

## Pulmonary Edema Caused by Levofolinate Treatment in Patients with Liver Metastases from Colorectal Cancer

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### Abstract

A liver tumor metastatic from a sigmoid colon carcinoma was diagnosed in a 70-year-old man. Because hepatectomy was not indicated, the patient was treated with a combination of oxaliplatin, levofolinate, and fluorouracil (5-FU) (modified FOLFOX 6 regimen). After 15 cycles of chemotherapy, this regimen was considered to have been ineffective; therefore, treatment was started with the topoisomerase inhibitor irinotecan and an intravenous infusion of 5-FU and levofolinate (FOLFIRI). After receiving irinotecan and levofolinate, the patient had chills, a severe cough, and dyspnea. We diagnosed pulmonary edema as a side effect due to oxaliplatin, and the chemotherapeutic regimen was changed from FOLFIRI to FOLFOX plus bevacizumab. After the third cycle of oxaliplatin and levofolinate, pulmonary edema recurred, and a preshock state developed again. We suspected that either oxaliplatin or irinotecan had caused the pulmonary edema and, therefore, administered levofolinate, 200 mg/m<sup>2</sup>; 5-FU, 400 mg/m<sup>2</sup>; and bevacizumab, 330 mg/m<sup>2</sup>; intravenously on day 1, followed by 5-FU, 2,400 mg/m<sup>2</sup>, as a continuous intravenous infusion at 46 hours without either of oxaliplatin, levofolinate, and bevacizumab. After being treated with levofolinate again, the patient suddenly complained of severe dyspnea; this symptom confirmed that levofolinate had caused the pulmonary edema. To our knowledge, severe pulmonary edema caused by levofolinate has not been reported previously. This adverse effect was clinically significant because it led to the patient's death. (J Nippon Med Sch 2013; 80: 460–466)

**Key words:** pulmonary edema, levofolinate, adverse effect

### Introduction

Levofolinate, generally administered as calcium or sodium folinate (or leucovorin calcium/sodium), is an adjuvant used in cancer chemotherapy with the drug methotrexate<sup>1</sup>. Levofolinate is in a class of medications that allow methotrexate to enter and

kill cancer cells. Levofolinate enhances the effect of fluorouracil (5-FU) by biochemical modulation<sup>2,3</sup>. Levofolinate is thought to affect the incidence and severity of 5-FU-related antitumor activity and those of adverse reactions. Diarrhea, oral mucositis, and hand-and-foot syndrome are typical adverse reactions associated with 5-FU<sup>3,4</sup>. The most clinically important adverse effects of 5-FU are shock and

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Fig. 1 An abdominal CT scan, showing that the tumor had grown to 53×30 mm in diameter despite no change in the size or number of lymph node metastases.

anaphylactic reactions.

We describe a case of severe pulmonary edema that occurred as an adverse effect of levofolinate. To our knowledge, severe pulmonary edema caused by levofolinate has not been reported previously. This adverse effect was clinically significant because it led to the patient's death.

### Case Report

A 70-year-old man had undergone sigmoidectomy for sigmoid colon carcinoma at another hospital 4 years earlier. The pathological stage was IIIa (SE, N1, H0, P0, M0). An intrahepatic tumor was detected on follow-up computed tomography (CT) of the abdomen, and the patient was admitted to our hospital's department of surgery for further evaluation. Abdominal CT showed an unenhanced tumor, 38 × 30 mm in diameter, in the posterosuperior segment (S7) of the liver. The tumor had invaded the inferior vena cava and right adrenal

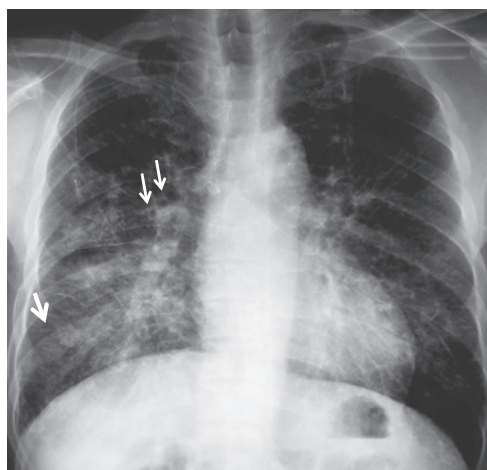


Fig. 2 A chest radiograph, showing alveolar infiltrates in both lungs, lobular vessel enlargement, peribronchial cuffing (**arrow**), and Kerley B lines (**arrow**).

gland and had metastasized to portal lymph nodes (6 mm). On the basis of these findings, a liver tumor metastatic from the sigmoid colon carcinoma was diagnosed; however, hepatectomy was not indicated. The patient was, therefore, treated with oxaliplatin in combination with levofolinate and an intravenous infusion of fluorouracil (5-FU) (modified FOLFOX 6 regimen). Oxaliplatin, 85 mg/m<sup>2</sup>; levofolinate, 200 mg/m<sup>2</sup>; and 5-FU, 400 mg/m<sup>2</sup>; were given intravenously on day 1, followed by a continuous intravenous infusion of 5-FU, 2,400 mg/m<sup>2</sup>, at 46 hours, repeated every 2 weeks. After 15 cycles of chemotherapy, abdominal CT showed that the tumor had enlarged to 53 × 30 mm in diameter despite no change in the size or number of metastatic lymph nodes (**Fig. 1**).

Because the modified FOLFOX 6 regimen was considered to have been ineffective, it was discontinued, and treatment was started with the topoisomerase inhibitor irinotecan plus the intravenous infusion of 5-FU and levofolinate (FOLFIRI). Irinotecan, 150 mg/m<sup>2</sup>; levofolinate, 200 mg/m<sup>2</sup>; and 5-FU, 400 mg/m<sup>2</sup>; were given intravenously on day 1, followed by a continuous intravenous infusion of 5-FU, 2,400 mg/m<sup>2</sup>, at 46 hours, repeated every 2 weeks.

After receiving irinotecan and levofolinate, the patient had chills, severe cough, and dyspnea. The systolic blood pressure decreased to 60 mm Hg, and the blood oxygenation level decreased to less than

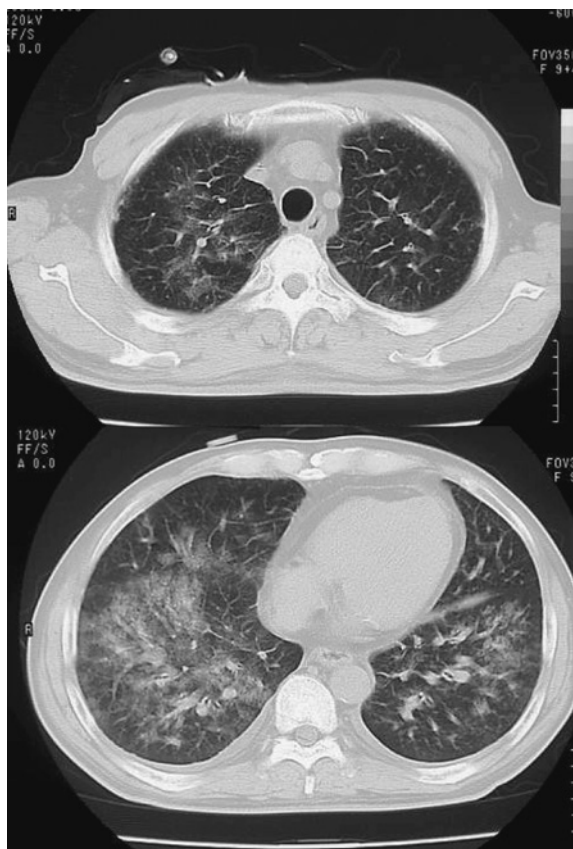


Fig. 3 A chest CT scan, showing ground-glass opacity and peribronchovascular interstitial thickening, predominantly located centrally in both lungs and suggesting pulmonary edema.

80%. Chest radiography revealed alveolar infiltrates in both lungs, lobular vessel enlargement, peribronchial cuffing (arrow), and Kerley B lines (arrow) (Fig. 2). Chest CT showed ground-glass opacity and peribronchovascular interstitial thickening, predominantly in central areas, of both lungs; these findings suggested pulmonary edema (Fig. 3). Table 1 shows laboratory data obtained when the pulmonary edema was recognized. There were no markedly abnormal findings, including those of the hematological examination. Eosinophilic leukocytosis was not detected, and the lymphocyte stimulation test was negative. Regrettably, a blood test for specific IgE was not performed (Table 1). The initial goal of treatment for this patient was maintaining adequate oxygenation. Furthermore, furosemide, 40 mg, was given to treat the pulmonary edema, and methylprednisolone, 500 mg, was given to treat shock. As soon as the blood pressure and

blood oxygenation level had normalized. After 5 days of admission, chest radiography showed no fluid in the alveolar walls or Kerley B lines (Fig. 4), and chest CT showed no ground-glass opacity (Fig. 5). Pulmonary edema was considered to have been an adverse effect of irinotecan, and the regimen was changed from FOLFIRI to FOLFOX plus bevacizumab. The dosage was the same as for the modified FOLFOX 6 regimen, with the addition of bevacizumab, 330 mg/m<sup>2</sup>.

After 2 cycles of FOLFOX plus bevacizumab, abdominal CT showed a reduction in tumor size to 35 × 25 mm. The metastatic liver tumor also showed a partial response to treatment. After the third cycle of oxaliplatin and levofolinate, a preshock state developed again. Pulmonary edema was diagnosed with chest radiography. Because this adverse effect was suspected to have been caused by oxaliplatin, oxaliplatin was discontinued, and treatment with TS-1 (100 mg/day), a novel oral anticancer drug, was started.

After 6 months of chemotherapy with TS-1, the metastatic liver tumor had enlarged to 80 × 88 mm on abdominal CT. We had some misgivings about administering oxaliplatin or irinotecan again owing to the risk of pulmonary edema. Therefore, we instead administered levofolinate, 200 mg/m<sup>2</sup>; 5-FU, 400 mg/m<sup>2</sup>; and bevacizumab, 330 mg/m<sup>2</sup>; intravenously on day 1, followed by 5-FU, 2,400 mg/m<sup>2</sup>; as a continuous intravenous infusion at 46 hours, repeated every 2 weeks. After treatment with levofolinate, the patient suddenly complained again of severe dyspnea, which confirmed that levofolinate had caused the pulmonary edema. The patient was then given 5 cycles of chemotherapy with oxaliplatin, 5-FU, and bevacizumab. The metastatic liver tumor and portal lymph node metastases continued to enlarge and the patient died 28 months after starting chemotherapy for the metastatic liver tumor and 79 months after sigmoidectomy for the underlying carcinoma of the sigmoid colon.

Figure 6 shows the details of the relationship between the drug history and the development of pulmonary edema. Pulmonary edema was recognized after treatment with FOLFIRI and the

Table 1 Laboratory date on admission

WBC	7,500 /mm <sup>3</sup>	AST	31 U/L	NH <sub>3</sub>	29 µg/dL
Neu	80 %	ALT	49 U/L	BS	84 mg/dL
Eos	0.8 %	GGTP	121 U/L		
Baso	0.1 %	ALP	246 U/L	Na	142 mEq/L
Mono	3.1 %	LDH	191 U/L	K	4.3 mEq/L
Lym	16 %	TP	6.6 g/dL	Cl	105 mEq/L
RBC	417×10 <sup>4</sup> /mm <sup>3</sup>	Alb	4.0 g/dL		
Hb	13.3 g/dL	T-Bil	0.7 mg/dL	lymphocyte stimulation test	
Ht	39.4 %	D-Bil	0.2 mg/dL	(-)	
Plt	10.7×10 <sup>4</sup> /mm <sup>3</sup>	T-Cho	195 mg/dL		
		TG	101 mg/dL		
PT	104.2 %	BUN	16.7 mg/dL		
PT/INR	1.04	Cr	0.64 mg/dL		
APTT	25 s	UA	4.0 mg/dL		
		AMY	40 U/L		

WBC, white blood count; Neu, neutrophil; Eos, eosinophil; Baso, basophil; Mono, monocyte; Lym, lymphocyte; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; PT, prothrombin time; PT/INR, prothrombin time/international normalized ratio; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGTP,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; TP, total protein; Alb, albumin; T-Bil, total bilirubin; D-Bil, direct bilirubin; T-Cho, total cholesterol; TG, triglyceride; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; Amy, amylase; NH<sub>3</sub>, ammonia; BS, blood sugar concentration.



Fig. 4 Chest radiography, showing no fluid in the alveolar walls or Kerley B lines.

third cycle of FOLFOX plus bevacizumab. The preshock state developed after levofolinate was given as an intravenous infusion.

### Discussion

The outcomes of patients with metastatic colorectal cancer remain poor. For many years, the treatment of choice for metastatic disease was 5-FU,

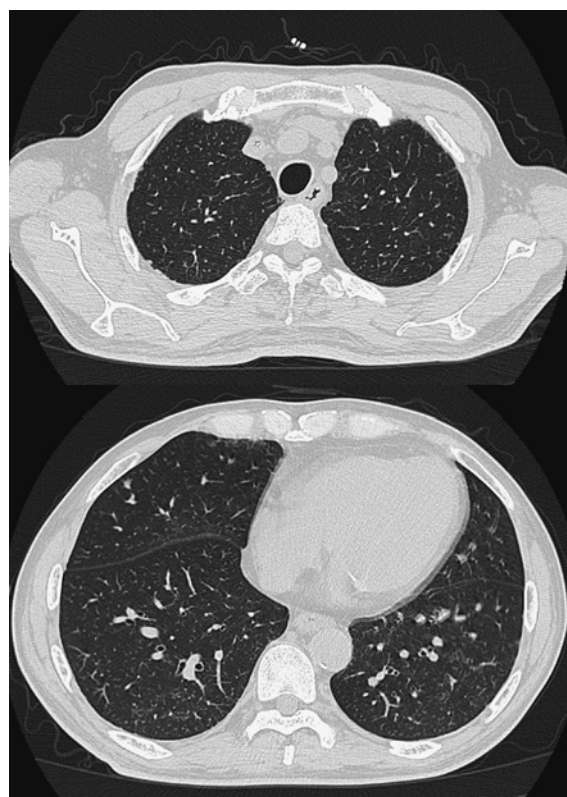


Fig. 5 A chest CT scan, showing no ground-glass opacity.

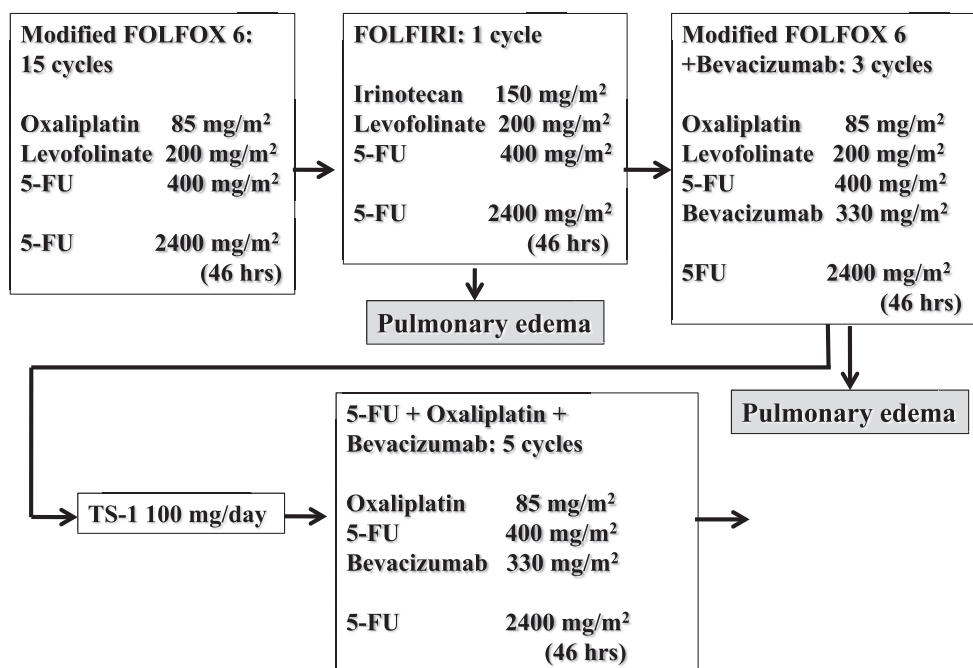


Fig. 6 The relationship between the drug history and the development of pulmonary edema.

alone or with biomodulation<sup>2</sup>. Oxaliplatin and irinotecan in combination with continuous infusion of 5-FU were subsequently shown to significantly improve response rates, progression-free survival, and overall survival<sup>5-7</sup>. Recently, bevacizumab, a monoclonal antibody against vascular endothelial growth factor, and cetuximab, an immunoglobulin G1 chimeric monoclonal antibody against epidermal growth factor receptor, were shown to produce significant and clinically meaningful improvements in survival in patients with metastatic colorectal cancer<sup>8,9</sup>.

Adverse effects of anticancer drug treatment include fatigue, nausea, vomiting, diarrhea, and neutropenia. The most commonside effect of oxaliplatin is neuropathy, which is both an acute reversible sensitivity to cold and numbness in the hands or feet and chronic, possibly irreversible, numbness in the feet, legs, hands, or arms, often accompanied by deficits in proprioception<sup>10</sup>. Because of the high rate of peripheral neuropathy, oxaliplatin is considered the main cause of FOLFOX-induced toxicity. In addition, oxaliplatin is classified as an agent having a moderate emetic risk, whereas 5-FU is classified as an agent having low emetic risk, according to the National Comprehensive Cancer Network Antiemesis Guidelines<sup>11</sup>. Neuropathy

reportedly occurs in about 70% of patients who receive oxaliplatin<sup>12,13</sup>.

The most clinically important adverse effects of irinotecan are severe diarrhea and immunosuppression<sup>14</sup>. In clinical studies of FOLFIRI, adverse effects include grade 3/4 neutropenia, febrile neutropenia, and diarrhea<sup>15,16</sup>. Bevacizumab inhibits the growth of blood vessels, which play vital roles in the body's normal healing and maintenance. The main adverse effects of bevacizumab are hypertension and a risk of bleeding. Bowel perforation has also been reported. Less than half of all patients with advanced lung cancer qualify for treatment with bevacizumab<sup>17,18</sup>.

Several anticancer drugs induce pulmonary damage, which can cause a variety of clinicopathological syndromes with minor to severe consequences<sup>19</sup>. Noncardiogenic pulmonary edema is a toxic effect of anticancer therapy which is less common and less easily recognized than are pneumonitis and fibrosis. Anticancer agents clearly associated with pulmonary edema include cytarabine, gemcitabine, and interleukin 2, as well as all-trans retinoic acid in patients with acute promyelocytic leukemia. A few other compounds have rarely or occasionally been implicated in pulmonary edema<sup>20</sup>.



To our knowledge, pulmonary edema had not previously been reported as a toxic effect of FOLFOX, FOLFIRI, or these regimens plus bevacizumab. In patients who receive FOLFOX, oxaliplatin has rarely caused infiltrative lung disease associated with such abnormalities as pleural effusion<sup>21</sup>. The irinotecan of FOLFIRI has been reported to cause pulmonary toxicity in more than 20% of patients, but irinotecan-related interstitial pneumonitis has been documented in only a few cases<sup>21</sup>.

In our patient, the suspected causes of pulmonary edema were irinotecan during treatment with FOLFIRI and oxaliplatin during treatment with FOLFOX. After these 2 anticancer drugs were withdrawn, levofolinate caused dyspnea due to pulmonary edema again. During first-line chemotherapy with the modified FOLFOX 6 regimen, no pulmonary toxicity developed in our patient. These findings suggest that high doses of oxaliplatin and irinotecan caused asymptomatic pulmonary dysfunction and inflammation, possibly priming the lungs for further injury by high cumulative doses of levofolinate. Therefore, the pulmonary edema in our patient cannot be attributed solely to the adverse effects of levofolinate.

Anaphylactic shock has been reported as a severe complication of levofolinate<sup>22,23</sup>. Anaphylaxis is a severe allergic reaction of rapid onset affecting many body systems; it is typically due to an immunological reaction but sometimes has a nonimmunologic mechanism<sup>24</sup>. Mediators, such as histamine, increase the leakage of fluid from blood vessels. In turn, this fluid enters the parenchyma and air spaces of the lung and causes pulmonary edema<sup>25</sup>. In the present patient, allergy testing was negative, the lymphocyte stimulation test was negative for levofolinate, and eosinophilic leukocytosis was not detected. Regrettably, a blood test for specific immunoglobulin E was not performed. Therefore, we concluded that the pulmonary edema was due not to anaphylactic shock but to cytotoxic damage to the lung. This damage might have been direct or have been mediated by high pressures within the pulmonary circulation.

We have described a case of severe pulmonary edema caused by levofolinate. To our knowledge, this adverse effect of levofolinate has not been reported previously. The effective management of drug-induced pulmonary edema requires early recognition of evolving lung toxicity and withdrawal of the suspected causative drug or drugs. Levofolinate should be considered a potential cause of pulmonary edema.

**Conflict of Interest:** We have no personal or financial interests to declare. Nor have we received any financial support from commercial sources for the research presented herein.

### References

1. Keshava C, Keshava N, Whong WZ, Nath J, Ong TM : Inhibition of methotrexate-induced chromosomal damage by folic acid in V79 cells. *Mutat Res* 1998; 397: 221-228.
2. Poon MA, O'Connell MJ, Moertel CG, et al: Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989; 7: 1407-1418.
3. Grem JL: Biochemical modulation of 5-FU in systemic treatment of advanced colorectal cancer. *Oncology* 2001; 15: 13-19.
4. Erlichman C, Fine S, Wong A, et al: A randomized trial of fluorouracil and folic acid in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1988; 6: 469-475.
5. Levi F, Zidani R, Misset JL: Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folic acid in metastatic colorectal cancer: International Organization for Cancer Chronotherapy. *Lancet* 1997; 350: 681-686.
6. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18: 136-147.
7. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. *Lancet* 2000; 355: 1041-1047.
8. Hurwitz H, Fehrbacher L, Novotny W, Cartwright T, Haainsworth J, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335-2342.
9. Jonker DJ, O'Callaghan CJ, Karapetis C, Zalcberg JR, Tu D, et al: Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007; 357: 2040-2048.
10. Pasetto LM, D'Andrea MR, Rossi E, Monfardini S: Oxaliplatin-related neurotoxicity: how and why? *Crit Rev Oncol Hematol* 2006; 59: 159-168.

11. Navari RM: Prevention of emesis from multiple-day and high-dose chemotherapy regimens. *J Natl Compr Canc Netw* 2007; 5: 51–59.
12. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18: 136–147.
13. De Gramont A, Figger A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18: 2938–2947.
14. Innocenti F, Undevia SD, Iyer L, et al: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; 22: 1382–1388.
15. Tournigand C, Andre T, Achille E, et al: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer. A randomized GERCOR study. *J Clin Oncol* 2004; 22: 229–237.
16. Fuchs CS, Marshall J, Mitchell E, et al: Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer; results from the BIC-C study. *J Clin Oncol* 2007; 25: 4779–4786.
17. Velcheti V, Viswanathan A, Govindan R: The proportion of patients with metastatic non-small cell lung cancer potentially eligible for treatment with bevacizumab: a single institutional survey. *J Thorac Oncol* 2006; 1: 501.
18. Vaughn C, Zhang L, Schiff D: Reversible posterior leukoencephalopathy syndrome in cancer. *Curr Oncol Rep* 2008; 10: 86–91.
19. Kreisman H, Wolkove N: Pulmonary toxicity of antineoplastic therapy. *Semin Oncol* 1992; 19: 508–520.
20. Briasoulis E, Pavlidis N: Noncardiogenic pulmonary edema: An unusual and serious complication of anticancer therapy. *Oncologist* 2001; 6: 153–161.
21. Dimopoulou I, Bamias A, Lyberopoulos P, Dimopoulos MA: Pulmonary toxicity from novel antineoplastic agents. *Ann Oncol* 2006; 17: 372–379.
22. Benchalal M, Yahchouchy-Chouillard E, Fouere S, Finegerhut A: Anaphylactic shock secondary to intravenous administration of folinic acid: a first report. *Ann Oncol* 2002; 13: 480–481.
23. Katirtzoglou NA, Hotchkiss S, Gambaccini M, Kaley K, Dyrigos KN, Saif MW: Anaphylactic reaction associated with intravenous administration of folinic acid on patient with colon cancer. *In Vivo* 2011; 25: 995–996.
24. Khan BQ, Kemp SF: Pathophysiology of anaphylaxis. *Current opinion in allergy and clinical immunology* 2011; 11: 319–325.
25. Ware LB, Matthay MA: Clinical practice. Acute pulmonary edema. *N Engl J Med* 2005; 353: 2788–2796.

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