Safety and Efficacy of Radiofrequency Ablation with Aflibercept and FOLFIRI in a Patient with Metastatic Colorectal Cancer

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Abstract. *Background: A vast majority of patients with metastatic colorectal cancer (mCRC) are not candidates for surgical resection. Radiofrequency ablation (RFA) is a safe and effective technique for treatment of isolated liver metastasis. After radiofrequency ablation, residual tumor can have aggressive growth, part of which is driven by the up-regulation of vascular endothelial growth factor (VEGF). Angiogenesis inhibitor bevacuzimab has been used in the management of mCRC with RFA. We present a patient with recurrent colorectal cancer and four hepatic metastases who was treated with RFA combined with aflibercept, another VEGF inhibitor and systemic chemotherapy. We believe that this is the first report of using aflibercept with RFA. Case report: A 35-year-old female with stage IV rectal cancer with metastasis to a lymph node and multiple hepatic metastases was treated with chemo-radiation, surgical resection of the tumor and surgical resection of two segments of the liver. She underwent RFA of the hepatic lesions that could not be resected. She received adjuvant chemotherapy consisting of 5-fluorouracil (5-FU) and oxaliplatin for a total of 6 months. However, a positron emission tomography (PET) scan showed progression of disease with new and growing lymph nodes. She was treated with 6 cycles of capecitabine monotherapy. A follow-up PET scan showed four new liver lesions. She has RFA of her four liver lesions and was started on a combination of aflibercept and FOLFIRI. She received 10 cycles and a repeat magnetic resonance imaging (MRI) and PET scan showed stable disease. Discussion: This is the first reported case of a patient managed with RFA with aflibercept, an anti-VEGF agent, and FOLFIRI. This case showed both efficacy, as well as safety for the combined modalities in the management of mCRC.*

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Colorectal cancer is the third most common cancer among both men and women in the USA and the second leading cause of cancer death (1). Liver is the most common site of metastasis for colorectal cancer. Approximately 50% of colorectal cancer patients will develop metastasis (2). Surgical resection is the only curative option for liver metastasis with a five-year survival reported to be 40-58% (3). A vast majority, as much as 80% of patients, have unresectable liver metastasis. Survival of such patients is limited to as much as 15-22 months (4). However, with the use of biological agents and local ablative therapies, these patients now have an increased chance for a better quality of life and overall survival.

The backbone for chemotherapy for metastatic colorectal cancer (mCRC) consists of fluoropyrimidines, irinotecan, and oxaliplatin (5). The first-line of treatment usually is doublet chemotherapy consisting of 5-fluorouracil (5-FU) and leucovorin (FU/LV), along with either oxaliplatin (FOLFOX) (6) or irinotecan (FOLFIRI) (7) combined with a biological agent. Another first-line treatment is capecitabine with oxaliplatin (XELOX) (8). An aggressive triplet regimen containing both oxaliplatin and irinotecan (FOLFOXIIRI) is sometimes used in patients who have limited liver metastases that might become potentially resectable (9). If patients are not able to tolerate an intensive regimen, single-agent 5-FU and leucovorin alone or in combination with bevacuzimab are an option (10).

The biologics used in metastatic colorectal cancer are either epidermal growth factor receptor (EGFR) antagonists, such as cetuximab or panitumumab or vascular endothelial growth factor (VEGF) antagonists, such as bevacizumab or aflibercept (11). Apart from these, a new drug regorafenib, a multikinase inhbitor, has been approved for use in patients

that have failed all approved standard therapies but still have a good performance status (12). The *RAS* mutation status allows us to select which patients might benefit from anti-EGFR therapy. Anti-EGFR monoclonal antibodies (cetuximab, panitumumab) should only be used in patients whose tumors are *RAS* wild-type, as those who have activating mutations in *KRAS* are resistant to anti-EGFR therapy (13). Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A). It is used as a component of first-line therapy with FOLFOX, FOLFIRI and FU/LV. More research is needed on who might benefit from the drug, as many patients have a variable response (14).

Aflibercept is a recombinant fusion protein. It acts as a soluble "decoy" receptor that binds VEGF-A, VEGF-B and placental growth factor (PIGF). This prevents their binding to their respective receptors (15). Aflibercept was approved in the United States for use in combination with FOLFIRI for the treatment of patients who have progressed on an oxaliplatin regimen or have become resistant to it (16). It was approved based on the results of the 2012 VELOUR trial. It showed significantly improved overall survival, progression-free survival and response rates compared to placebo for patients who had received prior oxaliplatin-containing regimen including the ones that had received bevacizumab (17).

Surgical resection remains the treatment-of-choice for hepatic metastasis whenever feasible and remains the only potentially curative option (18). However, a large number of patients are not able to get surgery due to the size or location of the tumor or due to a lack of adequate hepatic reserve. The options for these patients include systemic chemotherapy or regional hepatic artery chemotherapy, focal radiotherapy with radioactive isotopes (*e.g.*, 131-labeled-lipiodol or yttrium-90 [Y90]-tagged glass or resin microspheres) or regional tumor ablation (2). Regional tumor ablation is achieved through radiofrequency ablation (RFA), cryotherapy or intra-tumoral injection of ethanol or acetic acid (2). Radiofrequency ablation is one of the most frequently used method for ablation and might be superior to other methods of ablation (19). Herein, we present a case of recurrent stage IV rectal cancer treated with FOLFIRI and RFA but also combined with aflibercept. We believe that this is the first report of using aflibercept with RFA.

Case report

A 35-year-old woman presented to us with Stage IV (T4N1M1) rectal cancer in June 2012 for a second opinion. She had moderately large rectal carcinoma from 2 cm above the anorectal ring with metastasis to liver and regional lymph nodes. She had undergone chemo-radiation at an outside facility. Her course was complicated by radiation therapy related pruritus ani and large skin tags. She was operated in July 2012 and underwent low anterior resection with a loop ileostomy and a coloanal anastomosis. She had resection of her liver segments 2 and 3 and radiofrequency ablation of liver metastasis. She tolerated the procedure very well and finished adjuvant chemotherapy with 5-FU and oxaliplatin. She then had her ileostomy closed in January 2013.

She had a positron emission tomography (PET) scan in June 2013, which showed multiple enlarged para-aortic and retroperitoneal lymph nodes, as well as a lymph node along the medial margin of the left hepatic lobe, consistent with progressive nodal involvement by the metastatic process. She had a colonoscopy done in June 2013, which showed no evidence of recurrence and a clean anastomosis, although the colonic preparation was poor. She was given a choice between watchful waiting or to start chemotherapy. Her chemotherapy choices included FOLFIRI with aflibercept, capecitabine with bevacuzimab *versus* capecitabine-alone. She chose single-agent capecitabine. She had *KRAS* wild type mutation. The patient completed 6 cycles of chemotherapy with capecitabine. However, a PET scan in December 2013 showed progression of disease with four new metastatic liver lesions.

The patient underwent RFA of those lesions within the segment 2/4A, 5, 7 and 8 of the liver. The patient was started on FOLFIRI and aflibercept combination therapy. Patient received cycle 10 in May 2014. A repeat magnetic resonance imaging (MRI) and PET scan showed stable disease.

Discussion

RFA is a technique by which a needle electrode delivers a high frequency alternating current to a tissue that leads to tissue necrosis around the electrode (20). Whenever possible, surgical resection is preferred over RFA as surgery has been shown to have better outcomes than RFA alone (21). However, if the liver lesions are not resectable, often seen in a large majority of patients, RFA with systemic chemotherapy has better outcomes than systemic chemotherapy alone (22). The first randomized trial of use of RFA combined with systemic treatment *versus* systemic treatment-alone in patients with non-resectable colorectal liver metastases was published in 2012 (EORTC 40004). Progression-free survival (PFS) at 3 years for combined treatment was 27.6% compared to 10.6% for systemic treatment only. Median PFS was 16.8 months and 9.9 months (95% CI 9.3-13.7), respectively (22).

The limitation of using RFA alone is that the residual tumor can undergo rapid growth. The mechanism of rapid growth of the residual tumor is poorly-understood. In a murine model, Nijkamp *et al*. demonstrated that the accelerated growth of the residual tumor occurs due to hypoxia and leads to the stabilization of hypoxia inducible

factors, HIF-1α and HIF-2α in the tumor cells, which in turn leads to up-regulation of VEGF (23). Kong *et al*. demonstrated that HIF-1α and VEGF were up-regulated in sublines of HepG2 cells after heat treatment (24). They also demonstrated that bevacizumab, a VEGF inhibitor, could inhibit the tumor growth and angiogenesis.

Two VEGF inhibitors, bevacuzimab and aflibercept, are currently in use for metastatic colon cancer. Various studies have shown the benefit of addition of bevacizumab both in first-line and second-line treatment in patients with metastatic colorectal cancer. Aflibercept was approved in the United States for use in combination with FOLFIRI for the treatment of patients who have progressed on an oxaliplatin regimen or have become resistant to it on the basis of the VELOUR trial (17). There are only two pre-clinical studies and no clinical studies that have compared the benefit of adding bevacizumab to RFA or RFA alone (25). One pilot study showed that adding bevacizumab to transarterial chemoembolization (TACE) significantly reduced neovessel formation (26).

We added aflibercept to our patient. Our patient tolerated the dug well and did not experience hypertension, fatigue or bleeding, which are the most important side-effects of using aflibercept.The patient showed stable disease at the end of 10 cycles. We believe that there is value in adding aflibercept to a patient underdoing RFA to prevent neovascularization and relapse of the liver lesions. This needs to be studied further in a randomized control trial.

Conflicts of interest

The Authors have no potential conflicts of interest.

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