Anti-Cancer Drugs 2000, **11,** pp. 709–713

Case report

Irinotecan-associated pulmonary toxicity

Yolanda Madarnas,[1,4,5,6] Peter Webster,[3–5] Anne Marie Shorter[2,4,5] and Georg A Bjarnason[1,4,5]

[1]Division of Medical Oncology/Hematology, Toronto-Sunnybrook Regional Cancer Centre, [2]Department of Diagnostic Imaging, [3]Department of Respirology, [4]Sunnybrook and Women's College Health Sciences Centre, [5]Department of Medicine, University of Toronto, Toronto, Ontario M4N 3MS, Canada and [6]Present address: Department of Medical Oncology, Kingston Regional Cancer Centre, Kingston, Ontario K7L 5P9, Canada.

We present the circumstances surrounding a 57-year-old Caucasian man with advanced colorectal cancer who developed relapsing interstitial lung disease following a single exposure to irinotecan (CPT-11). Progressive pulmonary insufficiency and death were reported in the initial Japanese studies, despite institution of empiric steroid therapy for a syndrome similar to that which our patient experienced. As a result, patients with compromised pulmonary function were generally excluded from US clinical trials. Notwithstanding this, cough and dyspnea were reported in approximately 20% of patients in the US studies. As the clinical indications for the use of this agent expand, we describe irinotecan-associated interstitial pneumonitis as a serious potential adverse effect. Patients with pre-existing pulmonary disease may be at higher risk for this complication and clinicians should be alert to this possibility. [© 2000 Lippincott Williams & Wilkins.]

Key words: Irinotecan, pulmonary toxicity

Case report

We present the circumstances surrounding the case of a 57-year-old Caucasian man with advanced colorectal cancer who developed a severe unproductive cough and interstitial lung disease following a single exposure to irinotecan (CPT-11).

His past medical history was unremarkable except for a resection of a benign pulmonary carcinoid tumor 20 years prior to the current events. He also had a history of hay fever and mild asthma with exposure to animal dander. He was a lifelong non-smoker, non-drinker, had no known drug allergies and was on no concurrent medication at the time of the exposure. He originally presented with a Dukes B1 carcinoma of the sigmoid colon on a routine screening colonoscopy in the fall of 1994. No adjuvant systemic therapy was given following a low anterior resection and he was followed expectantly. In early 1996 an isolated asymptomatic hepatic metastasis was detected on surveillance imaging. Restaging investigations were negative and a biopsy confirmed this to be a recurrence, thus he underwent a left hepatic lobectomy with curative intent in the summer of 1996. He subsequently received 6 months of pseudoadjuvant 5-fluorouracil and leucovorin chemotherapy. Unfortunately within 4 months of completing therapy, multiple asymptomatic pulmonary and hepatic metastases were detected. He was then offered chronomodulated 5-fluorouracil (5-FU) and leucovorin, with which he obtained a partial response and subsequently maintained stable disease for nearly 1 year. In the summer of 1998 radiographic disease progression prompted the institution of chronomodulated oxaliplatinum in addition to 5-FU and leucovorin, with which he obtained an excellent partial response. Unfortunately by the spring of 1999 he developed significant oxaliplatin-related peripheral neurotoxicity, although with a continued radiographic disease response. The oxaliplatin was thus replaced with carboplatin, but he rapidly developed disease progression. It was at this juncture that treatment with irinotecan was proposed.

On 29 June 1999 he received a 90-min i.v. infusion of 255 mg of irinotecan (125 mg/m^2) via a left subclavian Port-A-Cath. This was administered in conjunction with: ondansetron 8 mg p.o. prechemotherapy and 8 mg p.o. b.i.d. for 3 days, dexamethasone 10 mg p.o., diphenhydramine 50 mg i.v.,

Correspondence to Y Madarnas, Department of Medical Oncology, Kingston Regional Cancer Centre, 25 King Street West, Kingston, Ontario K7L 5P9, Canada
Tel: (+1) 613 544-2631; Fax: (+1) 613 544-9708;
E-mail: yolanda.madarnas@krcc.on.ca

domperidone 10 mg p.o. a.c. meals and h.s. for 7 days and dexamethasone 4 mg p.o. t.i.d. with meals for 3 days. No other prescription or over-the-counter medication was administered concurrently. Interestingly, during the infusion the patient developed an ascending wheal and flare-like eruption over his right arm, although the infusion was being administered at a distant site. This resolved completely with an i.v. dose of 100 mg of hydrocortisone and was not accompanied by any respiratory or systemic symptoms.

Hematological profile at the start of treatment was normal except for modest anemia and thrombocytopenia (Table 1). However, upon reassessment on day 8 he was found to be profoundly neutropenic (ANC = 0.3×10^9) such that treatment was withheld. The neutropenia persisted on day 15 (ANC = 0.2×10^9), treatment was once again withheld and granulocyte colony stimulating factor was introduced. This patient had been essentially asymptomatic throughout the course of his disease, and had been followed radiographically and by CEA. At the time of treatment with irinotecan he had complained only of an intermittent dry cough that had not required any intervention. However, within a few days of treatment and for the ensuing 3 weeks the cough dramatically worsened in intensity and frequency. By the time he was seen in follow-up, he could not speak in full sentences and was having difficulty sleeping because of the cough. He denied exertional dyspnea, orthopnea or paroxysmal nocturnal dyspnea and in fact had been able to play 18 holes of golf on several occasions pulling his clubs himself in a trolley! He reported no symptoms suggestive of infection and remained constitutionally well up to the time of the first follow-up clinic assessment on day 21 following treatment.

On clinical examination on 20 July 1999 this man looked well, although he was coughing almost continuously throughout the assessment. He was afebrile. There were no signs of respiratory distress and he was not hypoxemic (S_aO_2 98% on room air). He was not tachypneic and was hemodynamically stable. There were no findings on chest examination, specifically no adventitious sounds and no wheezing, even on forced expiration. The remainder of his physical examination was unremarkable and unchanged from previous. The profound myelosuppression had resolved (Table 1). A chest radiograph revealed new findings in the form of diffuse reticulonodular interstitial disease, in addition to previously documented bilateral pulmonary metastases. Given the course of events, the recovery from myelosuppression and the lack of infectious signs, his symptoms were managed as drug-induced interstitial pneumonitis. Pulmonary function tests were not done at this time. An empiric course of oral corticosteroids was initiated with prednisone 50 mg p.o. daily and he was given a return appointment 1 week later. Telephone contact was maintained regularly and within 48 h of steroid therapy he had experienced a marked improvement of the cough. By the follow-up visit on 27 July he described the cough as 80% better, correlating with substantial radiographic improvement of the reticulonodular interstitial disease.

The steroids were rapidly tapered over the following 2 weeks but unfortunately the cough had returned by the time he was seen in follow-up on 10 August. The clinical examination was similar to that of 20 July, except that there was audible wheezing and he was febrile at 38.9°C. The chest radiograph remained unchanged. The prednisone was increased to 50 mg/day, to be tapered more slowly. He was asymptomatic

Table 1. Laboratory profile

	Normal value	Pre-treatment	07/06	29/06 CPT-11 1A	06/07 1B held	13/07 1C held	20/07 clinic visit	27/07 clinic visit	10/08 clinic visit	19/09 clinic visit	05/10 clinic visit
Hb		132	123	111	104	101	108	117	123	127	114
WBC		4.6	6.1	4.2	1.1	0.9	18.1	7.9	9.2	5.1	8.1
Neutrophils		3.2	4.3	3.1	0.3	0.2	15.5	5.6	7.3	3.9	6.5
Eosinophils		0.1	0	0	0	0	0.2	0.1	0.2	0	0.1
Platelets		113	81	115	78	91	170	189	127	76	203
Bilirubin (total)		40					14				15
AST		59					43		108		50
ALT		71					59				52
ALP		228					358				314
CEA		11.0				20.7					

on 50 mg of prednisone/day when assessed on 17 August. By 17 September, the dose of prednisone was 10 mg/day. Unfortunately, within 4 days his symptoms had returned to the point he required admission to hospital on 24 September. A chest radiograph revealed no infiltrate but slight progression of the metastatic nodules. Pulmonary function testing was normal. Although an even slower prednisone taper was planned, the patient's symptoms would return with each attempt. He remains on 40 mg of prednisone as of the last assessment on 14 December with no further resurgence of his symptoms. Further therapy with irinotecan has been abandoned and he has been offered a palliative course of mitomycin, as there has been radiographic evidence of progression in all previously documented sites of disease.

Background

A variety of new agents are being tested in advanced colorectal cancer with promising results. One of these agents, irinotecan (CPT-11), a semisynthetic camptothecin derivative, can induce objective tumor responses in approximately 15% of patients with metastatic colorectal cancer after failure of 5-FL plus leucovorin chemotherapy. Two randomized trials using a 3-week schedule of irinotecan in patients with 5-FU-refractory disease have demonstrated a significant improvement in 1-year survival for patients treated with irinotecan compared with those receiving best supportive care (BSC) (36 versus 14%),[1] and when compared to patients retreated with 5-FU infusion regimens (45 versus 32%).[2] The quality of life of patients on irinotecan was better than that of patients on BSC but no different from that of patients on 5-FU chemotherapy.

Pneumonitis following irinotecan administration has been reported in 1.8% of patients enrolled in the early Japanese registration trials.[3,4] Most of these individuals had primary lung cancer and the exact contribution of irinotecan to the pulmonary events remains unknown. The clinical presentation was that of dyspnea and fever, with a reticulonodular pulmonary infiltrate. Although empiric steroid therapy was recommended, some patients have died from progressive pulmonary insufficiency that was attributed to irinotecan-associated pulmonary toxicity. As a result of these observations, few patients with compromised pulmonary function were enrolled in US clinical trials. In the pivotal phase II US studies,[5–9] pulmonary events were assessed in detail and dyspnea of any grade throughout the course of treatment was reported by 22% of patients, half of whom had lung metastases. Grade 3/4 dyspnea was reported by only 3.6% of patients and over half of these also had lung metastases. Cough of any severity was recorded in 17.4% of patients, achieving grade III/IV in only 0.3% of patients. Diffusion capacity (DLCO) was assessed at baseline and at least once during or upon completion of treatment in 21% (64 of 304) of patients enrolled in the pivotal studies.[5,6,8,9] Although a small but statistically significant decline in DLCO was seen over the course of treatment (mean baseline DLCO: 90.3 l/s and mean follow-up DLCO: 83.9 l/s), it was not felt to be clinically significant given the inherent variability in evaluation and the broad ranges spanned. In addition, no correlation between cumulative irinotecan dose received and declining DLCO was seen. Pulmonary fibrosis has not been described during treatment with irinotecan in any patient enrolled in the US phase II studies and no patient has discontinued therapy primarily due to pulmonary events. Two patients did discontinue therapy in association with pulmonary events potentially related to the study drug[6,8,10]. One individual without pulmonary metastases developed grade 3 episodic dyspnea of uncertain etiology. The other patient had lung metastases and developed grade 1 dyspnea and a decline in DLCO. In both cases, the respiratory symptoms were not the primary cause of discontinuation of treatment. Of the 481 patients enrolled in phase I and II clinical trials in the US up until December of 1995, only one (0.4%) has died of pulmonary toxicity possibly related to irinotecan administration. This individual developed adult respiratory distress syndrome in the setting of polymicrobial sepsis, although the investigator felt that a potential relationship between the respiratory failure and irinotecan could not be excluded.

Discussion

Our patient had pre-existing pulmonary pathology from involvement with metastatic disease as well as a remote lobectomy. He also had an intermittent cough of unknown etiology as well as an unconfirmed history of reactive airway disease, although never requiring more than inhaled β-agonists for symptom relief. He was a lifelong non-smoker. It is possible that our patient was at higher risk for pulmonary toxicity on the basis of these co-existing conditions. Similarly, pre-existing hepatic metastases might have affected drug handling capacity and possibly made him more susceptible to an adverse event. However, he had been asymptomatic since the time of diagnosis and with minimal biochemical abnormalities at the time of treatment. The manufacturer does not recommend any

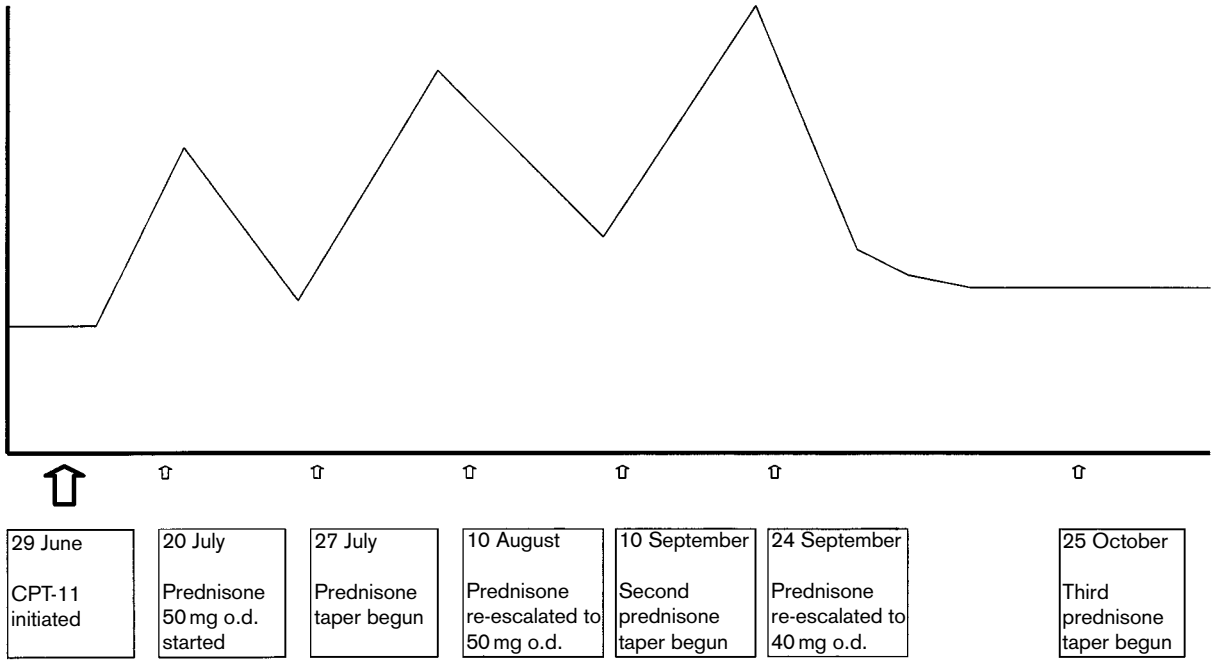

Figure 1. Symptom course.

dose modification for patients with hepatic metastases in the absence of hepatic dysfunction.

Deaths from progressive pulmonary insufficiency have been reported, in spite of institution of empiric steroid therapy for a syndrome similar to that which our patient experienced. The contribution of irinotecan to this process remains unknown, as all those individuals had pulmonary metastases, as well as non-malignant pulmonary disease in some. There are no published reports of attempts to rechallenge with irinotecan under these circumstances. As a result of these observations, patients with compromised pulmonary function were generally excluded from US clinical trials. Notwithstanding this, cough and dyspnea were reported in 17.4 and 22%, respectively, of patients in the US studies. While there is no baseline pulmonary function testing to compare to, current pulmonary function testing and diffusion capacity in our patient are normal as of the last clinical assessment on 30 September.

The severe neutropenia that this man experienced is unusual and may be taken as a surrogate for increased systemic exposure. One could speculate that such increased systemic exposure might also be associated with a higher likelihood of experiencing an uncommon side effect. The significance of the hives he developed on his right arm, a site remote from where the infusion was delivered, raises the possibility of an immunologically mediated reaction. While flushing and rashes were reported in 11.2 and 12.8% of patients, respectively, in the pivotal US studies, hypersensitivity reactions are not described in the product monograph. At no time was eosinophilia seen in this patient in the course of this episode.

As it is becoming common to offer treatment with irinotecan to select patients with good performance status in whom 5-FU-based chemotherapy has failed and as the clinical indications for the use of this agent expand, we present irinotecan-associated interstitial pneumonitis as a serious potential adverse effect. Patients with pre-existing pulmonary disease may be at higher risk for this complication and clinicians should be alert to this possibility.

References

1. Cunningham D, Pyrhonen S, James RD, *et al*. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998; **352**: 1413–8.
2. Rougier P, Van Cutsem E, Bajetta E, *et al*. Randomised trial of irinotecan versus fluoruracil by continuous infusion after fluoruracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; **352**: 1407–12.
3. Fukuoka M, Niitani H, Suzuki A, *et al*. A phase II study of CPT-11, a derivative of camptothecin, for previously untreated non small cell lung cancer. *J Clin Oncol* 1992; **10**: 16–20.

4. Masuda N, Fukuoka M, Kusunoki Y, *et al*. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. *J Clin Oncol* 1992; **10**: 1225–9.
5. Rothenberg ML, Eckardt JR, Kuhn JG, *et al*. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. *J Clin Oncol* 1996; **14**: 1128–35.
6. Pitot HC, Wender DB, O'Connell MJ, *et al*. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1997; **15**: 2910–9
7. Von Hoff DD, Rothenberg ML, Pitot HC, *et al*. Irinotecan (CPT-11) therapy for patients with previously treated metastatic colorectal cancer (CRC): overall results of FDA-reviewed pivotal US clinical trials. *Proc Am Soc Clin Oncol* 1997; **16**: 228a (abstr 803).
8. Upjohn. *In-house data for irinotecan* 1999.
9. Upjohn. *Camptosar® product monograph* 1999.
10. Conti JA, Kemeny NE, Saltz LB, *et al*. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. *J Clin Oncol* 1996; **14**: 709–15.

(Received 22 July 2000; accepted 1 August 2000)