-resistant/refractory: patients who do not achieve a complete response to primary chemotherapy (refractory) or have a recurrence within 6 months of completing chemotherapy (resistant).

4.2.1 First-Line Therapy

Oxaliplatin appears to have comparable efficacy to cisplatin as a first-line treatment for patients with advanced ovarian cancer. In a multicentre phase II/III trial, patients receiving oxaliplatin 130 mg/m^2/day (n = 69) or cisplatin 100 mg/m^2/day (n = 69) [both in combination with cyclophosphamide 1000 mg/m^2/day] once every 3 weeks achieved response rates of 33 and 42%, respectively. The median progression-free survival (13 months in both groups) and median duration of survival (36 *vs* 25 months) were also similar for patients receiving oxaliplatin or cisplatin, respectively. No significant differences were reported between the treatment arms for any efficacy parameters.[92]

4.2.2 Second-Line Therapy

Monotherapy

In patients receiving single-agent oxaliplatin therapy (100 to 130 mg/m^2 every 3 weeks), objective response rates ranged from 16 to 26.5% and the median duration of survival was between ≈10 and 15 months in phase II trials (table V).[93,95,100]

Both platinum-sensitive and platinum-refractory tumours responded to oxaliplatin monotherapy

Table V. Efficacy of intravenous oxaliplatin (OXA) in the treatment of patients with advanced ovarian cancer

Reference	No. of evaluable pts (sens; res)	Treatment regimen (mg/m^2/day) [frequency]	Overall objective response rate (% pts) [CR + PR] (objective response rate in sens; res)	Disease stabilisation (% pts)	Median time to disease progression (mo)	Median duration of progression-free survival (mo)	Median duration of survival (mo)
First-line therapy							
Misset et al.[92]a,b	69	OXA 130 + C 1000 [q3wk]	33[c] [NR]	NR	NR	13[c]	36[c]
	69	CIS 100 + C 1000 [q3wk]	42[c] [NR]	NR	NR	13[c]	25[c]
Second-line therapy (platinum pretreated)							
Monotherapy							
Bougnoux et al.[93]a	42 (24; 18)	OXA 130 2h inf [q3wk]	26 [5 + 21] (42; 5.5)	43	NR	5.2	15
Chollet et al.[94]	34 (13; 21)	OXA 100[d] 0.5-2h inf [q3wk]	26.5[e] [0 + 26.5] (46; 14)	23.5[e]	NR	NR	12
Piccart et al.[95]b	45[f] (NR)	OXA 130 2h inf [q3wk]	16[g] [0 + 16] (NR)	44	12wk[h]	12wk	42wk
	41[f] (NR)	PXL 175 3h inf [q3wk]	17[g] [0 + 17] (NR)	44	13wk[h]	14wk	37wk
Combination therapy							
Delaloge et al.[96]a	15[i] (NR)	PXL 135 24h inf d1 + OXA 100 + CIS 75 d2 [q3wk]	73 [53 + 20] (NR)	13	>10	NR	NR[j]
Faivre et al.[97]	31 (13; 18)	OXA 100-130 2-6h inf + PXL 135-175 3h inf d1 [q3-4wk]	48 [3 + 45] (69; 33)	29	9	NR	25.2
Soulié et al.[98]	25 (12; 13)	OXA 130 2h inf d1 + CIS 100 2h inf d1 [q3wk]	40[e] [8 + 32] (58; 23)	NR	4	NR	11

a Abstract report.

b Randomised trial.

c No significant difference between treatment groups.

d Median dose (range 58-130 mg/m^2/day).

e Intent-to-treat analysis.

f No patients had received prior paclitaxel therapy.

g No between treatment statistical analysis reported: 95% confidence intervals were 7 to 29% and 7 to 32% in OXA and PXL arms, respectively.

h Median time to treatment failure.

i Includes 8 patients who were previously untreated.

j Median survival duration not yet reached; after a median follow-up of 17 months, 12 (80%) patients are still alive.

C = cyclophosphamide; **CIS** = cisplatin; **CR** = complete response (defined in section 4); **d** = days; **inf** = intravenous infusion; **mo** = months; **NR** = not reported; **PXL** = paclitaxel; **PR** = partial response (defined in section 4.2); **pts** = patients; **q** = every; **res** = platinum-resistant/ refractory patients (defined in section 4.2); **sens** = platinum-sensitive patients (defined in section 4.2); **wk** = weeks.

(objective response rates of 42 and 46%, and 5.5 and 14%, respectively).[93,94]

In a comparative study,[95] oxaliplatin demonstrated similar efficacy to paclitaxel as a second-line monotherapy (objective response rates 16 and 17%, respectively); median progression-free survival (12 weeks in oxaliplatin arm and 14 weeks in paclitaxel arm) and median overall survival (42 and 37 weeks) were also similar between the groups (table V). Although paclitaxel achieved a higher objective response rate in a subgroup of patients with platinum-refractory disease (16 *vs* 6%), the patient numbers are too small to confirm the comparative efficacy of these 2 agents in this population.[95]

Combination Therapy

Various combination regimens including oxaliplatin with either paclitaxel[97] or cisplatin[98] or a combination of all 3 agents[96] have been trialled in patients with platinum-pretreated advanced ovarian cancer. Objective response rates have been promising (ranging from 40 to 73%), warranting further investigations of combination regimens in this patient group. Other results are summarised in table V.

4.3 Other Cancers

Oxaliplatin has also been investigated as a monotherapy and/or in combination with other agents for the treatment of prostate cancer[101] non-Hodgkin's lymphoma,[102,103] breast cancer,[104-106] squamous cell carcinoma of head and neck,[107] non-small cell lung cancer,[106,108] mesothelioma,[109] malignant melanoma,[103] glioblastoma[103] and pancreatic cancer.[110]

The results from these studies are summarised in table VI; however, due to the preliminary nature of the majority of these reports, data evaluating the survival of these patients is limited. Additional studies in larger patient populations are required to confirm these preliminary results.

The largest trials have been conducted in patients with mesothelioma (n = 58)[109] and breast cancer (n = 53)[105] in which oxaliplatin was combined with raltitrexed or fluorouracil, respectively (objective response rates 26 and 25%).

5. Tolerability

In most clinical trials, oxaliplatin toxicity was measured after each cycle and graded according to WHO[55] or National Cancer Institute Common Toxicity Criteria.[112] A specifically modified WHO grading system has been developed to assess the neurotoxicity occurring with oxaliplatin therapy which takes into account both intensity and duration of the neurosensory symptoms.[113]

The most common adverse events occurring with oxaliplatin therapy are gastrointestinal, haematological and neurological (fig. 2).

5.1 Oxaliplatin Alone or in Combination with Fluorouracil/Folinic Acid

Neurological toxicity, consisting of a peripheral sensory neuropathy, is the principal dose-limiting toxicity in patients receiving oxaliplatin.[115] It consists of an acute component as well as a cumulative component which is generally reversible within a few months of treatment discontinuation.

Acute neurotoxic manifestations, characterised by dysesthaesia and/or paraesthesia of the extremities, occur in 85 to 95% of patients and can be triggered or exacerbated by exposure to cold. These symptoms occur within hours of oxaliplatin infusion, are mild in most cases and resolve over the following hours or days.[46]

A sporadic laryngopharyngeal dysesthaesia, thought to result from decreased sensitivity of the larynx and pharynx, may be observed after infusion of oxaliplatin in ≈1 to 2% of patients. The resultant feeling of difficulty in breathing or swallowing is distressing to the patient, but symptoms resolve within hours of onset.[46,113]

Peripheral sensory symptoms increase in duration and intensity as the cumulative dose of oxaliplatin increases. These symptoms are sometimes associated with pain and cramps and can progress to a peripheral functional impairment in some patients. Functional impairment, which includes difficulty in executing activities requiring fine

Table VI. Efficacy of oxaliplatin (OXA) in the treatment of patients with other types of cancer

Reference	No. of evaluable pts (cancer type)	Median no. of previous treatments (type of treatment)	Treatment regimen (mg/m^2/day) [frequency]	Objective response rate (% pts) [CR + PR]	Disease stablisation (% pts)	Median time to disease progression (mo)	Median duration of survival (mo)
Monotherapy							
Degardin et al.[107]a	40 (SCCHN)	57% first-line; 43% platinum-pretreated	OXA 130 2h inf [q3wk]	10 [0 + 10]	7.5	NR	5
Garufi et al.[104]a	14 (breast)	≥1 (ANT)	OXA 130 2-3h inf [q3wk]	21.4 [0 + 21.4]	7	NR	NR
Gastiaburu et al.[103]a	15 (advanced malignant melanoma)	NR	OXA 130 2h inf [q3wk]	20 [7 + 13]	47	NR	NR
	10 (NHL low grade)	NR	OXA 130 2h inf [q3wk]	60 [0 + 60]	40	NR	NR
	9 (glioblastoma)	NR	OXA 130 2h inf [q3wk]	11 [11 + 0]	33	NR	NR
Germann et al.[102]	22 (NHL)	2 (ANT or CIS)	OXA 130 2h inf [q3wk]	41 [4.5 + 36.4]	32	27[b]	23
Monnet et al.[108]	33 (NSCLC)	0	OXA 130 2h inf [q3wk]	15 [3 + 12]	36	5.9[b]	8[c]
Ould Kaci et al.[101]a	6 (prostate)	1-2 (antiandrogen)	OXA 130 2h inf [q3wk]	17[d] [0 + 17]	67	NR	NR
Rougier et al.[110]a	17 (pancreas)	0	OXA 130 2h inf [q3wk]	0	12	2.1[e]	3.4
Combination therapy							
Agelaki et al.[106]a	21 (NSCLC/breast)	0	DOC 70-95 d1 + OXA 80-90 2h inf d1 or d2 [q3wk]	24 [0 + 24]	14	NR	NR
Cottu et al.[105]a	53 (breast)	2 (TX and/or ANT)	OXA 130 2h inf + 5-FU 1000 d1-4 [q3wk]	25 [0 + 25]	45	7.5[b]	NR
De Cremoux et al.[111]a	18 (NSCLC)	0	OXA 130 d1 + NVB 22-34 d1,d8 [q3wk]	44 [5 + 39]	22	NR	NR
Fizazi et al.[109]a	58 (mesothelioma)	83% first-line; 17% platinum-pretreated[f]	RTX 3 15min inf + OXA 130 2h inf d1 [q3wk]	26 [0 +26]	53	4.5	NR
Ould Kaci et al.[101]a	6 (prostate)	1-2 (antiandrogen)	OXA 130 2h inf d1 + 5-FU 1000 d1-4 [q3wk]	33[d] [0 + 33]	67[g]	NR	NR
Rougier et al.[110]a	28 (pancreas)	0	OXA 130 d1 + 5-FU 1000 d1-4 [q3wk]	11	61	4.1[e]	8.5

a Abstract.

b Median response duration.

c Median duration of survival = 17.1 months for responders.

d Response defined as a sustained ≥50% reduction from baseline in prostate specific antigen levels in patients with unmeasurable disease.

e Median time to treatment failure.

f Taken from total patient population (n = 72).

g Includes 2 unconfirmed PR.

5-FU = fluorouracil; **ANT** = anthracycline; **CIS** = cisplatin; **CR** = complete response (defined in section 4); **d** = days; **DOC** = docetaxel; **inf** = intravenous infusion; **mo** = months; **NHL** = non-Hodgkin's lymphoma; **NR** = not reported; **NSCLC** = non-small cell lung cancer; **NVB** = vinorelbine; **PR** = partial response (defined in section 4); **pts** = patients; **q** = every; **RTX** = ralitrixed; **SCHNC** = squamous cell carcinoma of head and neck; **TX** = taxane; **wk** = weeks.

sensory-motor coordination such as writing and buttoning clothing, may necessitate dosage reduction.[46]

In an analysis of data from 682 patients enrolled in 9 clinical trials, the risk of developing functional impairment was estimated to occur in 10% of patients receiving a cumulative oxaliplatin dose of 780 mg/m^2 (9 treatment cycles at 85 mg/m^2 once every 2 weeks or 6 treatment cycles at 130 mg/m^2 once every 3 weeks), and in 50% of patients at a cumulative dose of 1170 mg/m^2.[114]

In clinical practice, the onset of functional impairment usually occurs after the maximum response to therapy has been obtained.[59,60]

Clinical trials indicate that the incidence of neurotoxicity is higher when oxaliplatin is given in combination with fluorouracil-based regimens.[114] In the analysis of data from 9 clinical trials,[114] grade 3 or 4 neurotoxicity occurred in 3% of patients receiving oxaliplatin monotherapy (n = 273), and 19% receiving oxaliplatin in combination with fluorouracil/folinic acid chemotherapy (n = 409) [fig. 2].[114] Cumulative neurotoxicity was reversible in the majority of these cases, with 82% of patients with functional impairment showing regression of symptoms within 3 to 4 months after discontinuing treatment.

A preliminary report showed that re-introduction of oxaliplatin therapy did not cause an appreciable worsening of sensory neurotoxicity.[116]

Prolongation of oxaliplatin infusion may reduce the incidence of laryngopharyngeal dysesthaesia.[46] In 1 study,[60] no laryngopharyngeal dysesthaesia was reported when oxaliplatin was infused over 6 hours, whereas 22% of patients receiving oxaliplatin infused over 2 hours did report such an event in another study.[59]

A preliminary report suggests that gabapentin could lower the incidence of oxaliplatin-induced neurotoxicity.[117]

Gastrointestinal and haematological toxicities are common with oxaliplatin therapy, but are generally mild to moderate in severity and increase predictably when oxaliplatin is used in combination with fluorouracil/folinic acid. Gastrointestinal symptoms may be assuaged with prophylactic and/or therapeutic antiemetic treatment.

Oxaliplatin has not been associated with renal[46] or auditory[118] toxicity. Severe anaphylactic reactions have been observed rarely.[46,119,120]

Although no statistically significant differences were found in overall tolerability between oxaliplatin monotherapy and combination therapy, the incidences of severe diarrhoea, nausea/vomiting and neurological events were higher in patients given combination therapy (fig. 2).

Significantly higher incidences of severe nausea/vomiting and diarrhoea were found for patients receiving fluorouracil/folinic acid schedules con-

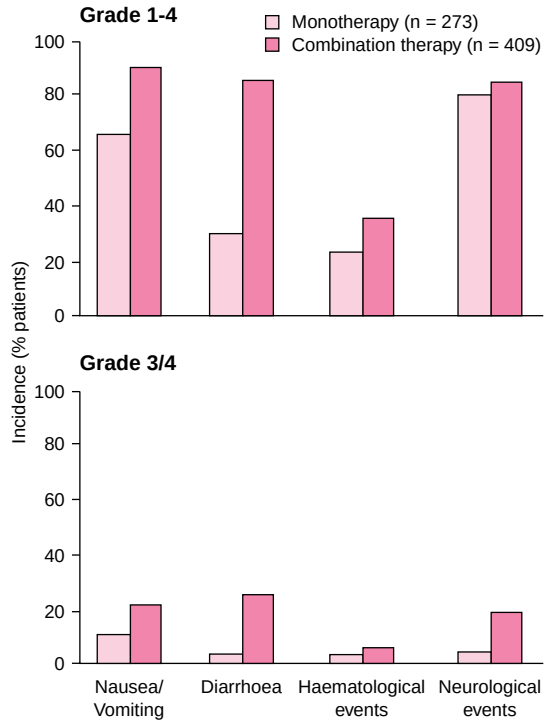

Fig. 2. Relative tolerability of oxaliplatin monotherapy and combination therapy with oxaliplatin/fluorouracil/folinic acid in patients with metastatic colorectal cancer.[114] WHO toxicity grades 1 to 4 and 3 and 4 are shown. Data are from an analysis of 682 patients enrolled in 9 clinical trials in which the dosage regimens varied.

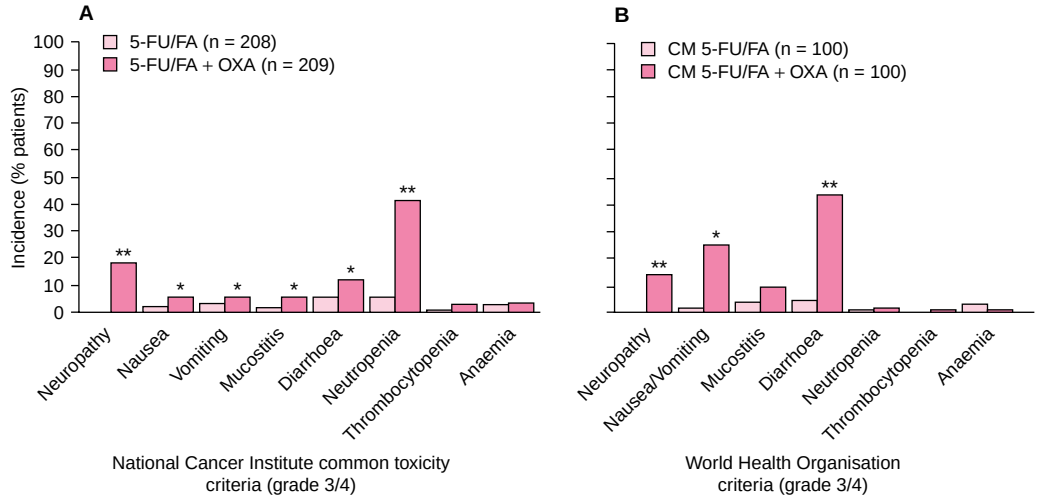

Fig. 3. Incidence of grade 3 or 4 adverse events reported during 2 randomised, phase III clinical trials in patients with colorectal cancer receiving fixed rate (A)[58] or chronomodulated (CM) [B][59] fluorouracil (5-FU)/folinic acid (FA) chemotherapy with or without oxaliplatin (OXA). Sensory neuropathy was graded differently according to the rating system used: National Cancer Institute Common Toxicity Criteria = sensory loss or paraesthesia interfering with activity of daily life; WHO criteria = difficulties in fine manual activities; ** $p < 0.001$, * $p < 0.05$ *vs* comparator.

taining oxaliplatin compared with those not receiving oxaliplatin in both chronomodulated[60] and fixed rate schedules[59] (fig. 3). In patients receiving fixed rate infusion schedules,[59] the incidence of severe neutropenia was also significantly higher in oxaliplatin recipients than those not receiving oxaliplatin.

The tolerability of oxaliplatin/fluorouracil/folinic acid therapy may be improved by sequential chronomodulated delivery of the drugs.[56,57] In 1 randomised, comparative trial,[56] patients receiving a fixed rate infusion schedule of oxaliplatin and fluorouracil chemotherapy had significantly higher rates of severe mucositis (76 *vs* 13%; $p < 0.0001$) and peripheral sensitive neuropathy (31 *vs* 16%; $p = 0.01$) than patients receiving chronomodulated schedules. The incidences of diarrhoea (35 *vs* 29%) and vomiting (25 *vs* 24%) were similar with both administration regimens. In addition, the rate of withdrawal because of intolerable adverse effects was significantly lower in patients given the chronomodulated regimen (28 *vs* 51%; $p = 0.002$), as was the rate of hospital admissions for grade 4 events (10 *vs* 31%; $p = 0.001$).[56]

5.2 Oxaliplatin Combined or Compared with Other Agents

Oxaliplatin has also shown acceptable tolerability when used in combination with other chemotherapies including irinotecan,[51,77] raltitrexed,[53,61,121] paclitaxel,[97] cisplatin[98] and cyclophosphamide,[92] and with 1 or more of these agents in combination with fluorouracil;[76,82,122] however, data are still limited.

Again, the incidence of adverse events increased predictably according to the tolerability profile of the concomitant therapy(ies).

In most cases, the addition of oxaliplatin did not necessitate dosage reduction of other agents below recommended doses established for single-agent therapy. Furthermore, the addition of oxaliplatin did not generally necessitate additional growth

factor support; however, granulocyte colony-stimulating factor was utilised when oxaliplatin was combined with cisplatin and paclitaxel,[96] and when oxaliplatin was combined with irinotecan in 1 study[77] (dose-limiting febrile neutropenia was reported in a previous study of this combination[51]).

Of note, an acute case of cholinergic syndrome, not apparent when irinotecan was administered in isolation, was reported in a patient receiving combined oxaliplatin and irinotecan therapy in 1 trial.[123,124]

In initial comparative studies, the tolerability profile of oxaliplatin generally compared equally or favourably with irinotecan, cisplatin and paclitaxel. In a comparative phase II/III trial, patients receiving oxaliplatin (130 mg/m^2; n = 85) had significantly less grade 3 to 4 anaemia (6 *vs* 34%; $p < 0.0001$), red blood cell transfusions (8 *vs* 22%; $p < 0.010$), grade 3 to 4 nausea/vomiting (26 *vs* 55%; $p < 0.001$) and grade 3 to 4 leucopenia (38 *vs* 55%; $p < 0.042$) compared with patients receiving cisplatin (100 mg/m^2; n = 92) [both administered with concomitant cyclophosphamide 1000 mg/m^2].[92] Furthermore, in contrast with cisplatin, oxaliplatin displays negligible renal[46,92] or auditory toxicity.[118]

The incidence of severe neutropenia was markedly higher in patients receiving paclitaxel (175 mg/m^2 every 3 weeks; n = 41) than those receiving oxaliplatin (130 mg/m^2 every 3 weeks; n = 45) in a comparative trial (23 *vs* 0%). The incidence of other adverse events were low and occurred with a similar frequency in both treatment groups.[95]

In another trial,[81] the incidence of severe adverse events requiring dose reduction (40 *vs* 11%), treatment delays (25 *vs* 10 courses) and early discontinuations (27 *vs* 11%) were higher for patients receiving irinotecan (120 mg/m^2) than in those receiving oxaliplatin (85 mg/m^2) every 2 weeks (both used in combination with mitomycin C 8000 mg/m^2 every 4 weeks). Of note, alopecia was reported in 97% of patients receiving the irinotecan combination and no patients receiving oxaliplatin; peripheral neuropathy was reported in 41% of patients receiving oxaliplatin and no irinotecan recipients.[81]

6. Dosage and Administration

Oxaliplatin is available in several countries in Europe, Asia and Latin America[99] for use in combination with fluoropyrimidines as a first-line therapy for metastatic colorectal cancer.[46,99] It is also available for use in combination with fluoropyrimidines as a second-line therapy for colorectal cancer in some Asian and South American countries.

The recommended dosage of oxaliplatin in combination with fluoropyrimidines is 85 mg/m^2 once every 2 weeks as a first-line therapy and 130 mg/m^2 once every 3 weeks as a second-line therapy. The dosage should be administered as a 2- to 6-hour intravenous infusion and given before fluoropyrimidine therapy. Oxaliplatin is not approved for use as monotherapy.[46]

The dosage should be adjusted according to tolerability; gastrointestinal toxicity may be reduced with prophylactic and/or therapeutic antiemetic therapy.[46]

Although oxaliplatin has also been investigated in combination with other agents (such as irinotecan and raltitrexed) and in other indications, formal dosage guidelines are not available for the use of oxaliplatin in these settings.

Contraindications to the use of oxaliplatin include known allergy to the drug, pregnancy, breastfeeding, severely impaired renal function, myelosuppression (neutrophils $< 2 \times 10^9$/L and/or platelet count $< 100 \times 10^9$/L) prior to starting therapy or peripheral sensory with functional impairment prior to starting therapy.[46]

Caution is advised in patients with a history of allergic reaction to platinum compounds. Patients should be monitored for neurological toxicity; if acute laryngopharyngeal dysesthaesia develops following the 2-hour infusion, the next infusion should be given over 6 hours.[46]

7. Place of Oxaliplatin in the Management of Advanced Colorectal Cancer and its Potential in Other Malignancies

Oxaliplatin has shown activity as a first- and second-line agent in advanced colorectal cancer, both as a monotherapy and in combination with other agents. It has also shown promise in the treatment of other cancers, most notably ovarian, in initial investigations.

7.1 Metastatic Colorectal Cancer

Colorectal cancer is one of the leading causes of cancer death in the industrialised world. It is estimated to claim the lives of over 55 000 people in the US each year with similar mortality rates in other industrialised countries.[125,126] Surgery is the only potentially curative treatment for colorectal cancer and remains the first-line treatment for patients with localised disease. However, approximately 50% of patients present with metastatic disease and surgery is only possible in 10 to 20% of patients with hepatic involvement.[89] Thus, the only option for the majority remains palliative chemotherapy, the aim being to improve quality of life.

For the last 4 decades, fluorouracil has been the most effective chemotherapeutic agent in the treatment of advanced colorectal cancer. However, it produces only modest response rates of ≈10% with a median survival duration of about 10 months when given as a single agent for first-line treatment of metastatic disease.[127] Folinic acid enhances fluorouracil cytotoxicity and increases the response rate by up to 2-fold, but has little effect on overall survival.[128] Furthermore, second-line treatment options in patients who do not respond to or who progress during or after fluorouracil-based therapy are few, and patients eventually become resistant to fluorouracil.

The focus of the past few decades has been to find agents that can modulate fluorouracil-based regimens to improve response rates and survival, and also to find alternative agents with activity against tumours refractory to fluorouracil.

Of the new agents that have emerged, oxaliplatin (the focus of this review), irinotecan (a semisynthetic derivative of the topoisomerase I inhibitor camptothecin)[129,130] and raltitrexed (a quinazoline-based folate analogue that inhibits thymidylate synthase)[131] have demonstrated clinical activity similar to or greater than that of fluorouracil in patients refractory to, or relapsing after, fluorouracil-based therapy.

Furthermore, objective response rates achieved with first-line oxaliplatin (20 to 24%), raltitrexed (14.3 to 19.3%)[131] and irinotecan (20 to 32.2%)[129] monotherapy appear similar to those achieved with fluorouracil/folinic acid (≈23%).[128]

However, comparative data are lacking. While monotherapy with irinotecan or raltitrexed has been directly compared with fluorouracil-based therapy in randomised trials,[132,133] oxaliplatin monotherapy has not, and additional clinical data are needed before the role of oxaliplatin as a single-agent in the treatment of metastatic colorectal cancer can be determined. Furthermore, the efficacy and tolerability of these novel agents have not been compared.

More clinically important are the high response rates achieved when these novel agents are used in combination with fluorouracil-based regimens.

Indeed, the addition of oxaliplatin to first-line fluorouracil/folinic acid therapy significantly increased objective response rates compared with fluorouracil/folinic acid therapy alone in 2 large phase III randomised trials.[59,60] Median progression-free survival was also significantly higher for patients receiving oxaliplatin in both trials; however, there was no significant difference in the median duration of overall survival. This could due to the fact that oxaliplatin and/or surgery was allowed after disease progression in patients who relapsed after fluorouracil/folinic acid therapy alone.

In fact, second-line chemotherapy was administered to over half the patients originally randomised to receive therapy without oxaliplatin in both trials. Furthermore, in 1 trial, secondary

resection of liver metastases was possible in 32 and 21% of patients receiving chronomodulated therapy with or without oxaliplatin, respectively; a further 10 patients originally randomised to receive fluorouracil/folinic acid therapy alone were able to undergo surgery after crossing-over to a schedule containing oxaliplatin.

Irinotecan,[134] and possibly raltitrexed,[135] also appear to have synergistic clinical effects when combined with fluorouracil/folinic acid therapy. As yet, there are no data comparing the relative efficacy of these new agents combined with fluorouracil; instead, recent clinical trials have focused on the potential benefits of combining these novel therapies.

Irinotecan, oxaliplatin and raltitrexed differ from each other in their mechanisms of action, suggesting that synergistic or additive effects may be observed with these combinations. Indeed, initial clinical data do suggest this, with objective response rates of 42 and 44% reported in patients receiving irinotecan and oxaliplatin combination therapy in 2 small trials,[77,78] and 37% in patients receiving oxaliplatin combined with raltitrexed in an initial dose-finding trial.[83] Investigations into the combination of oxaliplatin and these agents with or without fluorouracil-based therapies are on going.

Many patients with colorectal cancer present with hepatic metastases that are considered unresectable because of their size, location or number.[89] The relatively high percentage of patients who become eligible for secondary resection of liver metastases following oxaliplatin combination therapy (51% of 151 patients in a retrospective analysis[90]) represents an important aspect of this agent's profile. Indeed, of the 51% of patients eligible for surgery in the retrospective analysis, 75% had complete resection and the 5-year survival rate was 58% (versus 28% in the total population). It should be noted, however, that this study only included patients with unresectable metastases confined to the liver. In a preceding analysis,[88] the 5-year survival rate for patients with extrahepatic disease (14%) was lower than that seen in patients with multinodular or large lesions (40 and 62%, respectively).

This aggressive surgical approach in patients with primarily unresectable liver metastases is a comparatively novel neoadjuvant therapy concept which may offer a potential cure for a proportion of patients, particularly those with metastases confined to the liver, who could previously only look forward to palliative chemotherapy.

Clinical trials of oxaliplatin in colorectal cancer have used a variety of dosages and administration schedules; however, the optimal treatment regimen remains to be determined and investigations are ongoing into new regimens. Adapting the delivery of combined oxaliplatin/fluorouracil/folinic acid therapy to circadian rhythms has improved tolerability and has enhanced antitumour efficacy in some studies, however, the true benefit of this approach in terms of survival is again unclear.

7.2 Advanced Ovarian Cancer

Ovarian cancer is the fourth most common cancer killer of women in the US, with more than 20 000 new cases occurring annually in the US and over two-thirds of this number (14 000) expected to die from their disease this year.[125] Combination therapy with paclitaxel plus a platinum compound (cisplatin or carboplatin) is the current regimen of choice for the treatment of advanced ovarian cancer, with 70 to 80% of these patients responding to first-line therapy.[136] However, the majority of patients develop recurring disease and eventually become resistant to platinum compounds.

Only 1 trial has investigated the role of oxaliplatin as a first-line therapy for patients with advanced ovarian cancer. In this phase II/III study, oxaliplatin, combined with another well established first-line therapeutic agent, cyclophosphamide, showed similar efficacy to cisplatin/cyclophosphamide in terms of response rate (33 *vs* 42%), median progression-free survival (13 months) and overall survival (36 *vs* 25 months).[92] However, more data are necessary before conclusions can be made about the relative efficacies of these agents.

As a second-line agent, oxaliplatin produced objective response rates of 16 to 26.5% as a monotherapy and 40 to 73% when used in combination paclitaxel[97] or cisplatin[98] or both,[96] in patients relapsing or refractory to previous platinum therapy.

In these studies, oxaliplatin showed some activity in patients with tumours resistant to previous platinum therapy (objective response rates of 5.5 and 14% as monotherapy); which is in contrast to the other platinum compounds carboplatin,[137] iproplatin,[138] zeniplatin[139] and lobaplatin,[140,141] all of which have shown clinical cross-resistance with cisplatin.

However, oxaliplatin is not the only agent to show activity in this setting; altretamine, docetaxel, liposomal doxorubicin, oral etoposide, gemcitabine, ifosfamide, megesterol, paclitaxel, tamoxifen, topotecan and vinorelbine are also active in cisplatin-resistant tumours.[142,143]

Comparative data in the second-line setting are limited; however, in the 1 available comparison, overall objective response rates achieved with oxaliplatin were similar to those obtained in patients receiving paclitaxel (16 *vs* 17%), although paclitaxel showed more activity in patients with platinum-refractory tumours (objective response rates 16 *vs* 6%).[95]

The future position of oxaliplatin in the treatment of advanced ovarian cancer will depend on the results of ongoing clinical trials.

7.3 Other Cancers

Objective responses to single agent oxaliplatin have been reported in non-Hodgkin's lymphoma (9 of 22; 41%),[102] breast cancer (3 of 14; 21%),[104] non-small cell lung cancer (5 of 33; 15%),[108] prostate cancer (1 of 6; 17%),[101] squamous cell carcinoma of head and neck (4 of 40; 10%),[107] malignant melanoma (3 of 15; 20%)[103] and glioblastoma (1 of 9; 11%).[103] Oxaliplatin has also yielded good objective response rates when combined with raltitrexed in patients with mesothelioma (15 of 58; 26%), and combined with fluorouracil in patients with breast (13 of 53; 25%) or pancreatic cancer (3 of 28; 11%).[110] Again, the place of oxaliplatin in the management of these malignancies will depend on whether these promising results are replicated in larger patient populations.

7.4 Tolerability

The cumulative dose-limiting toxicity in patients receiving oxaliplatin therapy is sensory neuropathy. Acute symptoms, characterised by dysesthaesia and/or distal paraesthesia, are transient but increase in duration and severity as the cumulative dose of oxaliplatin increases. Some patients experience functional impairment which may necessitate dosage adjustment,[46] but this resolves in most patients within 3 to 4 months of oxaliplatin discontinuation.[59] Unlike cisplatin, oxaliplatin is not associated with appreciable renal or auditory toxicity, and haematological toxicities are generally limited.

The toxicities of other chemotherapeutic agents were moderately increased upon the addition of oxaliplatin into the regimen, especially when given in combination with agents with overlapping toxicity profiles. In 2 phase III trials, significantly higher incidences of diarrhoea and vomiting/nausea were observed in patients receiving fluorouracil-based chemotherapy with oxaliplatin compared with those receiving the same regimen without oxaliplatin.[59,60] However, in most studies in which oxaliplatin was combined with other agents, dosage reduction of oxaliplatin or concomitant therapies or additional growth factor support was not necessary.

The compatibility of oxaliplatin with other agents represents an important aspect of this drug's profile, allowing for maximally effective doses of both agents to be maintained without a dangerous rise in toxicity.

In the treatment of colorectal cancer, the future position of oxaliplatin relative to irinotecan or raltitrexed will depend not only on the relative efficacy of these agents, but also on their relative tolerability. At present, comparative data are lacking. In 1 preliminary report, oxaliplatin (combined

with mitomycin C) was shown to be better tolerated than irinotecan (also in combination with mitomycin C),[81] however, more data are necessary to confirm these results.

In addition, the tolerability profile of oxaliplatin has compared favourably with those of cisplatin and paclitaxel in initial comparative trials.

7.5 Conclusion

Oxaliplatin in combination with fluorouracil/folinic acid is an effective treatment option for patients with metastatic colorectal cancer. Although initial results have failed to show any overall survival advantage of this regimen over fluorouracil/folinic acid alone, this may be a consequence of trial design and requires further examination. Additional investigation of oxaliplatin in patients with other cancers is warranted given the promising results achieved in early trials, most notably in patients with platinum-pretreated advanced ovarian cancer.

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