



Oxaliplatin: A Review of Its Use in Advanced Colorectal Carcinoma

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Accepted on: 25-11-2012; Finalized on: 31-12-2012.

ABSTRACT

The purpose of the review is to consolidate the biological, chemical and therapeutic role of the third generation cytotoxic platinum analogue oxaliplatin [(1R,2R-diamminocyclohexane) oxalatoplatinum(II)] taking the pharmacokinetic and pharmacodynamic data in account. Oxaliplatin is the first derivative of Cisplatin with known therapeutic efficacy for the treatment of colorectal carcinoma. The disease free survival of the patients subjected to oxaliplatin based chemotherapy is associated with marked reduction in recurrence of the disease whereas oxaliplatin based regimens can be effectively administered in patients with relapse of disease treated formerly with cisplatin. This review summarizes the Chemical and biochemical attributes, platinum core remodeling, molecular mechanism of action, cytotoxic activity, initial clinical trials, landmark trials and toxicity associated with oxaliplatin in combination of 5FU/LV (FOLFOX) in patients of advanced colorectal carcinoma.

Keywords: Oxaliplatin, FOLFOX, toxicity, Colorectal Carcinoma.

INTRODUCTION

The standard chemotherapeutic regimen for colorectal carcinoma is 5-FU in combination with leucovorin whereas incorporation of oxaliplatin to this regimen enhances the therapeutic efficacy especially for metastatic colorectal carcinoma. The addition of oxaliplatin to 5FU/LV has doubled the response rate and increased the progression free survival in patients of metastatic disease. FOLFOX is established as the standard first line therapy for advanced disease colorectal Carcinoma. FOLFOX (an oxaliplatin/5-FU/LV regimen) is concluded to be the best first line treatment regimen for metastatic colorectal carcinoma, considerably improving the response rate and progression free survival as compared to 5FU/LV in lone therapy in different schedules of administration. Synergistic activity of oxaliplatin with 5-FU/LV is due to the down regulation of thymidylate synthase by oxaliplatin and hence potentiates the activity of 5-FU. The survival benefit after chemotherapy by FOLFOX 4 is increased as compared to IFL (Irinotecan/5-FU/LV) regimen and is shown effective for the treatment of patients who have failed response to IFL therapy. FOLFOX in combination with bevacuzimab is considered as the best regimen by the oncologists with enhanced efficacy and less untoward toxicity.

Chemical nature and development

Platinum based drugs have remarkable efficacy against different types of cancers and are considered as effective agents for chemotherapy of malignant tumors. A large number of platinum analogues are developed in the last three decades to broaden the spectrum of activity and overcome cellular resistance mechanisms, and to reduce the toxicity reported in both the first generation (cisplatin) and second generation (carboplatin) platinum

compounds¹. Among the new generation platinum compounds that has been developed and assessed for therapeutic action, those with the 1, 2-diaminocyclohexane (DACH) carrier ligand, such as oxaliplatin is the center of focus and research. The synthesis of DACH-Pt complexes were reported in 1970, showing that DACH carrier ligand compound had more profound activity than other carrier ligand Pt compounds against cisplatin-resistant mouse L1210 and P-388 leukemia cells^{2, 3}. The complete role of oxaliplatin in medical oncology is yet to be defined and it is perceived to be the most important anticancer agent⁴. Oxaliplatin is the first derivative of Cisplatin with known therapeutic efficacy for the treatment of colorectal carcinoma. Oxaliplatin (*trans*-1-diaminocyclohexane oxalatoplatinum) is a cytotoxic agent of a distinct diaminocyclohexane platinum family and a water soluble derivative, which has similar mode of action to the other platinum derivatives but the spectrum of antineoplastic activity varies in different tumors as compared to carboplatin or cisplatin⁵. The vision harbored for the quest of a novel Pt-complex with clinical efficacy against cisplatin and carboplatin is fulfilled by the development of oxaliplatin [trans-L-dach (1R, 2R-diaminocyclohexane) oxalatoplatinum, L-OHP], which remained ignored for ten years. The prolonged development period of the drug was due to the unique toxic reports of acute sensory, cold sensitive and dose related peripheral neuropathy, which was later on recognized as a reversible and benign adverse effect. Adding to the delay in drug development, was the confusion about the respective antineoplastic character of oxaliplatin, which was not clearly distinguished with effects of chromomodulation⁴. The heretical aspect of development of oxaliplatin is that most of the early relevant clinical knowledge about oxaliplatin is based on



its activity employed in the treatment of colorectal carcinoma however the clinical efficacy was taken into account when it was used in combination with protracted infusions of 5-FU and leucovorin and exhibited good response rate and PFS and OS in pretreated or refractory patients of colorectal carcinoma.^{6,7}

Molecular mechanism of Action and biochemistry

The cytotoxic actions of all the platinum compounds is due to DNA damage⁸. The cytotoxic action of oxaliplatin is by formation of DNA adducts that prevents the replication and transcription⁹⁻¹¹. After the platinum compound gains entry into the cell, a reactive monoaquamonochloro complex is formed by a dissociated chloride ligand, reacting rapidly with N(7) of guanines on the DNA to form monoadducts. This is followed by the subsequent dissociation of a second chloride ligand which allows the conversion of transiently formed monoadducts to diadducts¹². The majority are intrastrand diadduct which binds to a guanine residue, capable of blocking both the transcription and replication of DNA, and are considered the major cytotoxic lesions⁴. The DNA damage induced by oxaliplatin is other than cisplatin or carboplatin, shown in several in vitro and subsequent studies¹³. Molecular Biology studies have shown that Oxaliplatin has specific intracellular target(s), mechanism(s) of resistance and mechanism(s) of action⁴. In contrast to cisplatin-conditioned cells, deficiencies in mismatch repair (MMR) and increases in replicative bypass, which leads to cisplatin resistance, does not induce a similar resistance to oxaliplatin, and hence less chances of resistance development, turns oxaliplatin into a novel agent for first-line treatment¹⁴.

Antitumor Activity

Oxaliplatin has antitumor activity in not only platinum sensitive tumors such as ovarian or lung cancer, but also has activity against colorectal and breast carcinoma, in which cisplatin is not an established treatment preference⁴. Oxaliplatin has demonstrated antineoplastic activity against several human colon cancer lines in both in-vitro and in vivo models⁸. Oxaliplatin has incomplete cross resistance to cisplatin^{4, 15,16}. Both the first and second generation platinum compounds are inactive against colorectal carcinoma and have no effect of increase in DFS, alone or in combination of 5FU^{17, 18}. Oxaliplatin however has remarkable therapeutic effect in combination with Thymidylate synthase inhibitors for the treatment of CRC⁸. The therapeutic efficacy of oxaliplatin in relapse or cisplatin refractory patients has been investigated¹⁹. Several Phase I/II/III studies has shown the convenience to combine oxaliplatin with cytotoxic drugs like cyclophosphamide²⁰, gemcitabine, paclitaxel (Hinton et al, 2001,^{21, 22} and cisplatin as well²³. The synergistic combination of oxaliplatin with 5-FU is established in both preclinical models and various randomized and controlled trial studies which has nearly doubled the survival time⁸. Oxaliplatin is combined with

different schedules of 5-FU/LV administration which is the first line therapy for advanced colorectal carcinoma.

Phase I and II studies

The first short infusion Phase I study comprising of 23 patients was initiated by Mathe et al., with a starting dose of 0.45 mg/m² and was accelerated to nine dose levels to 67 mg/m², the maximum tolerated dose was not administered during this trial. During this trial, even with the low doses one PR and one CR was elucidated, mild nausea and vomiting was reported with no nephrotoxicity which is a characteristic toxicity of cisplatin²⁴. The second Phase I trial comprising of 44 patients was conducted by Extra et.al., with a dose ranging from 30-200 mg/m²²⁵. The most frequent acute side effect reported in the Phase I short infusion trials is transient peripheral neuropathy associated with paresthesia and dysesthesia in feet, hands and peri-oral area, increased by exposure to cold. Laryngo-Pharyngeal dysesthesia is also reported in some patients while ingesting cold food. Electromyogram shows sensory neuropathy with normal conduction mechanisms⁴. In most of the Phase II studies the dose of oxaliplatin was 130 mg/m² (CIV infusion for 2-4 hrs), q 3 weeks and the acute toxic profile was similar to phase I studies. The incidence of nephrotoxicity and ototoxicity was considerably less as compared to cisplatin^{6, 7, 26, 27}. 10% of grade 2/3 neurotoxicity were usually reported after a dose of 780 mg/m² (6 cycles of treatment) and 50% after a dose of 1170 mg/m² (9cycles of treatment). Unlike the cumulative neurotoxicity of cisplatin, the neurotoxicity was reversible in 82% of patients after 6-8 months of discontinuation of therapy^{28,4}.

Reports of Landmark trials

Results of a randomized trial show that incorporation of oxaliplatin with 5FVLV2 schedule (FOFOX 6) prolongs the Progression free survival (PFS)²⁹. The therapeutic efficacy of oxaliplatin in combination of infusional 5-FU/LV (FUFOX or FOLFOX) is compared in different phase three trials with the therapeutic efficacy of 5-FU/LV in advanced carcinoma. The median OS survival of the synergistic combination of oxaliplatin with 5-FU/LV is within the range of 17.5-20 months. It was shown in the (NCCTG)/Intergroup trial N9741(795 Patients),that the FOLFOX 4 regimen is superior to the IFL regimen which was considered a standard regimen for the treatment of colorectal carcinoma, with respect to response rate, overall survival and toxicity ratio. A trial by Tournigand et al., shows that the efficacy of FOLFIRI regimen is comparable to FOLFOX 6 regimen. The patients who were crossed over the two regimens during the course of treatment benefitted with the three active cytotoxic drugs and a median overall survival of 20 months is reported. Hence, substantial data advocates that the infusional 5-fu/LV in combination with oxaliplatin or even irinotecan is beneficial as compared to bolus 5fu/lv. The trial had shown that frequency of hematological toxicity was more in FOLFOX 6 first line therapy, whereas the frequency of GI toxicity except diarrhea, alopecia and



fatigue was more in FOLFIRI treatment group. An unexpected high rate of grade 3 neurotoxicity was reported in first line FOLFOX 6 patients (34%) probably because of higher dose of oxaliplatin in FOLFOX 6 as compared to FOLFOX 4 regimen.⁵

The MOSAIC (Multi-center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial comprising of 2,246 patients is the landmark which established the therapeutic efficacy of adjuvant oxaliplatin/5-FU/LV regimen for stage II and stage III colon cancer following curative resection. The patients were randomly assigned to be treated with FOLFOX and 5FU/LV regimen for 6 months. The primary end point for the study was the disease free survival. The oxaliplatin based regimen (FOLFOX4) was compared to bolus followed by infusional 5FU/LV. FOLFOX 4 regimen was found superior in terms of 3 years Disease Free Survival which is an important predictive marker of 5 years overall survival. 23% risk reduction for three-year recurrence, hazard ratio 0.77, 95% confidence interval (CI) 0.65–0.91, $p=0.002$ was shown in a combined analysis of stage II & III patients. Disease free survival after 3 years was 78.2% in FOLFOX4 treatment arm and 72.9% in 5FU/LV treatment arm. A stage-based subgroup analysis demonstrated significant difference in DFS is only for stage III patients. (3 yrs disease free survival 72.2% comparable to 65.3% & Hazard Ratio 0.76. The main toxic outcome in 12.3% patients was grade 3 reversible sensory neuropathy³⁰.

NSABP C-07, a parallel trial in North America included 2492 patients conducted in 2002, established that the addition of oxaliplatin (85 mg/m², 2 hrs infusion, d1) to 5FU/LV (LV 500 mg/m² bolus d1, 5 FU 500 mg/m² bolus d1) improves the disease free survival (DFS) in patients of stage II/III colon cancer following resection showing the superiority of FLOX regimen over FULV, Hazard ratio (FLOX VS FULV) is 0.80 with 20% risk reduction in favor of FLOX regimen. Grade 3 sensory neuropathy was reported 8.2% in FLOX treatment arm and 0.7% in FU/LV treatment arm. The treatment was repeated for a maximum duration of 24 weeks.³¹⁻³²

Toxicity

The most common toxicity of oxaliplatin are hematological and gastrointestinal with modest severity and incidence, which are tolerable and easily manageable³³. A report constructed to summarize the information on oxaliplatin by FDA shows that besides peripheral neuropathy the common adverse effects associated with oxaliplatin based chemotherapy are nausea and vomiting, mucositis, fatigue, abdominal pain and nausea, whereas the major hematological toxicity is neutropenia. Diarrhea and myelosuppression which is previously reported with 5FU/LV is increased in intensity and occurrence after incorporation of oxaliplatin to the regimen³⁴. It is reported earlier that addition of oxaliplatin to 5FU/LV regimen can although give way to hematological and gastrointestinal toxicity but does not

accentuate the renal and hepatic toxicity profile³⁵. The symptoms of diarrhea, dehydration hypokalemia and fatigue are more pronounced in the elderly patients³⁴. Dysphagia and dyspnea as symptoms of acute pharyngolaryngeal dysesthesia is also reported in patients treated with oxaliplatin based regimens³⁴. In phase I trials the dose limiting toxicity of Oxaliplatin is acute transient dysesthesias and cumulative distal toxicity which is reversible upon cessation of therapy. Oxaliplatin has not exhibited any dose limiting hematological, auditory or renal toxicity at the recommended doses (130 mg/m² q3 ks or 85 mg/m² q 2wks as 2 hrs i.v infusion)¹⁴. The frequently reported Grade 3 & 4 toxicity of oxaliplatin in combination of 5 FU/LV (FOLFOX) is neutropenia (48%), GIT toxicity (N&V(1%), Stomatitis (6%), Diarrhea(12%)), neurological toxicity (18%) and cutaneous toxicity (1%)³⁶. Allergic reactions to platinum compounds has been reported by Seguin et.al, with platinum sensitive IgE antibody formation, after platinum inhalation characterized by urticaria and dyspnea.²⁷ The occurrence rate of hypersensitivity reaction with oxaliplatin is reported to be 10-20%^{37, 38}. Hypersensitivity reactions to oxaliplatin can give way to oxaliplatin induced thrombocytopenia, a retrospective study has shown that thrombocytopenia develops in 7.1% of patients with allergic manifestations to oxaliplatin³⁹.

CONCLUSION

Oxaliplatin is one of the most important cytotoxic agents which cannot be replaced owing to its remarkable therapeutic efficacy in colorectal carcinoma for metastatic patients and in advanced stage patients following surgical resection. The most frequent dose limiting toxicity of oxaliplatin based chemotherapeutic regimens is peripheral neuropathy. Incorporation of Oxaliplatin in 5FU/LV regimen has increased the median overall survival rate and progression free survival in patients.

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Source of Support: Nil, Conflict of Interest: None.

