OXALIPLATIN (ELOXATIN®)

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Oxaliplatin is a diamino cyclohexane analogue of platinum with a wide spectrum of both in vitro cytotoxicity and in vivo activity in a variety of tumour model systems. Its mechanism of action is not completely elucidated but is believed to be related to the formation of DNA adducts, similar to those formed with cisplatin, however with increased ability to inhibit DNA synthesis. Unlike the standard platinums, the adducts formed with oxaliplatin are not repaired by proteins of the mismatch repair system (hMLH1 and hMSH2), explaining its activity in tumours known to be resistant to cisplatin and carboplatin. The drug has been commercially available in France since 1996 and in other European countries since 1999. It is currently under development for the treatment of advanced colorectal cancer in combination with other chemotherapy in Australia.

Oxaliplatin has predominantly been studied in the treatment of metastatic colorectal cancer. Most of the studies have examined the drug's activity in combination with standard fluorouracil-leucovorin. Its activity has also been evaluated in patients with advanced ovarian cancer and preliminary trials are examining its potential efficacy in a number of other tumour types including non-small cell lung cancer, non-Hodgkin's lymphoma, mesothelioma and breast cancer.

Metastatic colorectal cancer

Following initial promising in vitro data in human colorectal cancer cell lines oxaliplatin was investigated clinically as a monotherapy and in combination with other agents. The highest responses have been observed when it is used in combination with fluorouracil/folinic acid, typically ≥ 50% in the first line setting and 13% to 45% as a second-line treatment. Two preliminary small multicentric Phase II studies (EFC2960 and EFC2963) examined the activity of oxaliplatin as monotherapy in previously untreated patients with advanced colorectal cancer and confirmed a response rate of 18%14, similar to the response rate achieved with 5-Fluorouracil alone. However when oxaliplatin was added to first-line 5-Fluorouracil/folinic acid therapy the objective response rate was significantly increased.

Two large randomized trials have measured the objective response rate of standard fluorouracil/folinic acid with or without oxaliplatin (FOLFOX trials)14. 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. The median progression-free survival was significantly longer for patients receiving oxaliplatin in both trials (nine vs six months). There was no difference in overall survival, which was probably due to crossover and second line therapies with either oxaliplatin or irinotecan. These trials also demonstrated that the early introduction of oxaliplatin in the management of advanced colorectal cancer enabled a substantial reduction in the number of early deaths related to bulky or rapidly progressive disease.

EFC2964, an open label multicentric study, examined the addition of oxaliplatin in patients whose disease had progressed on 5-Fluorouracil/folinic acid. The patients were continued on the same 5FU regimen with the addition of oxaliplatin. Objective response rates were in the vicinity of 18% to 25% with the triple therapy. Median progression-free survival was in the order of five months and median overall survival nine to 13 months.

The triplet oxaliplatin/fluorouracil/folinic acid has also been shown to be effective in rendering previously unresectable liver metastases amenable to surgery with potential curative intent. In two 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)14. The five-year survival rates were 40% and 50%.

Although there is no universally accepted fluorouracil/folinic acid regimen, two-weekly high dose continuous infusion schedules have proved superior to bolus schedules in terms of response rate and progression-free survival.

Oxaliplatin has also shown promise in combination with irinotecan and raltitrexed for second-line treatment of metastatic colorectal cancer. Initial studies examining the combination of oxaliplatin and irinotecan produced response rates of 28% to 44%15. The addition of fluorouracil to oxaliplatin and irinotecan produced response rates of 16%16 and 58%17. These combination trials have not yet reached their primary and secondary goals. Studies examining sequential oxaliplatin/fluorouracil and irinotecan fluorouracil (FOLFOX/FOLFIRI) are also underway with initial response rates looking promising.

Advanced ovarian cancer

Oxaliplatin has been trialled as both monotherapy and in combination with either cyclophosphamide, cisplatin and/or paclitaxel in women with advanced ovarian cancer. Misset et al compared the combination of Oxaliplatin/Cyclophosphamide to Carboplatin/Cyclophosphamide in a multicentre phase III trial as first-line therapy in women with advanced ovarian cancer13. There was no significant difference between the two arms for objective response rate (33% vs 42%), median progression-free survival (13 months) and median overall survival (36 vs 25 months). Oxaliplatin appears to have comparable efficacy to cisplatin as first-line treatment for women with advanced ovarian cancer.

Oxaliplatin has also been investigated as second-line therapy in platinum pre-treated advanced ovarian cancer and demonstrated similar efficacy to paclitaxel (objective response rates 16% and 17% respectively)14. There was also no significant difference in median progression-free survival (12 weeks for the oxaliplatin arm and 14 weeks for the paclitaxel arm) and median overall survival (42 and 37 weeks).

Other cancers

Oxaliplatin has also been studied as monotherapy and in combination with other agents for the treatment of a number of different cancers including prostate, non-Hodgkin's lymphoma, breast cancer, squamous cell carcinoma of the head and neck, non-small cell lung cancer, mesothelioma, malignant melanoma, glioblastoma, and pancreatic cancer. The current data is from small patient studies in these tumours measuring response rate, with limited survival and progression time results reported. Additional large patient number studies
are required to evaluate its effect in these tumour types. The largest studies to date have been reported in breast cancer (n=53) and mesothelioma (n=58) examining oxaliplatin in combination with either fluorouracil or raltrexed with response rates of 25% and 26% respectively.

**Pharmacokinetics**

Oxaliplatin is given as a two to six hour infusion; 85mg/m^2 every two and 130mg/m^2 every three weeks. No intravenous hydration is required. After two hours only 15% of the platinum is present in the circulation with the remainder being distributed to the tissues. The drug binds irreversibly to red blood cells. Elimination is via the kidneys into the urine. Elimination is slowed in patients with renal impairment, although this does not appear to be associated with increased toxicity.

**Tolerability**

The side effects of oxaliplatin are similar to the other platinum derivatives with nausea, vomiting, diarrhoea, anaemia and altered liver function tests being common. However unlike the other platinums there is little to no nephrotoxicity, audiotoxicity or haematological dose-limiting toxicity at the recommended dose.

Phase I and II trials indicate that peripheral sensory neuropathy is the major dose limiting toxicity, associated with cold intolerance. This neuropathy is cumulative and dose-dependent, but reversible on treatment cessation. The symptoms are occasionally associated with pain and cramps. After an accumulative dose of 800mg/m^2 every two and 130mg/m^2 every three weeks. No intravenous hydration is required. After two hours only 15% of the platinum is present in the circulation with the remainder being distributed to the tissues. The drug binds irreversibly to red blood cells. Elimination is via the kidneys into the urine. Elimination is slowed in patients with renal impairment, although this does not appear to be associated with increased toxicity.

**References**