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CASE REPORT

Prolonged survival in metastatic colorectal cancer following chemotherapy

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Key Clinical Message

The cost of treating metastatic colorectal cancer has increased significantly after the introduction of targeted antivascular therapies. We report the unusual case of a patient with colorectal cancer with several large liver metastases at diagnosis, who was cured after removal of the primary tumor and treatment with 5-FU/LV only.

Keywords

5-Fluorouracil, cancer, chemotherapy, colorectal, cure, metastatic.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in both men and women and the third most common type of cancer in the United States. Until 2000, 5-fluorouracil/leucovorin (5-FU/LV) had been the standard of therapy for metastatic colorectal cancer (mCRC). Response rates (RR) of 21% and overall survivals (OS) of 11.7 months have been reported with 5-FU/LV compared to 11% and 11 months, respectively, with 5-FU alone [1]. Long-term survival in patients with mCRC receiving palliative 5-FU/LV chemotherapy only has been described but it occurs rarely [2–4]. We report an unusual case of a patient with recto-sigmoid cancer with several large liver metastases at diagnosis who underwent surgery of the primary tumor, received chemotherapy with 5-FU/LV for 1 year, and currently is alive with disease-free survival of more than 12 years.

Case Report

A 72-year-old woman with past medical history of hypertension and bronchial asthma presented to the emergency department in August 2000 complaining of intermittent rectal bleeding accompanied by 6 months of colicky abdominal pain. Family history was unremarkable for cancer and the patient had never used tobacco or alcohol. She had stable vital signs and a normal physical examination on admission. An abdomino-pelvic CT scan revealed irregular thickening of the sigmoid colon, suggesting a nonobstructing sigmoid mass. Three hypodense liver lesions, measuring 8×5 cm, 6×5 cm, and 2 cm, respectively, also were noted (Figs. 1).

She subsequently underwent colonoscopy with a biopsy of the apple-core lesion at the recto-sigmoid junction, which came back positive for an adenocarcinoma. Then, she underwent recto-sigmoid resection and liver inspection during the surgical intervention. Two large liver masses were palpated. Examination of the surgical specimen revealed moderately differentiated adenocarcinoma with subserosal invasion and negative surgical margins. Metastatic adenocarcinoma was removed from the pericolic fat ($8 \times 4 \times 2.5$ cm mass). The tumor was staged as T3N1M1. Carcinoembryonic antigen (CEA) levels were 9.14 ng/mL before surgery. Palliative chemotherapy was initiated within 4 weeks following resection, with the Roswell Park regimen [5] consisting in weekly 5-FU (500 mg/m^2) and LV (20 mg/m^2) for 6 weeks followed by a 2-week drug-free period for 1 year. She received the last dose of chemotherapy in September 2001. Of note,

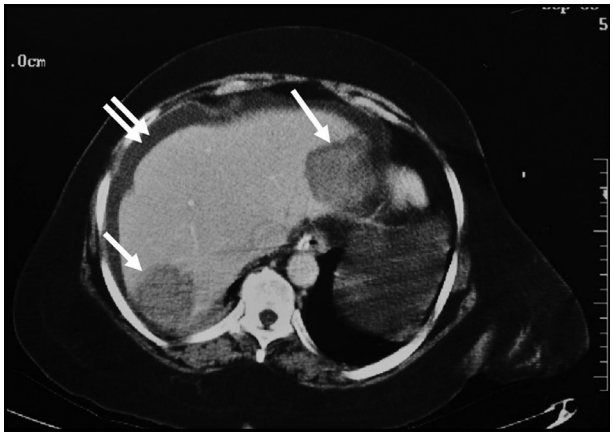

Figure 1. Postcontrast CT image through the upper abdomen at initial presentation showing two large hypo-attenuating masses in the right and left hepatic lobes, respectively, (single arrows). Note the perihepatic ascites (double arrows).

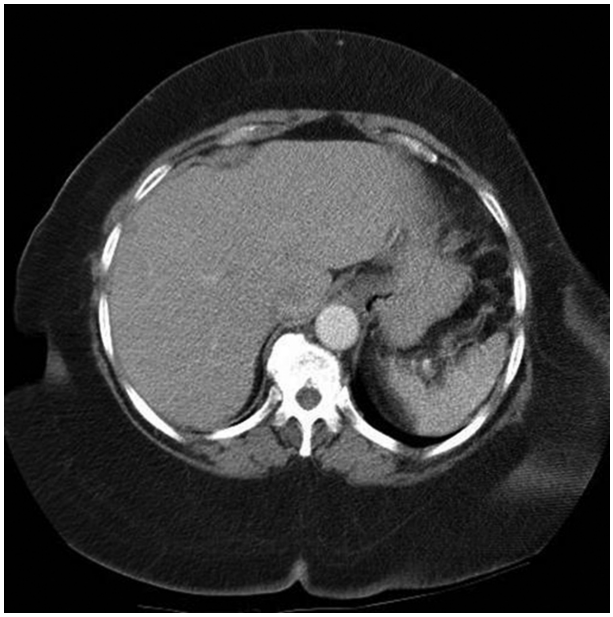

Figure 2. Postcontrast CT image through the upper abdomen acquired 10 years after the initial presentation demonstrates no residual or recurrent masses within the liver.

1 month following the initial diagnosis of colon cancer, the patient was readmitted to the hospital in September 2000 for an acute saddle pulmonary embolism. Anticoagulation with Coumadin was initiated and the patient was maintained on Coumadin until the present time.

A CT scan of the abdomen 3 months after completion of 1 year of chemotherapy revealed complete resolution of liver metastases. CEA levels decreased as well, from 9.14 ng/mL at diagnosis to 0.5 ng/mL 2 months after surgery. No mucosal recurrence was seen on follow-up colonoscopies in August 2005 and January 2009. Yearly follow-up CT scans of the abdomen and pelvis were grossly normal (Fig 2). The last CT scan of the abdomen and pelvis, done in September 2013, did not reveal any signs of metastatic disease. She has been in complete remission since 2001, off all treatment, with no evidence of tumor recurrence as of 6 September 2013. A complete sequencing of her genome done at Ludwig Center for Cancer Research did not reveal any salient features that may explain her long survival (Dr. Bert Vogelstein, pers. commun.).

Discussion

Survival of patients with mCRC has advanced steadily over the past decade. A retrospective review done on 2470 patients followed at two large cancer centers, MD Anderson and Mayo Clinic, found that the OS rate increased from 9.1% for patients diagnosed in 1990–1997 to 13% for those diagnosed in 1998–2001, 19.2% for those diagnosed in 2001–2003, and an estimated 5-year survival rate of 32% for patients diagnosed in 2004–2006 [6]. These improvements were likely due to both an increase in the number of hepatic metastetectomies and more efficacious chemotherapy regimens.

In 2000, Saltz published the results of a randomized Phase III study that compared Irinotecan and bolus 5-FU/LV with the Mayo Clinic regimen of 5-FU/LV. In this study, the Irinotecan combination demonstrated a near doubling of response rate (51% vs. 28%) [7]. Almost at the same time, in a European trial, de Gramont showed that an Oxaliplatin/infusional 5-FU/LV regimen (FOLFOX4) compared with 5-FU/LV alone produced a 51% versus 22% response rate, also with a statistically significant improvement in progression-free survival (9.0 months vs. 6.2 months) [8]. The median OS for patients with metastatic colon cancer treated with a 5-fluorouracil (5-FU)-based regimen improved from approximately 12 months to an OS of more than 18 months with the FOLFOX regimen [9]; primarily, it has been the newer combinations of chemotherapy and biological agents such as Bevacizumab, Cetuximab, and Panitumumab that led to a substantial jump in OS, which went beyond 2 years in some studies [10].

As per current NCCN guidelines (v.3.2014), combination therapy with FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI and Bevacizumab, Cetuximab, or Panitumumab as well as 5-FU/LV or Capecitabine alone or in combination with Bevacizumab are recommended regimens for the first-line treatment of mCRC.

In rare cases, mCRC patients may have prolonged survival with 5-FU-based regimens. There have been three

Table 1. mCRC long-term survival case series.

No. of patients treated only with chemotherapy with LTS	Treatment duration (months)	No evidence of disease (years) after CR	Percentage of patients achieving LTS	Reference
13	21 (average)	7.6–23	0.34%	[2]
3	8–12	6.3–13.5	0.67%	[3]
6	10–54	6.9–14.4	0.24%	[4]

case series published so far that showed long-term survival (LTS) of mCRC treated with systemic chemotherapy alone (Table 1).

The North Central Cancer Treatment Group and Mayo Clinic reported long-term survival beyond 5 years from initiation of chemotherapy for mCRC [2]. This study included patients treated from 1972 to 1995. Thirteen patients out of 3407 treated with chemotherapy (0.4%) had no evident site of disease involvement for >5 years from last treatment. The longest survival achieved in this series was 23 years after completing the chemotherapy. Twelve out of the thirteen patients who achieved LTS were treated with 5-FU-based regimens. The second study was a retrospective review of 2751 patients who presented with mCRC at MD Anderson from 1990 to 2003. [3]. In the final analysis, 2541 patients were included, of which six (0.24%) were without evidence of disease after an average follow-up of 10.3 years. In this series, the longest survival achieved was 15.1 years after diagnosis. The use of 5 FU-based regimens also was associated with LTS in this series, as five of the six patients who achieved LTS were treated with 5-FU-based regimens. A third study, published in the French literature, included 445 mCRC patients; three patients treated with 5-FU-based chemotherapy (of whom one was lost from follow-up after 6.3 years) achieved complete remission [4]. In this series, the longest survival achieved was 14 years. However, one of the limitations of studies and case reports on LTS is that the inherent tumor biology is unknown; thus, the contribution of this variable to treatment-associated LTS cannot be established and remains a potential confounding factor [2]. In general, it is difficult to distinguish between cases where response to treatment (i.e., complete remission) prolongs survival and cases where the favorable prognosis is due to intrinsic patient factors differing from response [11]. Individual patients may have both tumors that are uniquely sensitive to chemotherapy and genetic or epigenetic characteristics that confer them a survival advantage.

5-FU/LV still may be an effective treatment for a small subgroup of patients with tumors sensitive to this drug combination. 5-FU is a fluoropyrimidine that inhibits thymidylate synthase, which leads to inhibition of DNA synthesis and DNA repair [12]. Leucovorin (LV) is added to it in order to enhance its effect on cancer metabolism. Significant attempts have been made in order to identify biomarkers associated with 5-FU/LV response, with particular attention given to the enzymes involved in the metabolism of 5-FU. The results evaluating the levels of thymidylate synthase, thymidine phosphorylase, and dihydropyrimidine dehydrogenase have been inconclusive (reviewed in [13]). In 2003, using a gene expression profiling approach, John et al. described a panel of 50 genes significantly associated with 5-FU response [13]. More recent clinical data suggest an association between 5-FU response and replication error status. In an in vitro study using a large panel of CRC cell lines, 5-FU response was associated significantly with mismatch repair deficiency [14]. Also, a recent meta-analysis that reviewed data from 2,402 patients receiving 5-FU treatment for CRC found that the thymidylate synthetase genotype of the lowest protein expression (2R/2R) was associated significantly with improved clinical benefit (the pooled risk ratio was relative risk = 1.36 [1.11, 1.65]; $P = 0.003$); however, this effect size was too small to be considered clinically useful [15].

In our patient, the complete sequencing of her genome was noncontributory, but it is possible that her long survival may have been related to still unidentified specific genetic or epigenetic factors.

The resection of the primary tumor may have also had an impact on the LTS of our patient. Five of the six patients in the MD Anderson series underwent resection of their primary tumor and all three patients from the French series had their primary tumor resected. The status of the primary tumor was not reported in the series from North Central Cancer Treatment Group and Mayo Clinic. A multivariate analysis of 1155 individual patients' data from four randomized trials presented in 2012 at ASCO confirmed that primary tumor resection in patients with CRC and unresectable metastasis was an independent predictor of better OS (HR: 0.63 [0.53–0.75]; $P < 0.0001$) and may be a surrogate for progression-free survival (PFS) (HR: 0.82 [0.70–0.95]; $P = 0.0007$) [16].

Did Coumadin anticoagulation given in combination with the 5FU/LV chemotherapy plays a role in this patient's long-term survival? Thirty years ago, a study on the clinical and pharmacokinetic effects of combined Warfarin and 5-FU in advanced colon cancer showed a greater overall median survival for patients who received the combined therapy of Warfarin and 5-FU (19.2 months), but these earlier results were never reproduced [17]. Warfarin is extensively metabolized by several cytochrome P450 enzymes. 5FU is not a substrate for hepatic drug metabo-

lizing CYP enzymes but an interaction between 5FU and the CYP enzymes has been previously described [18, 19]. No toxicity related to the concomitant use of 5FU and Warfarin was observed in our patient.

Conclusion

The cost of treating mCRC has increased dramatically after the introduction of targeted antivascular therapies.

Colorectal cancer is a heterogeneous disease with a wide variety of biologic abnormalities, making each patient and each tumor unique. 5-FU/LV still may be an effective treatment for a small subgroup of patients with tumors that are sensitive to this drug combination. The development of more refined molecular biology techniques may allow oncology practitioners to predict which patients may benefit from this combination. Our case demonstrates the possibility of curing mCRC using 5-FU/LV, even in patients bearing a high tumor burden.

Conflict of Interest

None declared.

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