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Olgu Sunumu / Case Report

The Efficacy and Tolerability of Xeliri-Aflibercept Combination in A Metastatic Colorectal Cancer Patient After 5-Fu- Induced Symptomatic Bradycardia: A Case Report and A Brief Review of Literature

5-Fluorourasil İlişkili Semptomatik Bradikardi Gelişen Bir Metastatik Kolorektal Kanser Hastasında XELİRİ-Aflibercept Kombinasyonunun Etkinlik ve Tolerabilitesi: Bir Olgu Sunumu ve Kısa Literatür Derlemesi

Lutfiye Demir, Mustafa Ersoy

Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology, Eskisehir, Turkey

Abstract

5-Fluorouracil (5-FU) and oral fluoropyrimidines are the backbone of colorectal cancer (CRC) chemotherapy, but these have many traditional and cardiotoxic side effects. Rechallenge is usually not recommended due to high mortality rates after ischemic symptoms and other cardiac side effects, but replacing these drugs with another fluropyrimidine, or bolus 5-FU, can be considered for some patients. Aflibercept combined with a FOLFIRI regimen is an accepted second-line therapy for metastatic colorectal cancer (mCRC) patients. XELIRI is another effective and feasible irinotecan and fluoropyrimidine combination, which is more toxic than the FOLFIRI regimen and is not routinely recommended. However, modified doses of XELIRI (mXELIRI) were found to be non-inferior to FOLFIRI. The efficacy of the mXELIRI and aflibercept combination has not investigated yet. We present a patient with infusional 5-FU-induced sinus bradycardia that we could not continue FOLFIRI-aflibercept due to this cardiac side effect. We replaced infusional 5-FU with reduced dosages of capecitabine and irinotecan as in the mXELIRI regimen and combined those with aflibercept. The patient tolerated this regimen well without cardiac or severe gastrointestinal side effects, and had 12 months of progression-free survival. Replacing capecitabine with infusional 5-FU might be an option for some patients experiencing 5-FU-related sinus bradycardia. However, oncologists should arrange the treatment plan according to the risk/benefit ratio. Aflibercept combined with mXELIRI may be an alternative regimen for patients who refuse port catheter placement or who are not able to receive infusional-5-FU due to adverse side effects.

Keywords: XELIRI; Aflibercept; Bradycardia; 5-Fluorouracil; Capecitabine

Özet

5-Fluorouracil (5-FU) ve oral floropirimidinler kolorektal kanser (CRC) kemoterapisinde temel yapıtaşı ilaçlardan olmasına rağmen, bu ilaçların pek çok geleneksel ve kardiyotoksik yan etkileri bulunmaktadır. Oluşabilecek yüksek mortalite riskinden dolayı genellikle iskemik belirtiler ve diğer kardiyak yan etkilerden sonra bu ilaçların yeniden kullanımları önerilmemekle birlikte, bazı hastalarda başka bir floroprimidin ya da bolus 5-FU ile devam edilmesi düşünülebilir. Aflibercept ve FOLFIRI rejimi kombinasyonu metastatik kolorektal kanserli (mCRC) hastaların ikinci basamak tedavisinde kullanılan onaylı bir tedavidir. XELIRI, bir başka etkili ve kullanılması kolay bir irinotekan ve floropirimidin kombinasyonu rejimi olmasına rağmen FOLFIRI rejiminden daha toksik oldğundan artık rutin olarak önerilmemektedir. Buna rağmen, XELIRI rejiminin modifiye doz formunun (mXELIRI), FOLFIRI ile kıyaslandığında daha az etkin olmadığı ve tolerabl olduğu saptanmıştır. Ancak henüz mXELIRI ve aflibercept kombinasyonunun etkinliği araştırılmamıştır. Bu yazıda infüzyonel 5-FU sonrası semptomatik sinüs bradikardisi gelişen ve bu kardiyak yan etki nedenli FOLFIRI-aflibercept rejimine devam edilemeyen bir hasta sunulmuştur. Hastada infüzyonel 5-FU yerine azaltılmış doz kapesitabin ve irinotekan ile mXELIRI rejimi şeklinde verilmiş ve aflibercept ile kombine edilmiştir. Hasta bu tedaviyi kardiyak ya da ciddi gastrointestinal yan etkiler olmadan iyi bir şekilde tolere etmiş, ve 12 aylık progresyonsuz sağkalım süresi sağlanmıştır. İnfüzyonel 5-FU ilişkili sinüs bradikardisinde, infüzyonel 5-FU yerine kapesitabin kullanmak bazı hastalar için bir seçenek olabilir. Ancak, yine de onkoloji uzmanları bu durumlarda mutlaka tedavi planını yarar/zarar oranına göre düzenlemelidir. Aflibercept ve mXELIRI kombinasyonu port katater takılmasını istemeyen ya da yan etki nedenli infüzyonel 5-FU alamayan hastalarda alternatif bir rejim olabilir.

Anahtar Kelimeler: XELİRİ; Aflibercept; Bradikardi; 5-Fluorourasil; Kapesitabin

Correspondence:
Lütfiye DEMİR
Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology, Eskisehir, Turkey
e-mail: demir.lutfiye77@gmail.com

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1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. Approximately 20% of CRC patients are diagnosed with stage IV disease and the 5-year survival rates is approximately 15% for these patients.[1] Until the late 1990s, 5-FU combined with leucovorin (LV) was the only effective combination for treating CRC.[2] However, approval of the two drugs, irinotecan and oxaliplatin respectively, and the addition of each drug to standard 5-FU/LV-based chemotherapy improved survival of CRC patients compared to 5-FU/LV only.[3,4] In addition, after realizing the significance of molecular targets such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), new targeted therapies have become valuable in the treatment of metastatic CRC. The addition of either anti-EGFR or anti-VEGF monoclonal antibodies (bevacizumab) to 5-FU-LV/ irinotecan or oxaliplatin combinations increased median survival to 25 months.[5,6]

In 2012, the approval of two targeted agents aflibercept, in second-line and regorafenib, in third-line treatments resulted in a 5-month gain in median survival of mCRC patients.[7,8] Furthermore, personalized therapy was replaced with standard therapy after recognizing the predictive value of driver RAS mutations, the effect of tumor sidedness and the prognostic role of BRAF mutation in CRC.[9,10]

Aflibercept is a recombinant fusion protein containing VEGF-binding proteins from the extracellular domains of human VEGF receptors 1 and 2 that is fused to the Fc portion of human immunoglobulin G1. Aflibercept blocks the activity of VEGFA, VEGFB, and placental growth factor by acting as a high-affinity ligand trap to prevent the ligands from binding to their endogenous receptors.[11] Based on the results of the phase III VELOUR (Aflibercept Versus Placebo in Metastatic Colorectal Cancer After Failure of an Oxaliplatin-Based Regimen) study, Aflibercept was approved in combination with the conventional FOLFIRI regimen (infusional-5-FU, LV, irinotecan) as second-line treatment for patients who have progressed on an oxaliplatin-containing regimen.[7] XELIRI is another irinotecan and oral 5-FU derived combination used in the treatment of CRC. A modified form of the XELIRI regimen (mXELIRI) was recently compared to the FOLFIRI regimen and was found to be non-inferior in a phase III study.[12] However, there is lack of randomized studies about the use of aflibercept in combination with XELIRI.

Fluoropyrimidines (5-FU, capecitabine) are antimetabolites that frequently cause many side effects similar to those of other chemotheurapeutics, such as diarrhea, emesis, stomatitis and cytopenia. Besides these traditional side effects, 5-FU and its derivates are also related to carditoxicity. The relationship between 5-FU and cardiotoxicity was first reported in 1962,[13] followed by several case reports and retrospective studies thar reported different 5-FU and other fluoropyrimidine-related cardioxicity incidence and mortality rates ranging between 1-34 % and 0-13%, respectively.[14-19] The most frequent symptoms and manifestations are coronary vasospasm and ischemic electrocardiography (ECG) changes, myocardial infarction, arrhythmias, cardiac failure and ECG abnormalities. Sinus bradycardia is a relatively rare complication of 5-FU.[20] After experiencing 5-FU induced cardiotoxicity, experts usually recommend that patients discontinue therapy; however, as 5-FU is the major component of chemotherapy combinations for many cancers, such as mCRC, decision should not be made until after weighing the risks and benefits.[21]

In this report, we present a case of an mCRC patient with infusional 5-FU induced bradycardia, in whom capecitabine rechallenge was well-tolerated without cardiotoxicity. Moreover, the patient received a combination of aflibercept with XELIRI with manageable side effects and a long PFS.

2. Case Presentation

In March 2017, a 54-year-old female patient was admitted to the out-patient clinic of our hospital's surgery department with complaints of abdominal pain and constipation. Due to these symptoms, a colonoscopy was performed, and an obstructive mass with malign appearence in the sigmoid colon was observed. The biopsy taken from this mass was compatible with adenocarcinoma. Computed tomography (CT) screening was immediately performed and multiple metastatic lesions were detected; the one with largest diameter (3 cm) was found in the liver, and multiple paraaortic lymph nodes were also found. The surgeons decided to open a stoma through colostomy due to the risk of intestinal obstruction during treatment, and after the operation, they directed the patient to the Department of Medical Oncology. The presence of the NRAS codon 61 mutation was determined by genetic analysis of primary tumor. The basal carcinoembryonic antigen (CEA) level was 11 ng/ml. The ECOG performance score was 1, and the patient had no limiting comorbid diseases except hypotiroidism from a thyroidectomy, for which she was receiving thyroid hormone replacement therapy.

In April 2017, we initiated mFOLFOX6(modified FOLFOX6-oxaliplatin, infusional 5FU, leucovorin) and bevacizumab combination treatment for first-line therapy. After three months of treatment, a significant increase in the level of CEA (25.9 ng/ml) and progression of liver metastases was observed. Therefore, we decided to start second-line therapy as FOLFIRI-aflibercept, however, the patient quit follow-up, but she came back with abdominal pain, rectal bleeding and fatique in October 2017. Contol CEA was 117 ng/ml. The number and size of liver metastases were significantly increased, and newly developed para-aortic lymph nodes were detected on CT imaging. The patient performance status was ECOG 2 at that time, liver and renal function tests were still within normal ranges. However, she had grade II anemia due to rectal bleeding, so we could not start the second-line FOLFIRI-aflibercept treatment per our planning. We referred the patient to the Department of Radiation Oncology, where they decided to initiate radiotherapy to the primary lesion for bleeding control and restore anemia. After 10 fractions of radiotherapy, bleeding was controlled. Subsequently, the FOLFIRI regimen was started. On the second day of the first cycle, the patient experienced hypotension and bradycardia (Figure 1). We discontinued 5-FU infusion, symptomatic bradycardia lasted approximately for 6 hours and we tried to continue 5-FU infusion again, however symptomatic bradycardia and hypotension reappeared and we had to apply atropin 0.5 mg IV twice. Thyroid function tests and cardiac markers were all within normal ranges, and normal ejection fraction was observed on echocardiogram. We concluded that symptomatic bradycardia was due to 5-FU infusion, and we considered changing to bolus 5-FU. However, as side effects such as diarrhea and neutropenia are seen much more frequently with bolus 5-FU, we rescheduled the treatment as XELIRI, and we combined this regimen with aflibercept. Aflibercept was administered at the same dosage (4 mg/kg), but in three weekly cycles. Irinotecan was administered at 200 mg/m^2, and capecitabine was administered at 800 mg/m^2 twice per day for a two weeks on-one week off regimen (mXELIRI dosage). Due to the government policies, we requested permission from the Health of Ministry for the usage of this treatment combination and after getting the permission, The first XELIRI-aflibercept regimen was initiated in the hospital due to the possibility of bradycardia, bleeding and other complications. The patient hospitalized for one week; however no bradycardia, hypotension and bleeding were observed. The patient was carefully warned about serious adverse events, and the other cycles were given in an out-patient chemotherapy clinic. After one cycle of FOLFIRI and three cycles of mXELIRI-aflibercept, response evaluation was performed. CEA levels decreased to 22 ng/ml and partial response was observed in liver lesions (Figure 2a-2b). We reduced irinotecan dosage to 180 mg/m^2 due to grade II neutropenia/leucopenia and diarrhea after the second cycle, and then, she had no further dose-limiting adverse events. We observed grade I fatigue, diarrhea, and grade II hypertension, which was manageable with

amlodipine. Partial response proceeded on the six-month radiologic evaluation, and a stabile response was observed on the ninth month evaluation, at which time CEA level was 30 ng/ml. Unfortunately, in January 2019, one year after initiation of this regimen, liver lesions progressed, a new perihepatic fluid and periportal multiple lymph nodes were observed on CT imaging (Figure 2c), and the serum CEA level had increased to 234 ng/ml. The patient was tired and her ECOG performance score was 3 upon physical examination. After a one-month hiatus from treatment, she was reevaluated at outpatient clinic. She was quite well compared to her condition a month ago, and her liver function tests were still within normal ranges. We started Regorafenib at 80 mg, and planned to increase the dosage after the second week of examination. However, the patient had fatique, and grade I stomatitis, so we decided to continue with the same dosage (three weeks on, one week off). After three months of regorafenib, she visited the hospital with ascites and jaundice, and one month later, on June 8, 2019, 27 months after intial diagnosis, she died.

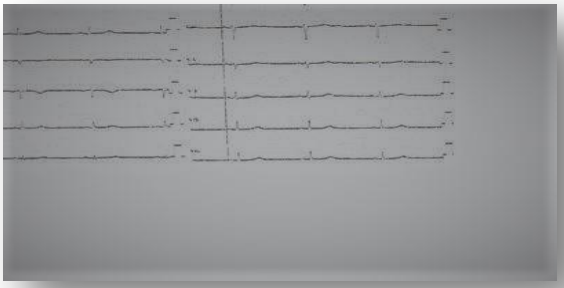

Figure 1. Electrocardiography of the patient during infusional 5-FU, sinus bradycardia; heart rate:46/minute

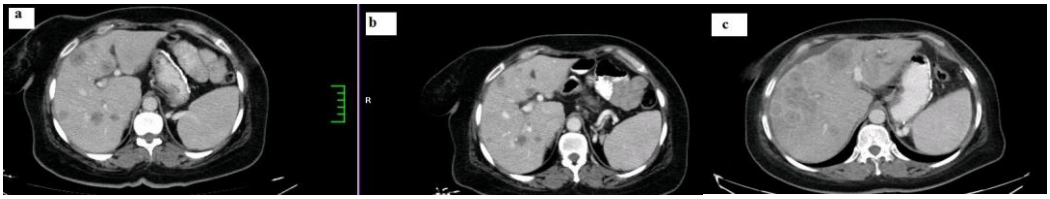

Figure 2. Liver metastases during patient follow-up a. before XELIRI-aflibercept b. Partial response in liver lesions after sixth month. C. Progression of liver metastases before regorafenib.

3. Discussion

We decided to report this case to focus on two topics. First, to discuss 5-FU-induced symptomatic bradycardia that did not occur after replacing infusional 5-FU/LV with another fluoropyrimine, capecitabine; and second, to discuss the combination of XELIRI with aflibercept, for which no randomized data regarding tolerability and efficacy were found in the literature.

Several retrospective and prospective studies have examined the link between 5-FU and cardiotoxicity. One of the larger studies involved 644 patients who were enrolled by Kosmas et al. [22] Among patients treated with infusional 5-FU/LV, the cardiotoxicity rate was 12.5%, it was 2.4% in bolus 5-FU/LV-treated patients, and 5.5% in capecitabine-treated patients.[22] Deboever et al. also reviewed the incidence of cardiotoxicity, which varied between 2.5% and 8.5% for the De Gramont's schedule, 3%–9% for capecitabine, 1.6%–3% for intravenous bolus regimens, and 5.3%–12.5% for high-dose and continuous infusion schedules of 5-FU.[21] Although capecitabine is also related to

cardiotoxicity in many reports, the fact that we did not observe toxicity after capecitabine treatment in our patient could be due to fluoropyrimidine metabolism. About 10% of 5-FU is cleared by renal excretion, and the remainder is deactivated to dihydrofluorouracil (DHFU) by dihydropyrimidine dihydrogenase (DPD).[23] The DPD activity and metabolism of 5-FU may become saturated at higher levels, and the tolerated daily dose of 5-FU decreases as the length of infusion increases.[23] However, the metabolism of oral fluoropyrimidines (and capecitabine) is different from infusional 5-FU. They undergo more diverse metabolism in the gastrointestinal system and in the liver through the action of multiple enzymes.

Sinus bradycardia is termed as a heart rate under 50 beats/minute, with otherwise normal function of the sinoatrial node and conduction systems and is an unusual presentation of 5-FU cardiotoxicity. Kosmas et al.[22] found that only four of their 26 patients developed bradycardia; three of these were due to a complete atrioventricular block, and only one, as in the case we describe here, was sinus bradycardia (50 beats/min). Hafeez et al.[24] investigated the effect of 5-FU on the sinoatrial node and conduction system of the heart. They observed ECG changes in 25 patients during 5-FU infusion. Sinus bradycardia was seen in 8% of patients, who were receiving continuous 5-FU infusion.[24] They also reported that heart rates increased to normal rates after intervention with atropine in those patients and concluded that 5-FU bradycardia might be a hypervagotonia, as vagolytics abolished it in a previous report.[24,25] In our case, we also observed that the patient's heart rate increased to normal ranges after atropine injection, so hypervagotonia may be the reason.

5-FU-related cardiotoxicity is more frequent during the first treatment cycle.[26] However, our patient had not experienced any cardiac side effects while she was receiving the mFOLFOX6 regimen; nor was bradycardia observed with capecitabine treatment. It is possible that the changes in the activity of the DPD enzyme could play a role in this situation. Another point to consider is that the autonomic imbalance of 5-FU is triggered by irinotecan, which is a well-known chemotherapeutic agent that induces cholinergic effects.[27] Apart from all these hypotheses, capecitabine may be a safer fluoropyrimidine than continuous infusion of 5-FU.

We previously mentioned that this is also the first case report about the efficacy and tolerability of the XELIRI-aflibercept combination, which was not tested before in phase II-III trials. In our case, after failure of FOLFOX-bevacizumab treatment, aflibercept-FOLFIRI therapy was planned, but could not be given due to serious symptomatic bradycardia.

Although XELIRI is an effective regimen for the treatment of mCRC, standard XELIRI regimen was found to be associated with high grades of gastrointestinal toxicity and lower PFS times compared to FOLFIRI in phase III BICC-C trials.[28] Following these results, standard XELIRI was not a recommended alternative to the FOLFIRI regimen. In contrast, a phase III second-line AXEPT trial demonstrated that mXELIRI with or without bevacizumab was non-inferior to FOLFIRI and was well-tolerated. In the AXEPT trial, mXELIRI included reduced irinotecan and capecitabine dosages, as irinotecan and capecitabine were administered in doses of 200 mg/m^2 and 1600 mg/m^2, respectively. Therefore, in contrast to XELIRI regimen, the mXELIRI regimen could be an alternative to the standard FOLFIRI as a second-line backbone therapy for metastatic colorectal cancer.[12]

A clinical trial with XELIRI-aflibercept therapy is not yet available. However, a phase I study recently evaluated the combination of capecitabine and aflibercept as three weekly cycles among refractory mCRC patients. They reported two-month PFS rates as 72% and defined this combination as tolerable and efficacious.[29] Similarly, the addition of irinotecan to capecitabine-aflibercept doublet did not increase serious adverse events in our patient and disease control was successfully provided during a significantly longer period. A progression-free survival time of 12 months in our patient was a respectable result and

mXELIRI-aflibercept combination seems to be an alternative regimen for CRC patients.

In conclusion, this is the first case report that shows replacing capecitabine with infusional 5-FU might be an option for some patients experiencing 5-FU-related sinus bradycardia. However, oncologists should arrange the treatment plan according to the risk/benefit ratio after cardiac side effects. Aflibercept may be combined with an mXELIRI regimen and may be an alternative for patients who refuse port catheter placement or who are not able to receive infusional-5-FU due to adverse side effect

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