MINI-REVIEW

Clinical Features of Oxaliplatin Induced Hypersensitivity Reactions and Therapeutic Approaches

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Abstract

Oxaliplatin, a third generation novel platinum compound is the most effective first line chemotherapeutic agent for colorectal cancer (CRC) in combination with 5FU and leucovorin. It is indicated for pancreatic, gastric and testicular cancers combined with bevacuzimab, capecitabine, irinotecan and other cytotoxic agents. However, moderate to severe hypersensitivity reactions (HSR) during or after oxaliplatin infusion usually require cessation of chemotherapy or substitution of the key therapeutic drug which largely interferes with improved patient prognosis. This mini- review showcases recent and accepted opinions/approaches in oxaliplatin induced HSR management. Physicians and oncologists have varying attitudes regarding the decision to rechallenge the patient after an HSR experience, efficacy of desensitization protocols, effectiveness and selection of drugs for premedication and possibilities of cross sensitivity to other platinum agents (e.g. carboplatin). A brief insight into underlying molecular mechanisms and clinical manifestations of oxaliplatin induced HSR is offered. We have also discussed the management of oxaliplatin induced HSR and risk stratification for a successful and complete chemotherapeutic plan.

Keywords: Oxaliplatin - hypersensitivity reactions - desensitization - management - rechallenge

Asian Pac J Cancer Prev, **17 (4)**, 1637-1641

Introduction

Oxaliplatin [trans-L-dach (1R, 2R-diaminocyclo hexane) oxalatoplatinum, L-OHP] is one of the mainstay chemotherapeutic drugs in gastrointestinal cancers and may cause hypersensitive reactions with fatal outcomes (Aroldi et al., 2015). Hypersensitivity reactions are reported in 12% of patients treated with oxaliplatin, whereas 1% of these patients may face a life threatening situation. Extended steroid premedication with slower oxaliplatin infusion can be employed for safety in patients after severe hypersensitivity reaction with oxaliplatin (Nisi et al., 2015). Coinfusion of dexamethasone with oxaliplatin is considered to effectively reduce oxaliplatin induced hypersensitivity reactions (Yoshida et al., 2015). Although desensitization of platinum compounds (carboplatin) is associated with poor efficacy (Dodgshun et al., 2016), the effectiveness of oxaliplatin desensitization is implied to be effective (Syrigou, 2015). Better therapeutic care with oxaliplatin may be achieved by desensitization protocol focusing on oxaliplatin specific immunoglobin E (Madrigal et al., 2013). The optimum oxaliplatin desensitization protocol is yet to be defined despite efficacy and tolerability of existing protocols (Okayama et al., 2015). On the other hand, false negative sensitivity reactions to oxaliplatin can be out ruled by risk-stratification protocol thus limiting unnecessary desensitization and better therapeutic effects (Wang et al., 2015).

Drug provocation tests in diagnostic protocols are shown to effectively indicate oxaliplatin hypersensitivity in susceptible patients and avoid unnecessary desensitization (Alvarez et al., 2015). Difficult breakthrough reactions are an added concern in patients with remote drug exposure during oxaliplatin desensitization (Kim et al., 2015). Although the risk of hypersensitivity reaction exists with each infusion of chemotherapeutic agent (Lundqvist et al., 2012), it is higher in heavily pretreated patients (Wang et al., 2012). Risk of hypersensitivity reaction to oxaliplatin (12-15%) usually exists after the sixth cycle of treatment (Lee et al., 2013). Chances of hypersensitivity reactions after desensitization of oxaliplatin lie in the initial 2-3 cycles of treatment (Pedersen, 2015).

Incidence Rate and Dose Intensity

Incidence rate of Type 1 anaphylactic reactions with platinum analogues like carboplatin and cisplatin is 5%, compared to which fewer allergic reactions attributed to oxaliplatin are reported in allergenic studies (Larzilliere et al., 1999; Alliot et al., 2001; Arotcarena et al., 2001). There are earlier reports of anaphylaxis during 6th cycle

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of chemotherapy in one out of 46 patient receiving a dose of 100 mg/m^2 oxaliplatin every 2nd week (de Gramount et al., 1997). The propensity of allergic reactions with platinum compounds lies with the increased number of cycles during chemotherapy (Shlebak et al., 1995; Polyzos et al., 2001). High incidence rate of allergic reactions (27%) is reported by Markman et al. (1999) in patients who received more than seven cycles of treatment.

Incidence rate of oxaliplatin based hypersensitivity reactions is higher in second line treatments with palliative concern (19.6-24%) compared to adjuvant chemotherapy (9-10%) particularly when the first regimen is based on irinotecan (Caiado and castells, 2015). Gerard et al. (1998) reported symptoms of allergy in one out of 37 patients in 8th cycle of treatment with 130 mg/m^2 oxaliplatin (2hrs infusion) every three week despite prophylactic pretreatment with corticosteroids. Severe anaphylaxis in two patients out of sixty (receiving dose of 100 mg/m2 every 2 weeks) is also reported during 8 and 9 cycle of treatment (Maindrault et al., 1999). Thomas et al. (2003) reported three cases of allergic reactions during a phase 1 trial of oxaliplatin (given D1 once 3 weekly) with capecitabine, although all of the patients received dexamethasone with ondasetron as pretreatment. A recent retrospective study reports HSR incidence rate (11.3%) at average total dose of oxaliplatin of 622.2 mg/m^2 (Yamauchi et al., 2015). Higher incidence rate of hypersensitivity reactions is associated with female gender and younger age (Parel et al., 2014).

Underlying Mechanisms of Oxaliplatin Induced HSR

Essentially unpredictable, patient specific and individual predisposing factors lead to hypersensitivity drug reactions (Brockow et al., 2015). Allergic reactions to platinum compounds are associated with platinum sensitive IgE antibody formation, after platinum inhalation characterized by urticaria and dyspnea (Leguy- Seguin et al., 2007). There can be a subsequent rise in serum levels of TNF (tumor necrosis factor) and Interleukin during the allergic episode which attained normal values when the allergy had subsided (Santini et al., 2001). Oxaliplatin induced allergic reactions are classified and distinguished as Hypersensitivity adverse effects or infusional idiosyncratic reactions (Thomas et al., 2003). Hypersensitivity or anaphylactic reaction by oxaliplatin is due to antigen to antibody (mast cell fixed, cytophilic (IgE) antibodies) reaction and causes smooth muscle contractions with capillary dilation, due to the release of mediators of inflammation from the mast cells rupture.

The second category of adverse reaction with oxaliplatin presenting allergy like symptoms are infusional or idiosyncratic reactions. These reactions are abnormal but they are not antibody dependent. They are usually delayed. In few such case reports (Santini et al., 2001; Tonini et al., 2002), hypotension was not associated with the symptoms of allergy (i.e. fever, chills, diarrhea, abdominal pain). The abnormal feature marked in these cases was no fall in blood pressure but a rise in TNF and IL-6 noted during the reactionary phase. In cases of Evans syndrome or hemolytic anemia associated with oxaliplatin, positive DAT results are reported for IgG or C3 complement proteins (Cobo et al., 2007). Decreased levels of ADAMTS13 were found in oxaliplatin-induced thrombotic thrombocytopenic purpura without specific antibodies to this protein (Baretta et al., 2013; Malkhasyan et al., 2015). Fibrinolysis induced by oxaliplatin may be the underlying mechanism of disseminated intravascular coagulation (DIC) (kurian et al., 2012). In a more recent case report of DIC, Malkhasyan et al. (2015) suggested that reactive oxaliplatin-dependent autoantibodies caused acute intravascular hemolysis which later on complicated DIC. Oxaliplatin-dependent antiplatelet antibodies or antibodies against GP IIIa may also have a role in DIC (Malkhasyan et al., 2015; Spearing et al., 1990). Adsorption of oxaliplatin on blood cells may result in the formation of autoantibodies to platelets and erythrocytes that lead to oxaliplatin induced hemolytic anemia and thrombocytopenia (Taleghani et al., 2005; Curtis et al., 2006; Caiado et al., 2015).

Clinical Manifestatons of Oxaliplatin Induced HSR

Presentation of unusual signs and symptoms during or after oxaliplatin infusion such as rigors, chills, fever, abdominal or back pain, hematuria, dark urine, ecchymosis, hematochezia, hematemesis, epistaxis, petechiae, or altered mental status require prompt complete blood test and evaluation (Forcello et al., 2015). Hypersensitivity reactions to oxaliplatin can give way to oxaliplatin induced thrombocytopenia. A recent study reports Grade 1 erythema in 4.1% patients (Yoshinda et al., 2015). Hypersensitivity reactions with oxaliplatin are manifested as urticaria, rash, itching flushing, flare, edema, dyspnea, laryngoedema, bronchospasm, diaphoresis, disorientation and syncope (Cheng et al., 2008). Machover et al (1996) reported a case of transient dyspnea in 1 out of 109 patients receiving 130 mg/m2 every three weeks. Few cases of HSR with oxaliplatin presented with urticaria and dyspnea are reported in a recent study (Pagani, 2015). FOLFOX (an oxaliplatin based regimen) is effective and considerably safe chemotherapeutic regimens in colorectal carcinoma (CRC) (Bano et al., 2014; Toki et al., 2014). Florit-Sureda et al. (2015) reported a case of HSR in a 56 year old male presented with pruritis, flushing, erythema, abdominal pain and oedema over face and thorax after 15 minutes of initiating infusion of oxaliplatin and folinic acid on the tenth cycle of FOLFOX 6. Tamura (2015) reported a case of anaphylactic shock leading to cardiopulmonary arrest. Allergic reaction with fever after oxaliplatin infusion is reported (Yanagihara, 2015).

A retrospective study has shown that thrombocytopenia develops in 7.1% of patients with allergic manifestations to oxaliplatin (Maindrault et al., 1999). Osumi et al. (2013) reported three cases of fatal thrombocytopenia after oxaliplatin chemotherapy. Tournigand (1998) reported a case of immediate allergic reaction in a patient who had received oxaliplatin infusion over 2-3 hrs, with the symptoms of flushing sweating, redness of face and neck associated with hypotension after initiation of 7th cycle of

oxaliplatin at a dose of 100 mg/m^2. The symptoms resolved after 9 hrs after oxygen ,volume expansion, epinephrine and dexamethasone. The patient was subjected to chemotherapy after 2 weeks, allowing a slower infusion rate but the symptoms of allergic reactions returned and required discontinuation of therapy. The study reported four other patients who experienced a similar pattern of allergy due to oxaliplatin treatment and discontinuation of treatment. HSRs were reported by Meyer et al. (2002) in eight patients who experienced mild symptoms of allergic reaction. Santini et al. (2001) reported two episodes of oxaliplatin hypersensitivity reactions with vomiting, chills and fever associated with abdominal pain and diarrhea. Whikle these resolved in the next cycle with prednisone pretreatment, allergic symptoms returned in the following cycle when the patient did not receive prednisone.

A case of systemic capillary leak syndrome is reported for the first time with oxaliplatin chemotherapy in a 63 year old male patient during 12th cycle of infusion (Anderson, 2015). Acute onset of fulminant disseminated intravascular coagulation with acute hemolytic anemia during oxaliplatin chemotherapy infusion is reported in a 61 year old male patient (Malkhasyan et al., 2015). Interstitial lung disease induced by single agent oxaliplatin as a less common adverse reaction is reported by Kumaran et al. (2015). Other than type II hypersensitive reactions (hemolytic anemia and thrombocytopenia), oxaliplatin is also associated with delayed hypersensitive reactions (De Vries et al., 2006; Tham et al., 2015)

To Rechallenge the Patient or Not

Temporary interruptions of the infusion can resolve mild to moderate allergic reactions and may further require reduction in rate of infusion with symptomatic management, however rechallenging the patient can be considered as an option only after the symptoms have completely resolved (Lenz, 2007). Thomas et al. (2003) advocate with literature reports backup that the patients who develop mild to moderate allergic and infusional reactions can be rechallenged safely after pretreatment with steroids and histamine receptor blockers. Ondasetron as an antiemetic pretreatment drug may however be replaced by metochlopramide as it has a tendency to elucidate allergy. However the patients with severe allergic manifestations should not be rechallenged to oxaliplatin exposure even is if appropriate symptomatic management is given/planned (Polyzos, 2001). Ichikawa et al. (2009) reported recurrence of allergic reactions within 3 cycles of chemotherapy when the patients were rechallenged. Some studies report that patients who experienced allergy with carboplatin were successfully shifted to oxaliplatin (Shukunami et al., 1999; Zanotti et al., 2001; Gutierrez et al., 2002). On the contrary, there are case reports when patients prone to allergy with carboplatin experience cross reactivity with oxaliplatin (Shlebak et al., 1995; Polyzos et al., 2001).

Management of Oxaliplatin Induced HSR

In hypersensitivity reactions during platinum infusion antigen-stimulated mast cells release prostaglandins, leukotrienes, histamine and other factors (Bahl and Dean, 2015). Premedication, skin testing and desensitization protocols are employed for continuation of chemotherapy in patients who have had an allergic reaction to the drug but the treatment options for the disease are limited (Boulanger et al., 2014).

On the other hand severity of oxaliplatin induced HSR may require cessation of chemotherapy (Benedik et al., 2015). Rapid drug desensitization is considered to be the only effective procedure for overcoming HSR to first-line chemotherapy (Giavina et al., 2015). In severe chemotherapy induced anaphylactic reactions, acute management ensues with epinephrine (Intramuscular), supplemental oxygen, fluid resuscitation, steroids and bronchodilators. Premedication with antihistamines (H1 blocker-diphenhydramine 50 mg IV, H2 blocker-ranitidine 50mg IV) before chemotherapeutic infusion is required to ameliorate and attenuate risk of allergic reactions (Tham et al., 2015).

Coinfusion of oxaliplatin and dexamethasone followed by premedication with steroids and palonosetron is also reported to effectively reduce the incidences of oxaliplatin induced HSR (Yoshinda et al., 2015). Monteleukast and ASA has rendered effective therapeutic solution to reduce the risk and severity of platinum induced HSR (Breslow et al., 2009). Cheng et al. (2008) reported 25 (11 females and 14 males) cases of allergic reactions in a prospective study in CRC patients treated with FOLFOX 4. Grade 1 allergy was reported in thirteen patients; grade 2 allergy in eight patients and grade 3 allergic reactions in 4 patients. On the onset of allergic reactions, oxaliplatin infusion was interrupted and substituted with fluid support. Symptomatic management with corticosteroids, histamine receptor blockers and oxygen led to alleviation of the symptoms. The anaphylactic reaction in these cases was sufficiently contained and none of the patients required intensive monitoring and no case of mortality was reported. The study reported 76% (19 of 25 patients) success rate of completion of oxaliplatin based chemotherapy in the patients despite the onset of allergic reactions which was effectively tackled with symptomatic management. Prolongation of oxaliplatin infusion time of is an effective measure for management of the allergic reactions (Schull et al., 2001; Cheng et al., 2008).

Conclusions

Oxaliplatin induced HSR is presented with clinical signs of both acute and delayed allergies ranging in severity and require close monitoring for accurate diagnosis and quantification of dose. Although the standard of therapeutic care can be attained by rapid desensitization, risk of hypersensitivity reactions to oxaliplatin can be reduced by the effective use of premedication to stabilize the mast cells and promptly block receptors for the mediators of inflammation. Prolongation of infusion time is an effective strategy to cope with allergenic tendency of oxaliplatin in susceptible patients. Cross sensitivity to carboplatin cannot be entirely neglected. Longer platinum free survival adds to the risk of HSR.

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