Hypersensitivity reaction caused by folinic acid administration: a case report and literature review

Short title: Folinic acid hypersensitivity reaction

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Abstract

Fluorouracil (5-FU) is combined with folinic acid (FA) for enhancing its cytotoxic effects in the colon cancer chemotherapy treatment. FA has rarely been involved in hypersensitivity reactions. Here, we report a case of FA hypersensitivity in an adult patient initially attributed to oxaliplatin administered concurrently.

A 56-year-old male patient diagnosed with colon cancer received 12 cycles of FOLFOX4, 1 cycle of FOLFIRI plus cetuximab and 9 cycles of FOLFOX6 uneventful. At the 10th cycle of FOLFOX6 chemotherapy, after 15 minutes of starting the infusion of oxaliplatin and FA the patient reported flushing, pruritus and abdominal pain, and erythema and oedema developed over the face and thorax. After progression, FOLFIRI plus aflibercept was scheduled and another reaction occurred. At this time, FA was discontinued and the patient received another cycle consisted on irinotecan plus 5-FU without incidences. This episode of hypersensitivity reaction following FA infusion with no oxaliplatin empirically confirmed that the hypersensitivity reaction was secondary to FA.

Clinicians should be aware of hypersensitivity reaction with FA, especially when FA is administered concomitantly with oxaliplatin, despite its lower risk to cause hypersensitivity reactions. Furthermore, the similar signs and symptoms associated to the hypersensitivity reactions of each agent, highlight the importance to have a specialized allergist team for to make a prompt diagnose of the causative agent in order to prevent patient harm and proceed properly without unnecessary delays in the scheduled chemotherapy treatments.

Key words: Hypersensitivity reaction, Chemotherapy, Folinic acid, Colon cancer

Introduction

In oncology, chemotherapy regimens based on 5-fluorouracil (5-FU) represent the main treatment of colorectal cancer. To enhance its cytotoxic effects, 5-FU is usually combined with folinic acid (FA). In addition, the combination of 5-FU/FA and oxaliplatin proved to be superior to 5-FU/FA in advanced colorectalcancer[1]. Hypersensitivity reactions to chemotherapeutic agents are rare and those secondary to FA administration are even more scarce[2-6].Here, we report a case of FA hypersensitivity in an adult patient with colon cancer initially attributed to oxaliplatin as both agents were administered concurrently.

Case report

A 56-year-old Caucasian male with no significant medical history and unknown allergies was diagnosed with stage III sigmoid KRAS-wild-type colon cancer in May 2011. The patient underwent sigmoid colectomy and initiated adjuvant chemotherapy with FOLFOX4 consisting on oxaliplatin, 85 mg/m^2 administered as a 2-hour infusion on day 1; FA, 200 mg/m^2 administered as a 2-hour infusion on day 1 and day 2; followed by a loading dose of 5-FU, 400 mg/m^2 IV bolus, then 5-FU, 600 mg/m^2 administered via ambulatory pump for a period of 22 hours on day 1 and day 2 every 2 weeks. Oxaliplatin was administered on day 1 only and was given as a 2-hour infusion in 250mL of dextrose 5%, concurrent with FA. He completed all 12 cycles of FOLFOX4 by December 2011 with a good tolerance and no relevant side effects reported other than grade 2 neurotoxicity. In September 2013 the tumor progressed with metastases in liver, lung, bone and suprarenal glands. Then, a new chemotherapy with FOLFIRI regimen was scheduled consisting on irinotecan, 180 mg/m^2 administered as a 2-hour infusion on day 1; FA, 400 mg/m^2 administered as a 2-hour infusion on day 1; followed by a loading dose of 5-FU, 400 mg/m^2 IV bolus administered on day 1, then 5-FU, 400-3,000 mg/m^2 administered via ambulatory pump for a period of 46 hours every 2 weeks plus cetuximab. Antiemetic and anticholinergic prophylaxis included granisetron,

dexamethasone and atropine. After the first cycle of chemotherapy, the patient was admitted to the oncology ward because of grade 3 diarrhoea, grade 2 nausea and grade 1 asthenia and rash attributed to cetuximab. He discontinued treatment due to unacceptable toxicity and once symptoms resolved, in October 2013, he started chemotherapy with FOLFOX6 regimen consisting on oxaliplatin, 85 mg/m^2 administered as a 2-hour infusion on day 1 (reduced at 50% of dose because of persistence of grade 2 neurotoxicity) concurrent with FA, 400 mg/m^2 administered as a 2-hour infusion on day 1; followed by a loading dose of 5-FU, 400 mg/m^2 IV bolus on day 1, then 5-FU, 3,000 mg/m^2 administered via ambulatory pump for a period of 46 hours every 2 weeks. He received 9 cycles uneventful and with no reduction of the dose. During the 10th cycle of chemotherapy, after 15 minutes of beginning the concomitant infusion of oxaliplatin and FA he felt heat, facial and thoracic erythema, oedema, pruritus and abdominal pain. It was diagnosed as a grade 2 hypersensitivity reaction and the infusion was stopped with the subsequent administration of dexchlorpheniramine, acetaminophen and hydrocortisone with a good response. At that moment, the hypersensitivity reaction was attributed to oxaliplatin. The next cycle of chemotherapy treatment, the 11th, according to our internal protocol of our hospital, it was decided to reduce by 50% the oxaliplatin infusion rate. When there is a suspicion of chemotherapy hypersensitivity, this procedure was performed under medical specialized surveillance with crash cart if needed in a special area for these techniques. Despite these measures, the patient experienced again a grade 2 hypersensitivity reaction with facial and thoracic erythema, pruritus and dyspnoea within the 10 minutes after the starting of the infusion of oxaliplatin and FA. The infusion was immediately stopped and dexchlorpheniramine and hydrocortisone were administrated and the symptoms completely resolved. For the next cycle, the 12th, oxaliplatin was not administered as it was assumed as the causative agent of the previous hypersensitivity reactions. However, the patient began to experience facial

redness, pruritus and dyspnoea similar to the previous hypersensitivity reactions also approximately 10 minutes after the beginning of the administration of FA. Again, the infusion was stopped, and dexchlorpheniramine, acetaminophen and hydrocortisone were administered with a good evolution.

One week later, after 12 cycles of FOLFOX6 treatment a CT-scan was performed to evaluate response to treatment. The CT-scan showed progression of the disease in the liver and lung leading to discontinuation of treatment with FOLFOX. Then, a further line of chemotherapy treatment was started with FOLFIRI plus aflibercept. At 15 minutes after the starting of the infusion, the patient experienced redness over the face, similar to previous episodes. The FA infusion was stopped and dexchlorpheniramine was administered. He received irinotecan plus 5-FU with a good tolerance. This episode of hypersensitivity reaction following FA infusion with no oxaliplatin empirically confirmed that the hypersensitivity reaction was secondary to FA. Moreover, FA was removed in further administrations and the patient did not present more hypersensitivity reactions.

Discussion

Here we report a case report of FA hypersensitivity reaction initially attributed to oxaliplatin as of both drugs were administered concomitantly.

In fact, hypersensitivity reactions tend to occur only in association with the use of a limited number of agents in a small number of patients. In our case, the hypersensitivity reaction was initially attributed to oxaliplatin due also to its higher frequency of hypersensitivity reaction than FA. Actually, the incidence of oxaliplatin hypersensitivity reactions was estimated to be around 12%[7]. Hypersensitivity reactions to platin salts occur typically with multiple administrations during the first few minutes of infusion. The hypersensitivity reactions of oxaliplatin are usually mild to moderate in nature and clinical manifestations often comprises itching or erythema (mainly of the palms and soles).More severe reactions to oxaliplatin are characterized by tachycardia, wheezing, facial swelling, throat and chest tightness, hypertension or hypotension or even

respiratory arrest in about 1% of cases[8]. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds. Anaphylactic reactions are usually managed with standard epinephrine[9], corticosteroid, antihistamine therapy, and require discontinuation of therapy. Given that (according to the patient's referring physicians) our patient could not discontinue therapy, given that oxaliplatin-reactive patients may suffer severe reactions when rechallenged, given that we lacked access to risk-assessment techniques (management by experts in drug allergy, skin tests, and other in vivo and vitro tools), and given that we lacked access to therapeutic techniques for drug-reactive patients (like rapid desensitization): we administered the previously reactive chemotherapy according to our internal protocol and under medical specialized surveillance in a special area for these techniques with a readily available crash cart.

The main limitation of our case is the lack of an allergological study because of the absence of a specialized allergist team on chemotherapy hypersensitivity. Our patient was not tested for allergies or a process of desensitization. The diagnosis of a hypersensitivity reaction is indeed based on patient’s history, on clinical manifestations, and if possible, in vivo test and in vitro biological tests[12].It is known that Intradermal skin tests are sensitive for the diagnosis of oxaliplatin-associated hypersensitivity reactions, with a sensitivity of 75% to100%[13].Desensitization is a complicated and potentially very dangerous methodology and should only be administered in highly selected cases by expert health personnel[14].

In our case the diagnosis of probable hypersensitivity reaction secondary to FA was only performed by the clinical history of our patient. The fact that the patient repeatedly reacted with a FOLFOX treatment (including FA and oxaliplatin) and also with a FOLFIRI treatment (including FA but not oxaliplatin) make the diagnosis of hypersensitivity to FA very probable, even if no allergological assessment could be

performed. However, the diagnosis of hypersensitivity to oxaliplatin could not be excluded (due to the lack of allergological study and to a non-systematic approach of re-challenge). Our patient was previously informed and gives oral consent to be repeatedly exposed at the same drug with intensified pre-medications and slower infusion rate, as reported elsewhere[10,11]. Damaske *et al.* reported that the patient received more cycles of chemotherapy treatment to confirm the hypersensitivity reaction secondary to FA[5].

Reviewing previous case reports with FA hypersensitivity reactions (table 1), in 6 out 9 of them (66.7%) the patient was diagnosed with a colon cancer. In all cases, the patients were rechallenged with FA after the diagnosis of hypersensitivity reaction. But at the end, the chemotherapy regimen with FA was definitely discontinued (Table 1). In our case, the signs and symptoms of hypersensitivity to FA were similar to those reported in the literature (Table 1)[2-6].Furthermore, in the majority of case reports, 6 out 9, patients had received several previous cycles of chemotherapy with FA uneventful (Table 1)[2-6] similar to other drugs such as platins.

The mechanism of hypersensitivity reaction to FA is still unknown, although the late occurrence of FA hypersensitivity reaction, after several administrations of courses, suggests a type I, an immediate hypersensitivity reaction IgE-mediated reaction as platins.

As mentioned above, the main limitation of our case is the lack of skin tests or lab tests related to hypersensitivity reactions such as prick, patch, intradermal tests, and determination of tryptase or IgE blood levels to undoubtedly support the diagnosis of hypersensitivity. Routine tests are not currently available, done in our hospital. However, the sequence of events described in our case a very probable diagnosis of hypersensitivity reaction to FA.

As in most Hospitals, our center doesn't have a specialized team for the diagnoses and treatment of hypersensitivity reactions and skin or lab tests are not currently done. This

case shows the importance of having a specialized allergist team for a better management of our patients.

Conclusion

Clinicians should be aware of hypersensitivity reaction with FA, especially when FA is administered concomitantly with oxaliplatin, despite its lower risk to cause hypersensitivity reactions. Furthermore, the similar signs and symptoms associated to the hypersensitivity reactions of each agent, highlight the importance to have a specialized allergist team for to make of a prompt diagnose of the causative agent in order to prevent patient harm and proceed properly without unnecessary delays in the scheduled chemotherapy treatments.

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Table 1. Case reports of FA reactions

Variables	**Benchalal M, *et al.* 2002**	**Prabu R, *et al.* 2008**	**Katirtzoglou NA, *et al.* 2011**	**Damaske A, *et al.* 2011**	**Ureña-Tavera A,*et al.* 2014 1st case**	**Ureña-Tavera A,*et al.* 2014 2nd case**	**Ureña-Tavera A,*et al.* 2014 3rd case**	**Ureña-Tavera A,*et al.* 2014 4th case**	**Ureña-Tavera A,*et al.* 2014 5th case**
Demographics	80 years Not reported	16 years Male	67 years Female	53 years Male	65 years Male	66 years Female	52 years Female	73 years Male	80 years Female
Pathology	Dukes' C stage colon adenocarcinoma	Stage III T cell lymphoblastic lymphoma	Stage IV KRAS wild-type colon cancer	Stage IV KRAS mutation colon cancer	Stage IV gastric adenocarcinoma	Stage IV colon adenocarcinoma	Stage IV rectal adenocarcinoma	Stage IV colon adenocarcinoma	Stage IV colon adenocarcinoma
Previous chemotherapy regimen uneventfully with FA	6 cycles of 5-FU and FA	1 cycle of Methotrexate and FA	18 cycles of FOLFOX6 and cetuximab	12 cycles of FOLFOX6 and bevacizumab 12 cycles of FOLFIRI and bevacizumab 12 cycles of FOLFOX6 and bevacizumab	NO	17cycles of FOLFOX	18cycles of FOLFOX	NO	10cycles of FOLFOX and 7cycles of FOLFIRI

Number of cycle of chemotherapy regimen related with FA reaction	1st cycle of FOLFIRI	2nd cycle of methotrexate and FA	19th cycle of FOLFOX6 and cetuximab	13th cycle of FOLFOX6 plus bevacizumab	1st cycle of FOLFOX	18th cycle of FOLFOX	19th cycle of FOLFOX	1st cycle of FOLFIRI	8th cycle of FOLFIRI
Prophylaxis 1	Ondansetron Atropin	NO	NO	Dexamethasone Palonosetron	Not reported	Not reported	Not reported	Not reported	Not reported
Reaction 1	Nettle rash	Chills Rigors Erythematous rash over face, neck and upper limbs Temperature spike of 38.8ºC	Hot and facial flushing Cough Shortness of breath Hypertension Vomiting	Flushing and pruritus on his scalp Scattered wheals on his neck and chest	Facial erythema and general urticaria	Genital and scalp itching, rhinoconjunctivitis and general malaise	Intense chills	Facial erythema, general urticarial and eyelid angioedema	Dyspnea, chest pain, oxygen desaturation and facial erythema
Treatment 1	Metoclopramide Prednisone	Antihistaminics	Hydrocortisone Phenhydramine Famitidine Demerol Ordansteron Oxygen	Diphenhydramine Ranitidine	Not reported	Not reported	Not reported	Not reported	Not reported

Prophylaxis 2	Metoclopramide Prednisone	NO	Dexamethasone	Dexamethasone Palonosetron Diphenhydramine Ranitidine	Not reported	Not reported	Not reported	Not reported	Not reported
Reaction 2	Rash hypotension	Generalized erythematous rash Vomiting Dizziness Hypotension	Flushing Burning sensation all over the body Diarrhoea	Hives to the upper chest, forehead and scalp Itching Tingling	Urticaria	General Urticaria Rhinoconjunctivitis	Chills Back pain Elevated blood pressure Fever	General Urticaria Eyelid angioedema	Chills Chest pain Facial erythema
Treatment 2	Epinephrine	Dopamine Antihistaminics Hydrocortisone Hydration Alkalinization Antibiotics	Diphenhydramine Hydrocortisone Famotidine	Completed the remaining infusion without complication	Not reported	Not reported	Not reported	Not reported	Not reported