Hypersensitivity reactions related to oxaliplatin (OHP)

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Patients treated with platinum compounds are subject to hypersensitivity reactions. Our study has highlighted the reactions related to oxaliplatin (OHP) infusion. One hundred and twenty-four patients affected by advanced colorectal cancer were treated with different schedules containing OHP, at the Institute of Haematology and Medical Oncology ‘L. and A. Seragnoli’ of Bologna and at the Medical Oncology Division of Livorno Hospital. Seventeen patients (13%) showed hypersensitivity reactions after a few minutes from the start of the OHP infusion. Usually, these reactions were seen after 2–17 exposures to OHP (Mean ± s.e.: 9.4 ± 1.07). No patient experienced allergic reactions at his/her first OHP infusion. Eight patients developed a mild reaction consisting of flushing and swelling of the face and hands, itching, sweating and lacrimation. The remaining nine patients showed a moderate–severe reaction with dyspnoea, wheezing, laryngospasm, psycho-motor agitation, tachycardia, precordial pain, diffuse erythema, itching and sweating. Six patients out of 17 were re-exposed to the drug with premedication of steroids and all except one developed the hypersensitivity reaction again. The cumulative dose, the time of exposure to OHP and the clinical features are variable and unpredictable. The risk of developing hypersensitivity reactions in patients treated with a short infusion of OHP cannot be underestimated.

British Journal of Cancer (2003) 89, 477–481. doi:10.1038/sj.bjc.6601155 www.bjcancer.com

Keywords: Hypersensitivity reaction; platinum compound; colorectal cancer; chemotherapy

Oxaliplatin (OHP) is the most recent platinum compound entering the clinical practice. It is an alkylating agent on DNA and forms DACH-platinum DNA adducts more hydrophobic than those formed by cisplatin (CDDP) and carboplatin (CBDCA). It is effective in advanced colorectal cancer both as a first-line therapy and in 5-fluorouracil (5-FU) refractory patients (Bertheault-Cvetkovic et al, 1996; De Gramont et al, 1997; Andre’ et al, 1999; Mainfrault-Goebel et al, 1999).

OHP is less nephro-toxic than CDDP and less mielotoxic than CBDCA (Misset 1998). The most characteristic and dose-limiting toxicity of OHP is sensory neuropathy, which is dose cumulative and schedule related. It is clinically characterised by a transient acute cold-related dysaesthesias, sometimes pain-associated, or with cramps and functional failure, although it is generally reversible (Causanel et al, 1990, Misset, 1998). Hypersensitivity reactions to oxaliplatin have been described only sporadically.

For other platinum compounds, this kind of reaction is well known (Cleare et al, 1976; Wiesenfeld et al, 1979; Planner et al, 1991; Morgan et al, 1994; Weideman et al, 1994; Shleback et al, 1995; Markman et al, 1999; Özgüroğlu et al, 1999). On data sheets of OHP, these clinical features are not stressed. In fact, only the main severe form of hypersensitivity, that is to say anaphylaxis, is reported in 0.5% of patients treated. This reaction is clinically characterised by laryngospasm and wheezing and immunologically linked to the release of histamine and other vaso-active substances.

As a result of the increasing use of OHP in colorectal cancer, we have found frequent hypersensitivity reactions. In this study, we report the epidemiological and clinical features of these reactions, as well as their management.

MATERIALS AND METHODS

From February 1999 to February 2002 at the Institute of Haematology and Medical Oncology ‘L. and A. Seragnoli’ of Bologna and at the Medical Oncology Division of Livorno, 124 outpatients with advanced colorectal cancer were treated with OHP-based therapies. Eighty-four out of 124 patients (67.7%) received OHP as a first-line treatment. Fifty-five patients (44.3%) were treated with a FOLFOX-4 regimen (Andre’ et al, 1999; De Gramont et al, 2000), 34 patients (27.4%) with FOLFOX-3 regimen (De Gramont et al, 1999), 30 patients (24.1%) with the association of OHP/CPT-11/c.i.5-FU/FA regimen (Falcone et al, 2002), three patients (2.4%) with OHP alone (Diaz-Rubio et al, 1998) and two patients (1.6%) with OHP/ Raltitrexed regimen (Seitz et al, 1999). All patients received a standard antiemetic treatment with ondansetron 8 mg by a i.v. administration before chemotherapy. We did not use dexamethasone in this population.

Major sites of metastases were the liver, lungs and peritoneum. Among these patients, 17 out of 124 (13.7%) reported a hypersensitivity reaction attributable to OHP. There were eight males and nine female patients, with a mean age of 60.3 years (range 37–76). In 11 out of 17 patients with hypersensitivity reaction, OHP was administered in first-line chemotherapy.
RESULTS

Results are shown in Table 1. The reaction occurs after a mean ± s.e. = 9.4 ± 1.07 infusions of chemotherapy (range 2–17). Only two patients experienced early hypersensitivity at the second and third infusion, respectively.

Table 1 Patients with hypersensitivity reactions

| Case | Sites of metastases | Chemotherapy regimen | Infusion number at reaction | Total dose of OHP (mg) | Clinical features of reaction | Length of reaction (min) | Treatment of reaction | Re-exposure to OHP with premedication and outcome |
|------|---------------------|-----------------------|-----------------------------|------------------------|-----------------------------|-------------------------|----------------------|-----------------------------------|
| 1    | Lung                | FOLFOX-4              | 3                           | 382                    | Bronchospasm                | 7 days                  | Hospitalisation/high dose of steroid | No                                |
| 2    | Peritoneum          | FOLFOX-4              | 14                          | 2100                   | Laryngospasm, Dyspnoea      | 60                      | Oxygen, Steroids               | No                                |
| 3    | Liver               | Oxaliplatin           | 10                          | 2070                   | Bronchospasm, Dyspnoea, Erythema | 50                    | Steroids                        | No                                |
| 4    | Liver, Lung         | FOLFOX-3              | 17                          | 2271                   | Hand, face oedema, Erythema, Itching | 5–10                  | Steroids, Antihistaminic         | Yes, with reaction                        |
| 5    | Peritoneum          | Oxaliplatin           | 2                           | 360                    | Laryngospasm, Dyspnoea      | 120                    | Steroids                        | No                                |
| 6    | Liver               | Irinotecan, Fluorouracil, Folinic acid | 11                          | 1620                   | Eye oedema, Face erythema, Itching, Sweating | 15–20                  | Steroids, Antihistaminic         | No                                |
| 7    | Liver, Lung         | FOLFOX-3              | 17                          | 2720                   | Dyspnoea, Oedema, Erythema, Sweating, Lachrymation | 15–20                  | Steroids, Antihistaminic         | Yes, with reaction                        |
| 8    | Liver               | FOLFOX-4              | 6                           | 900                    | Dyspnoea, Erythema, Itching, Mouth oedema | 30                      | Steroids, Antihistaminic         | No                                |
| 9    | Liver, Lung         | FOLFOX-4              | 8                           | 1120                   | Dyspnoea, Hand, face erythema, Erythema, Tachycardia, Preordial pain, Pruritus | 60                      | Steroids, Antihistaminic         | No                                |
| 10   | Liver               | FOLFOX-4              | 8                           | 1360                   | Erythema, Hand oedema, Hand genital itching, Hand, face erythema, Hand face erythema, Hand oedema, Hand itching | 15–20                  | Steroids, Antihistaminic         | No                                |
| 11   | Peritoneum          | FOLFOX-4              | 9                           | 630                    | Erythema, Tachycardia, Preordial pain, Pruritus, lachrymation | 20                      | Antihistaminic                  | Yes, without reaction                       |
| 12   | Peritoneum          | FOLFOX-4              | 5                           | 940                    | Erythema, Hand oedema, Hand genital itching, Hand, face erythema, Hand face erythema, Hand oedema, Hand itching | 20–30                  | Antihistaminic                  | No                                |
| 13   | Liver, Peritoneum   | Irinotecan, Oxaliplatin, Fluorouracil, Folinic acid | 14                          | 2600                   | Itching, Sweating, Lachrymation, Face oedema, Face erythema | 15–20                  | Steroids, Antihistaminic         | Yes, with reaction                        |
| 14   | Liver               | FOLFOX-4              | 7                           | 1040                   | Face, chest erythema, Itching | 120                    | Steroids, Antihistaminic         | Yes, with reaction                        |
| 15   | Liver, Peritoneum   | FOLFOX-4              | 13                          | 1705                   | Face, chest erythema, Shiver without fever, Tremor | 50                      | Steroids, Antihistaminic         | No                                |
| 16   | Diaphragm           | FOLFOX-4              | 8                           | 1080                   | Arms, chest erythema, With pomphoid reaction | 50                      | Steroids                        | Yes, with reaction                        |
| 17   | Peritoneum          | FOLFOX-3              | 9                           | 1377                   | Sweating, Erythema, Hypotension, Nausea | 15–20                  | Steroids                        | No                                |

On average, there were 217.7 ± 32.5 days (mean ± s.e.) (range 74–575) between the first exposure to OHP and the reaction.

Eight out of 124 (6.5%) patients reported only erythema and itching of the palms and flushing of the face and hands after the beginning of OHP infusion. Nine out of 124 (7.3%) patients developed a more severe reaction with dyspnoea, wheezing,
Hypersensitivity reactions to platinum compounds are a well-known phenomena (Weiss, 1992). In the 1950s, literature reported the capacity of platinum salts to induce bronchial asthma among platinum-refinery workers (Hunter et al, 1945). It is not surprising that after the introduction of platinum compounds into chemotherapy, their association with type I hypersensitivity reactions was confirmed (Cleare et al, 1976). These reactions were first described for CDDP with a 5–20% incidence (Wiesenfeld et al, 1979; Shleback et al, 1995; Özgüroğlu et al, 1999), and evidence regarding similar reactions for CBDDA are also available (Planner et al, 1991; Morgan et al, 1994; Weideman et al, 1994; Markman et al, 1999).

This kind of toxicity has been sporadically reported in clinical trials focusing on the effectiveness of OHP in chemotherapy or described as case reports (Machover et al, 1996; Diaz Rubio et al, 1998; Tournigand et al, 1998; Larzilliere et al, 2000; Medioni et al, 1999; De Gramont et al, 2000; Dold et al, 2002; Monnet et al, 2002).

Our results support the assumption that this side effect should not be underestimated. More than 13% of OHP-treated patients developed hypersensitivity reaction. This phenomenon is not well known, probably because OHP entered clinical practice only a few years ago. Moreover, according to our experience, the reactions generally develop after about 9–10 infusions. The relationship between the hypersensitivity reaction and OHP is supported by the following evidence. First, the symptoms developed a few minutes after starting the OPH infusion; secondly, the patients re-exposed to successive OHP administration developed a similar reaction; thirdly, two patients developed a reaction after monochemotherapy OHP infusion; finally, in patients treated with OHP/CPT-11/c.i. 5-FU/FA regimen, the reaction could be confused with a cholinergic syndrome due to CPT-11, but the responsibility of CPT-11 can be excluded since the re-exposure to CPT-11/c.i. 5-FU/FA without OHP was not able to provoke the hypersensitivity reaction.

The pathophysiology of hypersensitivity reactions is not clear, but the finding that almost all patients developed the reaction after multiple infusions of treatment suggests the need to be sensitised during previous cycles. Symptoms usually develop early after the start of the infusion and have been ascribed to a type I hypersensitivity Ig-E-mediated reaction (Stahl et al, 2001).

A different hypothesis suggests that platinum salts could induce an oligo or polyclonal T-cells expansion. These compounds can act as a superantigen on the peripheral blood mononuclear cells, thus releasing a large amount of proinflammatory cytokines (IL-6, TNFα, γ interferon) (Santini et al, 2001). The other possible mechanism consists in binding the platinum salts to different peptides of major histocompatibility complex (MHC).

In fact, HLA phenotype is a significant determinant of occupational sensitisation to inhaled hapten of complex platinum salts and the strength of this association varies according to the intensity of exposure (Newman Taylor et al, 1999).

Furthermore, the relationship between hypersensitivity reactions and HLA-haplotype has been described for other drugs (Hetherington et al, 2002). Additional factors are deemed to be necessary to the immune system for developing the reaction after several infusions.

Apart from hypersensitivity-related dyspnoea and wheezing, the lung may also be the target of a particular toxicity. A patient treated with OHP-5FU therapy developed severe dyspnoea. A bronchus alveolar lavage (BAL) and a lung biopsy diagnosed a diffuse alveolar damage that disappeared with steroid therapy (Trisolini et al, 2001).

In our experience, when a hypersensitivity reaction occurred, the infusion of OHP was immediately stopped and replaced by a saline infusion, an intravenous antihistaminic drug and a low-dose corticosteroids administration. In the case of more severe reactions (dyspnoea, sweating, bronchospasm, laryngospasm), we immediately administered a high dose of steroid. The steroid dose ranged between 100 and 1000 mg of hydrocortisone. After the reaction disappeared, the OHP infusion was not restarted and the decision to administer the other scheduled drugs was taken evaluating the clinical status of the patient after the reaction, the risk of additional toxicity and the clinical utility of the chemotherapy. In this way, about two-thirds of patients (11 patients) continued the infusion of other planned antibiotic drugs without any additional clinical problems.

In order to avoid further hypersensitivity problems in successive cycles, one can presumably explore a maximum prophylactic immunological blockade with a high dose of steroids and antihistaminic drugs for several days before the infusion of OHP, but the real benefit is uncertain because five out of six patients

| Chemotherapy regimen | No. of patients | No. of reactions | % reaction according to the regimen | Mean no. of infusions at the reaction onset |
|----------------------|----------------|-----------------|-------------------------------------|------------------------------------------|
| FOLFOX-4             | 55             | 10              | 18.1                                | 8.1                                      |
| FOLFOX-3             | 34             | 3               | 8.8                                 | 14.3                                     |
| Irinotecan Oxaliplatin | 30           | 2               | 6.6                                 | 12.5                                     |
| Fuorouracil Folinic acid | 3            | 2               | 66.6                                | 6                                        |
| Oxaliplatin          |                |                 |                                     |                                          |

Table 2: Number of reactions according to the regimen
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British Journal of Cancer (2003) 89(3), 477 – 481