

Chemotherapy with thalidomide, celecoxib, valproic acid, and irinotecan enabled resection of liver metastases in patients with initially unresectable metastatic colorectal cancer: case report

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Abstract

Despite improvements in chemotherapies and biological agents, colorectal cancer (CRC) with liver metastases largely remains incurable. Oxaliplatin-irinotecan based chemotherapy allows 12.5% of patients with unresectable colorectal liver metastases to be rescued by liver surgery. Surgical resection offers the best opportunity for survival in patients with CRC metastatic to the liver. Therefore we proposed the combination method with thalidomide, celecoxib, valproic acid and low-dose irinotecan as a way to be expected considerably effective in a short period of time and regressive in image. We report two cases of CRC with liver metastases that had a favorable response to thalidomide, celecoxib and the histone deacetylase inhibitor valproic acid with low dose irinotecan infused metronomically.

Keywords:

thalidomide, celecoxib, valproic acid, CRC with liver metastases, liver resection

Introduction

The treatment of colorectal cancer accompanied by liver metastases is considerably difficult. Approximately 50% of the patients tend to have involvement of liver during the course of their disease [1](#)). Approximately 80% of patients with colorectal liver metastases present with unresectable disease at diagnosis [2](#)). Oxaliplatin-irinotecan based chemotherapy allows 12.5% of patients with unresectable colorectal liver metastases to be rescued by liver surgery. Despite a high rate of recurrence, 5-year survival is 33% overall, with a wide use of repeat liver and extrahepatic resections [3](#))

Therefore we proposed the combination method with thalidomide, celecoxib, valproic acid and low-dose irinotecan as a way to be expected considerably effective in a short period of time and regressive in image.

Case Reports

Patient 1 was a 64-year-old woman who was diagnosed with sigmoid adenocarcinoma (T4aN2bM1a) in September 2014. On imaging (computed tomography [CT] of chest, abdomen, and pelvis), there was no chest metastasis except multiple liver metastases. On October 10, 2014, she underwent a laparoscopic low anterior resection (sigmoid and rectal resection) being diagnosed with sigmoid colon cancer. The final pathology reading demonstrated moderately differentiated tubular adenocarcinoma invading through the subserosa with 10 out of 29 lymph nodes infiltrated by carcinoma. She was found to have enlarging liver metastases after the laparoscopic rectosigmoid resection at Shizuoka Cancer Center in Japan.

The patient received adjuvant chemotherapy with oxaliplatin, capecitabine(XELOX) from November 5, 2014, but because of poor tolerance this treatment was changed after 2 cycles to thalidomide 200mg/day, celecoxib 400mg/day, valproic acid 600mg/day and irinotecan 40mg/ week(TCVI therapy)from January 6, 2015.

The first restaging CT of chest, abdomen, and pelvis after 2 months of FOLFOX therapy showed disease progression, and the second restaging after 2 months of thalidomide therapy showed an improvement to be able to resect liver metastases. The operation has been postponed without reason. She continued on TCVI therapy for 6 months. On August 8 2015, she underwent liver resection, which removed S2/3, S6/8,S8(moderately differentiated adenocarcinoma) and then continued on chemotherapy with UFT/LV from September 2015 to March 2016.

She remained progression-free until March 2016, when she was found to have enlarging pulmonary metastases and para-aortic lymph nodes. Then in April 2016, chemotherapy was initiated with thalidomide 200mg/day, celecoxib 400mg/day, sorafenib 200mg/day and irinotecan 40mg/ week, resulting in stable disease.

Patient 2 was a 47-year-old man who was diagnosed with adenocarcinoma of transverse colon in February 2016. A CT of chest, abdomen, and pelvis showed distant metastases (T4N2M1)-multiple liver metastases. On February 15, the patient then underwent regional treatment for colon cancer with stent placement. Eventually, he was diagnosed to be unresectable because the main lesion adhered to stomach, and the liver metastases were multiple. From March 1 2016, he received 1 month of adjuvant chemotherapy with thalidomide 200mg/day, celecoxib 400mg/day, valproic acid 600mg/day and irinotecan 40mg/twice a week (TCVI therapy) with a response noted in a follow up CT (T4aN1bM1b Stage IVB). The total dose of irinotecan a month was 360mg.

Then he was referred to Shizuoka Cancer Center in Japan, the first restaging CT of chest, abdomen, and pelvis after 5 weeks of therapy showed an improvement to be able to resect primary lesion and liver metastases. But his operation, because of stent setting, was rejected as a TREATMENT POLICY.

Discussion

In order to achieve increased survival in patients with unresectable CRC with liver metastases, liver surgery should be proposed to all patients with unresectable metastases responding to chemotherapy²). To increase the resectability, the improvement of chemotherapy is essential.

This is the first immunomodulatory⁴) and epigenetic chemotherapy of CRC with liver metastases.

Thalidomide has been shown to have antiangiogenic and immunomodulatory effects, including the inhibition of vascular endothelial growth factor, basic fibroblast growth factor and tumor necrosis factor alpha. The reported biological consequences of COX-2 up-regulation include inhibition of apoptosis, increased metastatic potential and promotion of angiogenesis. These events may contribute to cell transformation and tumor progression. Antiangiogenesis represents a significant new strategy for cancer treatment⁵); however, most tumors are biologically heterogeneous, especially in endothelial cell diversity. As vessels of most solid tumors are structurally and functionally abnormal, tumor vessels differ from normal blood vessels in their responses to antiangiogenic agents⁶)

COX inhibitors have been shown to inhibit proliferation, induce apoptosis, inhibit angiogenesis, reduce carcinogen activation, and stimulate the immune system⁹).

Therapy with specific COX-2 inhibitors might be an effective approach to colorectal cancer prevention and treatment¹⁹. Because thalidomide does not completely inhibit COX-2 expression or PG biosynthesis, a therapeutic strategy combining celecoxib with thalidomide might be more effective than using either agent alone. Thalidomide and celecoxib have different mechanisms of action and activity in various malignant tumors. Both have been evaluated and shown to demonstrate activity against CRC with liver metastases¹⁰) and other solid tumors^{8,9,10,11,12,13}).

Thalidomide decreased the stability of TNF-mRNA and COX-2 mRNA⁷). A combination of molecular target inhibitors (thalidomide and celecoxib) and standard cytotoxic drugs appear to increase efficacy of each drug, decrease the side effects of cytotoxic drugs and prolong life¹⁰). In order to accomplish new treatment strategies for CRC with liver metastases, we have been using thalidomide, celecoxib, valproic acid and irinotecan in low-doses. We

believe this combination represents a viable treatment for patients of colorectal cancer with recurrence or metastases.

VPA is a well established histone deacetylase (HDAC) inhibitor and affects cell growth in different types of cancer in vitro and in vivo as an epigenetic agent [14](#)). Epigenetic changes such as aberrant DNA methylation and histone acetylation are common in cancer, providing a strong rationale for the use of epigenetic therapies [15](#)). HDAC inhibitor have been shown to have antiproliferative activity through cell-cycle arrest, differentiation, and apoptosis in CRC cells, suggested that VPA can trigger the epithelial. mesenchymal transition (EMT) of CRC cells. [16](#))

When valproic acid is combined with irinotecan, a clinically significant interaction may lead to unintended, severe and even life-threatening adverse events [17](#)). But another report pointed out that the toxicity profile and plasma disposition of irinotecan and SN-38 were not strongly influenced by anticonvulsant valproic acid therapy [18](#)).

The in vitro experiments [19,20](#)) provide new cellular pathways affected by lenalidomide, a thalidomide derivative, propose new potential clinical uses, such as bone marrow regeneration, and suggest that the combination of lenalidomide with valproic acid may elevate the therapeutic index in the treatment of hematologic malignancies.

Combined VPA and celecoxib treatment also induced more cytotoxicity and apoptosis in neuroblastoma cells than individual drug treatment [21](#)). It is suggested that VPA can trigger the epithelial. mesenchymal transition (EMT) of CRC cells, more attention should be paid when VPA used as a new anticancer drug for CRC patients [22](#))

It is well known (probably known as Biot's principle) that the combination of low doses of cancer chemotherapeutic agents with different modes of action may produce synergistic effects on efficacy and minimize possible side-effects associated with high-dose administration [23](#)).

In summary, we demonstrated that thalidomide, celecoxib, valproic acid and irinotecan produced a strong synergy in growth inhibition of colorectal cancer, and this was associated with their synergistic actions on cell cycle arrest and apoptosis. Unfortunately this clinical trial, for the use of thalidomide, have been banned from the Japanese Ministry of Health, Labour and Welfare in the fact that cannot be maintained safety [24](#)). But various drugs like thalidomide, celecoxib, bortezomib, valproic acid and others have already entered clinical studies and show promising results to treat various types of cancer except Japan [25](#)).

We believed that chemotherapy with these agents enables resection of liver metastases in

patients with initially unresectable metastatic colorectal cancer.

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