Anaphylactic Reaction Associated with Intravenous Administration of Folinic Acid in a Patient with Colon Cancer

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Abstract. It is known that in colon cancer patients, folinic acid (FA) given intravenously (i.v.) with 5-fluorouracil (5-FU) enhances the cytotoxic effects of chemotherapy. Adverse events regarding administration of FA have rarely been reported in the medical literature. A review of the existing data revealed just one case report of a colon cancer patient, who developed allergic reaction secondary to FA administration. Here, we report a second case of anaphylactic shock of an adult female patient with colon cancer at the end of i.v. FA administration. Finally the patient recovered and the reaction resolved, after she received i.v. epinephrine. Although the patient received combination chemotherapy with multiple targeted agents, which are believed to mainly cause allergic events during their iv administration, symptoms of an allergic event were shown just after FA was given; the etiology of this adverse reaction remains unclear for the time being and a challenging future field for oncologists to investigate.

Combining folinic acid (FA) with 5-fluorouracil (5-FU) enhances the cytotoxic effects of chemotherapy in colon cancer patients (CRC) (1). FA has rarely been involved in adverse allergic reactions (2, 3) and a review of the literature revealed only one case report of a cancer patient to date (4). We here report the second case of anaphylactic reaction secondary to FA administration in an adult patient with metastatic CRC.

Case Report

Our patient was a 67-year-old Caucasian female with stage IV K-RAS wild-type mutation colon cancer. She was receiving mFOLFOX-6 plus cetuximab as first-line therapy (5). The patient received the first 18 cycles uneventfully except for grade 1 peripheral neuropathy, grade-1 nausea, grade-1 fatigue and grade-1 diarrhea. During the 19th cycle of chemotherapy, she felt hot and developed facial flushing, cough, shortness of breath, hypertension and vomiting at the beginning of cetuximab infusion (62.5 ml infused) following leucovorin, oxaliplatin and bolus 5-FU. She was given intravenous hydrocortisone (100 mg), diphenhydramine (25 mg; in addition to 25 mg pre-cetuximab), famitidine (20 mg), Demerol (50 mg, 1×2) and ordansteron (8 mg). She was placed on oxygen at 2 liters via nasal canula and transferred to the Emergency Department for further observation. Since it was felt that the allergic reaction could be related to cetuximab, the patient consented to receiving panitumumab. She was premedicated with dexamethasone (20 mg) intravenously prior to FOLFOX and then panitumumab was given. After only 33.9 ml of panitumumab were infused, the patient again developed flushing reaction, burning sensation all over the body and acute diarrhea. However, she denied any shortness of breath and remained hemodynamically stable. Intravenous diphenhydramine (25 mg), hydrocortisone (100 mg) and famotidine (10 mg) were administered and the reaction resolved. The patient returned in 2 weeks and it was decided to continue with FOLFOX alone. We decided to separate FA from oxaliplatin administration. She was premedicated with dexamethasone (20 mg) and kytril (1 mg). At end of FA infusion (1.35 h), the patient developed flushing, heaviness in the chest, shortness of breath, and vomiting. Her blood pressure dropped to 90/60 mm Hg and few crackles were heard at the base of the lungs. FA infusion was stopped, hydrocortisone (100 mg), diphenhydramine (25 mg × 2) and an albuterol inhaler were administered, and finally she received intravenous epinephrine 1/1000. The patient then developed rigors and Demerol was given. She
was then transferred to the Emergency Department and observed for the next 24 h. She recovered, but developed grade 2 diarrhea.

The patient returned to the clinic and after consent, was started on oral capecitabine. She tolerated capecitabine with minimal toxicity (grade 1 Hand-Foot syndrome, grade-1 diarrhea). It was presumed that the patient had an anaphylactic reaction secondary to FA in the chemotherapy for colon cancer. Since she had grade 2 peripheral neuropathy, it was decided not to rechallenge her with oxaliplatin.

Discussion

The association of 5-FU and FA has demonstrated its clinical efficacy in CRC (1). Fluorodeoxyuridylate, one of the 5-FU metabolites, binds to thymidylate synthase in the presence of FA leading to its inhibition via a covalent ternary complex. FA, at high doses, increases 5-FU toxicity by stabilizing the ternary complex (6). Although folates are regarded as not being toxic for humans, they may interfere with zinc absorption or mask vitamin B12 deficiency (7). The medical literature revealed only one case published in 2002 in which an 80-year-old colon cancer patient developed an anaphylactic shock following FA as chemotherapy consisting of FA, 5-FU and irinotecan. We believe that our case represents the second report. The real etiology is not clear at present (2, 8).

Our case was also challenging as this patient was receiving combination of chemotherapy with targeted agents, among which cetuximab and oxaliplatin are more prone to cause anaphylactic reactions. This complexity of regimens and combination chemotherapy with biologic agents, both presenting a potential hazard to cause an anaphylactic reaction, underline the importance of publishing such cases. Anaphylactic reaction may be an adverse reaction to FA in patients receiving chemotherapy for colon cancer and oncologists treating these patients should be aware of this rare but real acute toxicity.

References


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