Case Reports in Oncology

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413

Published online:
November 14, 2012

ISSN 1662–6575
www.karger.com/cro

Laparoscopic Splenectomy in Colorectal Cancer Patients with Chemotherapy-Associated Thrombocytopenia due to Hypersplenism

David A. Litvak[a] Salman Malad[b, c] Robert A. Wascher[a]
Maurie Markman[d] Jiaxin Niu[b]

Departments of [a]Surgery and [b]Medical Oncology, Cancer Treatment Centers of America at Western Regional Medical Center, Goodyear, Ariz., [c]Department of Medical Oncology, Cancer Center of Acadiana, Lafayette, La., and [d]Department of Medical Oncology, Cancer Treatment Centers of America, Philadelphia, Pa., USA

Key Words
Laparoscopic surgery · Splenectomy · Hypersplenism · Splenomegaly · Thrombocytopenia · Colorectal cancer · Neoplasm metastasis

Abstract
Background: Hypersplenism due to chemotherapy-related liver injury has been associated with severe thrombocytopenia that may preclude continuation of systemic therapy for cancer patients. Patients treated for metastatic colorectal cancer (mCRC) are among the most common patients affected by hypersplenism. Cessation of systemic therapy invariably leads to progression of disease. While partial splenic embolization has been employed successfully to reverse the effects of hypersplenism, the role of laparoscopic splenectomy for this problem has not been completely defined.
Methods: A retrospective review was conducted of mCRC patients treated with laparoscopic splenectomy at our institution to reverse severe thrombocytopenia due to chemotherapy-related hypersplenism. An endpoint assessed was the ability to resume therapy after splenectomy.
Results: Six patients with mCRC and hypersplenism requiring cessation of systemic therapy underwent laparoscopic splenectomy. All (6) patients had a postsurgical platelet count >150 × 10^3/μl and resumed chemotherapy after surgery. Median platelet count prior to surgery was 66 × 10^3/μl, and just prior to resuming systemic therapy it was 399.5 × 10^3/μl. Median spleen size was 14.0 cm. There were no surgical complications. Mean hospital stay was 2.8 days and the median time from surgery to resumption of therapy was 23.5 days.

David A. Litvak, MD

Cancer Treatment Centers of America at Western Regional Medical Center
14200 W. Fillmore Street
Goodyear, AZ 85338 (USA)
E-Mail david.litvak@ctca-hope.com

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

Conclusions: Laparoscopic splenectomy appears to offer selected patients with mCRC the opportunity to resume systemic therapy that otherwise would be discontinued due to thrombocytopenia from hypersplenism.

Introduction

Metastatic colorectal cancer (mCRC) affects approximately 50,000 people a year [1]. The cornerstone of treatment for these patients is systemic chemotherapy, especially with oxaliplatin-based regimens. Acquired thrombocytopenia is a condition that complicates treatment with many chemotherapy regimens. Of the known mechanisms of chemotherapy-induced thrombocytopenia, bone marrow suppression is the most common. Oxaliplatin is also associated with two other etiologies of thrombocytopenia. The first etiology is rare and is related to drug-specific antiplatelet antibodies [2, 3]. The second etiology is much more common and is related to hypersplenism due to portal hypertension as a result of oxaliplatin-induced hepatic sinusoidal injury [4–12]. This effect of oxaliplatin is largely reversible and the size of the spleen as well as platelet counts may return to baseline over 18–24 months following discontinuation of therapy [4, 11]. Other chemotherapeutic agents, including 5-fluorodeoxyuridine and irinotecan have also been associated with thrombocytopenia due to hypersplenism but to a much lesser degree than oxaliplatin [4, 8, 13].

Unfortunately, prolonged withdrawal of a drug causing the thrombocytopenia in the presence of active metastatic disease may preclude systemic treatment indefinitely. Cessation of otherwise effective treatment in patients with mCRC is generally associated with progression of their disease. Partial splenic embolization (PSE) has been shown to reverse hypersplenism and to allow certain cancer patients to resume chemotherapy [13, 14]. Splenectomy, on the other hand, while utilized under other circumstances, has not been well described for the treatment of hypersplenism due to chemotherapy [15–20]. Nonetheless, prior studies have demonstrated the value of splenectomy in slightly different clinical scenarios. Splenectomy has allowed patients with viral hepatitis and hepatocellular cancer (HCC) to start or resume antiviral therapy in addition to cancer-specific interventions [15–20]. In the present study, we retrospectively reviewed the use of laparoscopic splenectomy in patients with hypersplenism-related thrombocytopenia related to the systemic treatment of mCRC.

Methods

Between March 2010 and May 2012, 6 patients (4 males, 2 females) who were diagnosed with mCRC and experienced persistent thrombocytopenia associated with splenomegaly underwent laparoscopic or hand-assisted laparoscopic splenectomy to correct thrombocytopenia requiring cessation of chemotherapy (**table 1**). The patients' median age was 51.8 years (range 43–66). In this study, medical records were retrospectively reviewed and the data utilized were de-identified and password-secured. The study was granted exemption status by our Institutional Review Board.

Splenomegaly was defined by a single measurement of the long axis of the spleen by computed axial tomography (CT) scan greater than 9.76 cm as described by Bezerra et al. [21]. Median splenic length in our study was 14.0 cm (range 9.8–20). Five of the 6 patients underwent bone marrow aspiration to exclude bone marrow suppression as a cause of thrombocytopenia. The results of all 5 aspirates were normal (data not shown). Patients were evaluated for causes of thrombocytopenia

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

other than hypersplenism and bone marrow suppression, where applicable. There was no evidence of portal vein thrombosis in any of these patients.

In all cases, splenectomy was initiated laparoscopically. In 2 cases, this was converted to a hand-assisted laparoscopic approach due to the size of the spleen. This cohort of patients represents all patients with mCRC with treatment-related hypersplenism referred for possible splenectomy. Patients were admitted postoperatively to the hospital with patient-controlled analgesia and were converted to oral pain medication as determined by their level of pain. Patients were discharged when they tolerated a diet and their pain was controlled with only oral medication (in addition to any baseline pain medication patients might have used for unrelated and pre-existing pain issues; 1 patient).

The endpoints of the study were platelet counts >150 × 10^3/μl and the resumption of chemotherapy after splenectomy. Additional data collected were pre- and post-splenectomy platelet counts, perioperative complications and readmission rates within 30 days of surgery, length of hospital stay, overall survival since diagnosis of mCRC, and overall survival following surgery.

Results

In the 4 patients who underwent laparoscopic splenectomy and the 2 patients who had laparoscopic converted to hand-assisted laparoscopic splenectomy, the mean length of hospital stay was 2.8 days (range 2–4). There were no complications. One patient was admitted within 30 days of surgery for shortness of breath related to his underlying pulmonary disease and was discharged within 23 h.

In all patients, platelet counts returned to >150 × 10^3/μl after splenectomy (fig. 1). The median lowest platelet count was 66 × 10^3/μl (range 57–77) prior to splenectomy. Immediately prior to splenectomy, the median platelet count was 94 × 10^3/μl (range 59–126). Within 4 weeks post-splenectomy, platelet counts increased to a median of 631.5 × 10^3/μl (range 465–759) and remained at a median of 399.5 × 10^3/μl (range 280–506) immediately before resuming chemotherapy.

All 6 patients resumed systemic treatment after splenectomy. The median time to treatment after splenectomy was 23.5 days (range 14–90). Some patients resumed treatment with bevacizumab, which was not initiated until approximately 8 weeks after splenectomy (data not shown). The mean number of systemic therapy regimens (including targeted therapies and single or multiple combined agents) prior to splenectomy was 1.8 (range 1–4), with all patients having received oxaliplatin. After splenectomy, the mean number of regimens utilized for these 6 patients was 2.2 (range 1–3). When comparing regimens used before and after splenectomy, there was overlap of parts of chemotherapy regimens in 5 out of 6 patients. Of the 6 patients who underwent splenectomy, 5 are alive and currently continuing treatment (data not shown). For the entire group, the mean overall survival from the date of diagnosis of mCRC was 32.9 months (range 15.5–75) with a mean survival after splenectomy of 10.4 months (range 2.1–19.0).

Discussion

Thrombocytopenia due to hypersplenism may complicate adjuvant treatment with chemotherapy for colorectal cancer patients, but usually this problem is self-limited and reversible. This etiology of thrombocytopenia has been noted particularly in

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

patients who receive oxaliplatin [4–6, 8–10, 12]. In studies by Overman et al. [4] and Angitapalli et al. [11], splenomegaly in colorectal cancer patients who received adjuvant therapy with oxaliplatin resolved after 18–24 months. This type of thrombocytopenia, if it occurs during treatment for metastatic disease, is far more problematic. When persistent and significant thrombocytopenia develops during therapy for mCRC, chemotherapy must often be stopped, resulting in a significant risk of disease progression. Interventions directed at the spleen may allow patients with chemotherapy-induced hypersplenism to resume therapy. In this study, our cohort of 6 patients with mCRC who had developed hypersplenism precluding the continuation of systemic therapy were treated successfully with laparoscopic splenectomy allowing the resumption of chemotherapy in each patient.

PSE is an effective means of reversing thrombocytopenia due to hypersplenism. In the study by Kauffman et al. [13], somewhere between 79 and 96% of the cancer patients studied resumed systemic therapy after PSE [13]. Similar to our study, that study included 14 patients with mCRC, many of whom were treated with oxaliplatin prior to developing hypersplenism [13]. Although this previous study included a heterogeneous group of patients, a median survival of 9.4 months was noted after PSE [13]. In our study, including only patients with mCRC, we noted a mean survival of 10.4 months after splenectomy.

PSE also has been utilized to treat hypersplenism in patients with either viral hepatitis or HCC to facilitate initiating or resuming therapy [22–25]. In patients with hepatitis C, PSE resulted in greater patient adherence to the planned therapy with interferon [22]. In patients with HCC, PSE when combined with transcatheter hepatic arterial chemoembolization resulted in fewer bleeding complications due to the disease [23, 24]. Most of the limitations on using PSE relate to the systemic inflammatory effects or risk of complications due to ischemia of the spleen. These include abdominal pain, small bowel ileus, fever, and a risk of splenic abscess. These associations may be reflected in the length of hospitalization and generally are proportional to the volume of the spleen which is embolized [13, 23, 24].

Splenectomy is another effective way to address thrombocytopenia due to hypersplenism. The benefits of laparoscopic splenectomy have been shown in studies of patients with cirrhosis-related hypersplenism in which thrombocytopenia contributed to bleeding complications and/or limited treatment options [18, 19]. Some studies, although not performed in a randomized fashion, also suggest that splenectomy actually may extend survival and, in that regard, may be superior to PSE among patients with HCC [15, 19]. In our study, the mean survival from diagnosis of mCRC was 32.9 months, during which time patients received an average of 2.2 different treatment regimens after splenectomy. The mean length of hospitalization in the present study of 2.8 days also compares favorably with the 4.5 days reported previously for PSE.

Our study represents a highly select patient population, which is a limitation of the study. Nonetheless, our results and those of others suggest that laparoscopic splenectomy is a viable option to address treatment-related hypersplenism. Oxaliplatin and to a lesser degree other chemotherapy agents have been associated with hepatic injury and yet often remain the best treatment options for patients with mCRC. The extent to which thrombocytopenia due to hypersplenism complicates treatment with

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

oxaliplatin is unclear, but up to 24% of patients treated with oxaliplatin are thought to develop splenomegaly [4]. Laparoscopic splenectomy, like PSE, may represent an effective means to treat hypersplenism and allow such patients to resume treatment. Moreover, collectively, data regarding laparoscopic splenectomy or PSE suggest that these interventions may improve longevity with low associated morbidity in cancer patients, especially patients with mCRC.

Disclosure Statement

There are no financial or funding source disclosures from any authors.

Table 1. Patient characteristics

Patient No.	Age years	Gender	Spleen size, cm	Distribution of metastasis	Procedure	Survival since splenectomy months	Survival since diagnosis of mCRC, months
1	51	F	13	liver	Lap	19	34.7
2	66	F	9.8	multiple	Lap	10.8	19.9
3	43	M	15.5	multiple	HAL	14.6	28.4
4	55	M	20	multiple	Lap	12.6	23.6
5	49	M	13.4	liver	Lap	9.7	15.5
6	47	M	14.6	liver, lung	HAL	2.1	75.1

Lap = Laparoscopic splenectomy; HAL = hand-assisted laparoscopic splenectomy.

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

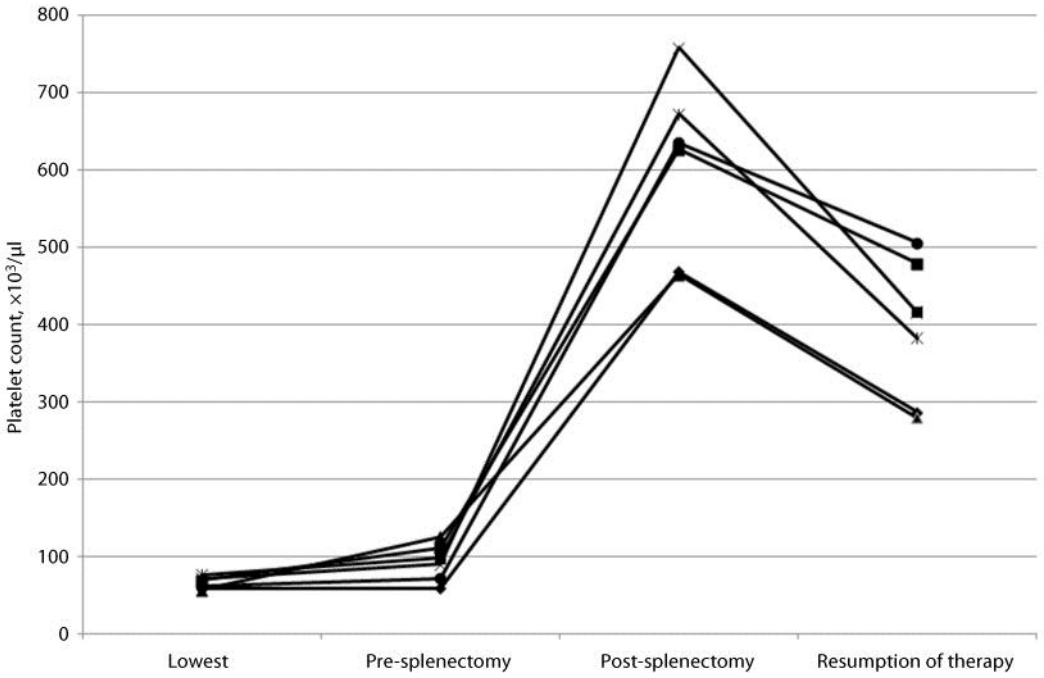

Fig. 1. Platelet counts of the 6 patients at different points in time before and after splenectomy. Median lowest platelet count was 66 × 10^3/µl (range 57–77). Immediately prior to splenectomy, the median platelet count was 94 × 10^3/µl (range 59–126). Within 4 weeks after splenectomy, platelet counts increased to a median of 631.5 × 10^3/µl (range 465–759) and remained at a median of 399.5 × 10^3/µl (range 280–506) immediately prior to resuming chemotherapy.

References

1 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
2 Dold FG, Mitchell EP: Sudden-onset thrombocytopenia with oxaliplatin. Ann Intern Med 2003;139:E156.
3 Curtis BR, Kaliszewski J, Marques MB, et al: Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. Am J Hematol 2006;81:193–198.
4 Overman MJ, Maru DM, Charnsangavej C, et al: Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010;28:2549–2555.
5 Kandutsch S, Klinger M, Hacker S, Wrba F, Gruenberger B, Gruenberger T: Patterns of hepatotoxicity after chemotherapy for colorectal cancer liver metastases. Eur J Surg Oncol 2008;34:1231–1236.
6 Slade JH, Alattar ML, Fogelman DR, et al: Portal hypertension associated with oxaliplatin administration: clinical manifestations of hepatic sinusoidal injury. Clin Colorectal Cancer 2009;8:225–230.
7 Soubrane O, Brouquet A, Zalinski S, et al: Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg 2010;251:454–460.
8 Rubbia-Brandt L, Audard V, Sartoretti P, et al: Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460–466.
9 Nakano H, Oussoultzoglou E, Rosso E, et al: Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008;247:118–124.
10 Ward J, Guthrie JA, Sheridan MB, et al: Sinusoidal obstructive syndrome diagnosed with superparamagnetic iron oxide-enhanced magnetic resonance imaging in patients with chemotherapy-treated colorectal liver metastases. J Clin Oncol 2008;26:4304–4310.

Case Rep Oncol 2012;5:601–607
DOI: 10.1159/000345413
Published online: November 14, 2012

ISSN 1662–6575
www.karger.com/cro

11 Angitapalli R, Litwin AM, Kumar PR, et al: Adjuvant FOLFOX chemotherapy and splenomegaly in patients with stages II–III colorectal cancer. Oncology 2009;76:363–368.

12 Miura K, Nakano H, Sakurai J, et al: Splenomegaly in FOLFOX-naive stage IV or recurrent colorectal cancer patients due to chemotherapy-associated hepatotoxicity can be predicted by the aspartate aminotransferase to platelet ratio before chemotherapy. Int J Clin Oncol 2011;16:257–263.

13 Kauffman CR, Mahvash A, Kopetz S, Wolff RA, Ensor J, Wallace MJ: Partial splenic embolization for cancer patients with thrombocytopenia requiring systemic chemotherapy. Cancer 2008;112:2283–2288.

14 Hiramoto K, Kuroki M, Nakano E, et al: Successful management with partial splenic embolization (PSE) of splenomegaly and thrombocytopenia caused by oxaliplatin-based chemotherapy for advanced colorectal cancer (in Japanese). Gan To Kagaku Ryoho 2011;38:835–839.

15 Hashimoto N, Akahoshi T, Tomikawa M, et al: Value of laparoscopic splenectomy as salvage treatment for relapsed thrombocytopenia after partial splenic arterial embolization. Dig Surg 2010;27:515–520.

16 Chen XP, Wu ZD, Huang ZY, Qiu FZ: Use of hepatectomy and splenectomy to treat hepatocellular carcinoma with cirrhotic hypersplenism. Br J Surg 2005;92:334–339.

17 Akahoshi T, Tomikawa M, Korenaga D, Ikejiri K, Saku M, Takenaka K: Laparoscopic splenectomy with peginterferon and ribavirin therapy for patients with hepatitis C virus cirrhosis and hypersplenism. Surg Endosc 2010;24:680–685.

18 Akahoshi T, Tomikawa M, Kawanaka H, et al: Laparoscopic splenectomy with interferon therapy in 100 hepatitis-C-virus-cirrhotic patients with hypersplenism and thrombocytopenia. J Gastroenterol Hepatol 2012;27:286–290.

19 Tomikawa M, Akahoshi T, Sugimachi K, et al: Laparoscopic splenectomy may be a superior supportive intervention for cirrhotic patients with hypersplenism. J Gastroenterol Hepatol 2010;25:397–402.

20 Shigekawa Y, Uchiyama K, Takifuji K, et al: A laparoscopic splenectomy allows the induction of antiviral therapy for patients with cirrhosis associated with hepatitis C virus. Am Surg 2011;77:174–179.

21 Bezerra AS, D'Ippolito G, Faintuch S, Szejnfeld J, Ahmed M: Determination of splenomegaly by CT: is there a place for a single measurement? AJR Am J Roentgenol 2005;184:1510–1513.

22 Tahara H, Takagi H, Sato K, et al: A retrospective cohort study of partial splenic embolization for antiviral therapy in chronic hepatitis C with thrombocytopenia. J Gastroenterol 2011;46:1010–1019.

23 Han MJ, Zhao HG, Ren K, Zhao DC, Xu K, Zhang XT: Partial splenic embolization for hypersplenism concomitant with or after arterial embolization of hepatocellular carcinoma in 30 patients. Cardiovasc Intervent Radiol 1997;20:125–127.

24 Zhu K, Meng X, Qian J, et al: Partial splenic embolization for hypersplenism in cirrhosis: a long-term outcome in 62 patients. Dig Liver Dis 2009;41:411–416.

25 Huang JH, Gao F, Gu YK, Li WQ, Lu LW: Combined treatment of hepatocellular carcinoma with partial splenic embolization and transcatheter hepatic arterial chemoembolization. World J Gastroenterol 2007;13:6593–6597.