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Investigation of The Effects of FOLFOX and CAPOX Chemotherapy Protocols on CEA and CA 19-9 in Colon Cancer

Kolon Kanseri Hastalarında FOLFOX ve CAPOX'un CEA ve CA 19-9 Üzerine Etkisinin Araştırılması

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ABSTRACT

The most common markers used in the diagnosis of the colon cancer are CEA and CA 19-9. Chemotherapy is applied as an adjuvant and a neo-adjuvant treatment in colon cancer. Our aim was to investigate the effects of FOLFOX and CAPOX on CEA and CA 19-9 levels before and after chemotherapy in different patient groups. The CEA and CA 19-9 values before and after chemotherapy for the 60 patients diagnosed with metastatic colon cancer having FOLFOX or CAPOX therapy age over 18 whom hospitalised between 2017-2020, were used. The mean value for CA 19-9 of T0 for FOLFOX receiving group was calculated as 263.71 ± 709.87 U/ml and was 119.57 ± 246.34 U/ml of for the 3rd month. The mean value for CEA for receiving FOLFOX was calculated as 76.11 ± 204.22 ng/g at T0, and 50.53 ± 142.50 ng/g at the 3rd month. The mean value of CEA for receiving CAPOX was calculated as 139.62 ± 388.87 ng/g at T0, and 117.05 ± 272.08 ng/g at the 3rd month. Intertemporal CEA levels of individuals receiving CAPOX were found to show significant differences (p=0.074). CA 19-9 mean of T0 was calculated as 218.43 ± 605.53 U/ml and the 3rd month mean of 174.40 ± 465.61 U/ml of the patients receiving CAPOX. It was found that the intertemporal values of the individuals in terms of CA 19-9 levels were not statistically significant (p=0.649).

In conclusion, CA 19-9 and CEA levels of the patients decreased even more in the 3rd month when treated with FOLFOX. The decrease in CEA was found to be more significant. In terms of CAPOX treatment, the interquartile range T0 and the 3rd month levels did not show a significant difference, statistically (p=0.143 and p=0.089).

Keywords: CA 19-9, CAPOX, CEA, Colon Cancer, FOLFOX

ÖZ

Kolon kanseri tanısında en sık kullanılan belirteçler CEA ve CA 19-9'dur. Kolon kanserinde Kemoterapi uygulaması adjuvan ve neo-adjuvan olarak yapılmaktadır. Çalışmadaki amacımız, FOLFOX ve CAPOX 'un farklı hasta gruplarında kemoterapi öncesi ve sonrası CEA ve CA 19-9 düzeylerine etkilerini araştırmaktı. 2017-2020 yılları arasındaki, 18 yaş üstü FOLFOX veya CAPOX kemoterapi protokolü alan, metastatik kolon kanseri tanısı almış 60 hastanın kemoterapi öncesi (T0) ve 3. aydaki CEA ve CA 19-9 değerleri kullanılmıştır. FOLFOX tedavisi alan hastaların ortalama CA 19-9 değerleri T0'da 263,71 ± 709,87 U/mL ve 3.ayda 119,57 ± 246,34 U/mL, CEA değerleri T0'da 76,11 ± 204,22 ng/gr ve 3.ayda 50,53 ± 142,50 ng/gr olarak hesaplanmıştır. CAPOX alan grupta ortalama CEA değeri T0'da 139,62 ± 388,87 ng/gr ve 3.ayda 117,05 ± 272,08 ng/gr olarak hesaplanmıştır. CAPOX alan bireylerde başlangıç ve 3.ayda CEA düzeylerindeki farklılıklar anlamlı bulunmuştur (p=0,074). CAPOX alan hastaların CA 19-9 ortalaması T0'da 218,43 ± 605,53 U/mL ve 3.ayda 174,40 ± 465,61 U/mL olarak hesaplanmıştır. Bireylerin başlangıç ve 3.ay CA 19-9 değerleri istatistiksel olarak anlamlı bulunmamıştır (p=0,649).

Sonuç olarak, FOLFOX ile tedavi edilen hastaların CA 19-9 ve CEA seviyelerinin 3. ayda daha da düştüğü bulunmuş ve CEA seviyelerindeki azalma daha anlamlı bulunmuştur. CAPOX tedavisi alanlarda, çeyrekler arası başlangıç ve 3. ay seviyeleri istatistiksel olarak anlamlı bulunmamıştır (p=0,143 ve p=0,089).

Anahtar Kelimeler: CA 19-9, CAPOX, CEA, FOLFOX, Kolon Kanseri

Ethics committee approval was obtained from Ankara Yildirim Beyazit University Non-Invasive Clinical Research Ethics Committee with the number (File No:2020-373, Decision No:23, Date:24.11.2020). This study was written by abridging Birsen Ecem İbabay's Ankara Yildirim Beyazit University, Institute of Health Sciences, Cancer Biology Department master thesis. FOLFOX results were presented as an oral presentation at the 5th International Health Science and Life Congress.

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INTRODUCTION

Colon cancer affects approximately one million people per year.[1] Colon cancers differ in the changes that occur in the normal grandular structures and cytological features of the cells. The prognosis is determined with these differentiations. [2]

The prognosis of colon cancer has five main stages. Stage 0: Cancer cells are only in the inner lining of the colon mucosa. Stage 1: Cancer cells have progressed in the mucosa and surrounded the colon muscle layer. Stage 2: The cancer has grown through the colon wall. However, it has not spread to the nearby tissues and lymph nodes. Stage 3: Cancer cells have spread to the surrounding tissues of the colon wall and to the lymph nodes. Stage 4: Cancer cells metastasize to distant organs and tissues.[3] The signs and symptoms of colon cancer also play a role in the diagnosis. In stages 0 and 1 symptoms are less common which, thereby, causes a poor prognosis. Common signs and symptoms associated with progressive prognosis are abdominal pain, changes in defecation habits, weight loss, weakness, hematochezia, or melena.[4-6] CEA and CA 19-9 are the markers, which are used in the diagnosis of colon cancer.

Surgery, radiotherapy and chemotherapy are commonly used in the treatment of colon cancer. Chemotherapy is applied in high-risk patients with stage 2, in stage 3 as an adjuvant therapy and also is applied in palliative patients in stage 4 with the aim of increasing the survival time. Adjuvant therapy is the treatment that is performed after surgery. Neoadjuvant treatment is the treatment that is performed prior to surgery. In this study, the difference between the effects of FOLFOX (Folinic acid, Fluororasil, Oxaliplatin) and CAPOX (Capestabin, Oxaliplatin), which are chemotherapy protocols used in the treatment of colon cancer, on cancer markers in different patient groups were investigated biochemically.

MATERIAL AND METHOD

Material

In the study, the data was included from total of 60 out- and inpatient over the age of 18 who received FOLFOX and CAPOX regimen in Ankara Bilkent City Hospital Department of Medical Oncology between 2017-2020. Out of 30 patients received FOLFOX are 7 male in stage 3, 13 male in stage 4, 3 female in stage 3 and 7 female in stage 4. Out of 30 patients received CAPOX are 12 male in stage 3, 7 male in stage 4, 8 female in stage 3 and 3 female in stage 4. The age range for 60 patients changed between 30 and 79 (21 female and 39 male, 30 of them with stage 3, 30 of them with stage 4 colon cancer). When examining the cancer marker levels for the study group, age, gender and stage classification were not taken into consideration.

Method

In order to evaluate the changes in the levels of the cancer markers, the venous blood of the selected patient group, which was taken under appropriate conditions, was retrospectively analyzed from the patient files and hospital database. The thesis project was started with the approval of Ankara Yildirim Beyazit University Ethics Committee for the retrospective evaluation of cancer markers in the patients who received chemotherapy between 2017-2020.

Folinic acid and oxaliplatin (85 mg/m^2) are given as a 2-hour infusion, followed by a short-term and low dose of fluororacil (400 mg/m^2) 46 hour continuous infusion for 12 cycles once every 2 weeks. The CAPOX regimen was composed of intravenous oxaliplatin at a dose of 130 mg/m^2 on the first day and oral capecitabine at a dose of 850 mg/m^2 every 12 hours on days 1 and 14.

This protocol was applied every 21 days for eight cycles.

The blood samples of the selected patient population were collected into the biochemistry tubes before and at the 3rd month of the chemotherapy for the evaluation of CEA and CA 19-9 levels. The CA 19-9 and CEA results are produced when the treatment completed and 3-month follow-up which is an accepted protocol in the out-patient where the study performed. CA 19-9 and CEA levels in blood were measured by Advia Centaur XPT Immunoassay System device in the Laboratory of Ankara Bilkent City Hospital. The normal levels of CEA and CA 19-9 cancer markers were accepted as 0-2,5 nanograms (ng/g) and 0-37 units/milliliter (U/ml), respectively.

Ethical Considerations

Ethics committee approval was obtained from Ankara Yildirim Beyazit University Non-Invasive Clinical Research Ethics Committee with the number (File No:2020-373, Decision No:23, Date:24.11.2020).

Data Analysis

The T0 and the 3rd month levels were analyzed with the Wilcoxon signed rank. Mann Whitney U non-parametric test was used to determine the effect of the duration of chemotherapy treatments.

IBM SPSS Statistics 26.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) program was used for statistical analysis ($p<0.05$).

RESULTS AND DISCUSSION

The mean value for T0 was calculated as 76.11 ± 204.22 ng/g and the mean value of the 3rd month 50.53 ± 142.50 ng/g of the individuals who received FOLFOX treatment with the cancer marker CEA. It has been found that there is a significant difference between the levels of the individuals in terms of the intertemporal levels ($p=0.003$). It was determined that CEA levels decreased even more in the 3rd month period (Table 1).

Table 1. The Comparison for the 0th and the 3rd Month Values of Individuals Receiving FOLFOX.

	Time		Test Statistics	
Cancer Markers	**0th Month Mean ± SD**	**3rd Month Mean ± SD**	**Z**	**p**
CEA	76.11 ± 204.22	50.53 ± 142.50	3.013	***0.003***
CA 19-9	263.71 ± 709.87	119.57 ± 246.34	2.638	***0.008***

The mean value for T0 was calculated as 263.71 ± 709.87 U/ml. and mean of the 3rd month was 119.57 ± 246.34 U/ml of the individuals who received FOLFOX treatment with the cancer marker CA 19-9. Intertemporal levels of the individuals in terms of CA 19-9 were found to differ significantly ($p=0.008$). It was determined that CA 19-9 levels decreased even more in the 3rd month period (Table 1) (Figure 1).

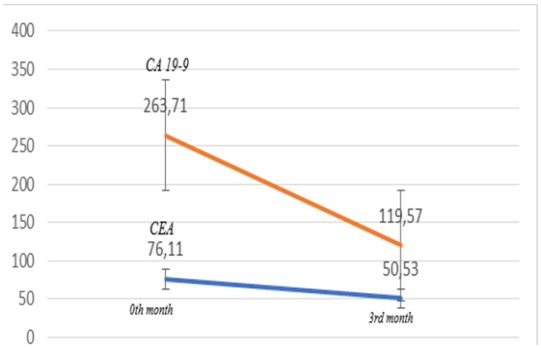

Figure 1. Comparison of T0 and 3rd Month Values of The Treatment Types of Individuals Receiving FOLFOX.

The mean value of T0 was calculated as 139.62 ± 388.87 ng/g and the mean value of the 3rd month 117.05 ± 272.08 ng/g of the individuals who received CAPOX treatment with the cancer marker CEA. It has been found that there is statistically a significant difference between the levels of the individuals in terms of the intertemporal levels (p=0.074) (Table 2).

Table 2. The Comparison for the 0th and the 3rd Month Values Of Individuals Receiving CAPOX.

	Time		Test Statistics	
Cancer Markers	**Month 0 Mean ± SD**	**Month 0 Mean ± SD**	**Z**	**p**
CEA	139.62 ± 388.87	117.05 ± 272.08	1.784	0.074
CA 19-9	218.43 ± 605.53	174.40 ± 465.61	0.455	0.649

The mean of T0 was calculated as 218.43±605.53 U/ml. and mean of the 3rd month 174.40±465.61 U/ml of the individuals who received CAPOX treatment with the the cancer marker CA 19-9. Intertemporal levels of individuals in terms of CA 19-9 were not statistically significant (p=0.649). It was determined that CA 19-9 levels decreased even more in the 3rd month period (Table 2).

CONCLUSION AND RECOMMENDATIONS

CEA levels have previously been examined in colorectal, medullary thyroid cancer, breast, stomach, liver, lung, ovarian, pancreatic and prostate cancers. CA 19-9 levels were investigated in pancreatic, colon, cholangio and stomach cancers. Those studies are discussed below. In the current study, we examined the CEA and CA 19-9 levels at T0 and the 3rd months of colon cancer patients receiving FOLFOX and CAPOX chemotherapy.

In a study by Thomsen *et al*., the prognostic role of CEA and CA 19-9 levels in patients received FLOX in combination with cetuximab as first-line chemotherapy in unresectable metastatic colorectal cancer (CRC) were investigated. The presence of RAF and BRAF mutations have found to be associated with increased CEA and CA 19-9 levels and decreased survival rate.[7]

The study by Jin Kim *et al*., examined the levels of CEA and CA 19-9 in metastatic gastric cancer patients receiving chemotherapy.and CEA and CA 19-9 fluctuations were reported. All patients with these fluctuations experienced clinical benefit from chemotherapy. Therefore, the increase in CEA and CA 19-9 levels after the beginning of the chemotherapy should not be considered as a sign of progress in the disease.[8]

Another study by Jia *et al*., examined the serum levels of CEA and CA 19-9 in advanced CRC patients receiving combined chemotherapy with cetuximab. In the period when these values increased, the survival rate decreased. Also, while CEA and CA 19-9 levels were decreased, longer progression-free survival was obtained. Jia *et al*., showed that CEA and CA 19-9 markers are useful indicators in the first-line chemotherapy combined with cetuximab. In addition, these two cancer markers have been shown to be helpful in the evaluation of cetuximab resistance.[9]

Hashimuze *et al*., investigated whether CEA and CA 19-9 levels were useful indicators of survival in patients with

metastatic CRC. They showed that the CA 19-9 value is one of the independent indicators for survival after receiving first-line oxaplatin-based chemotherapy.[10]

In a study by Vukobrat-Bijedic *et al*., CEA and CA 19-9 levels were increased in metastatic colon cancer patients. Therefore, it couldan be considered as a late manifestation of carcinogenesis.[11]

Mizuno *et al*., examined the optimal limits of preoperative serum CEA and CA 19-9 markers to prognose stage 2 and 3 colon cancer patients. Optimal threshold levels for CEA and CA 19-9 markers were determined as 5.4 ng/ml and 22.4 U/ml. It was concluded that these values can be used for further relapse risk classification.[12]

Urvay *et al*. analyzed the relationship between pre-treatment CEA and CA 19-9 levels and survival in patients with metastatic CRC. According to their results, high CA 19-9 levels before treatment is more beneficial than CEA levels in evaluating survival rate in stage 4 CRC patients. In addition, the factors affecting the survival rate include primary tumor resection and tumor location.[13]

Değirmencioğlu *et al*. investigated the level of efficacy in patients with stage 3 colon cancer receiving CAPOX and FOLFOX treatment. 243 patients were evaluated of whom 106 received CAPOX and 137 received FOLFOX. According to the results, it was stated that KRAS and NRAS mutations adversely affected the prognosis of the disease and metastatic lymph node involvement increased the progression of the disease. In the patient population, CAPOX receiving patients were older than the patients receiving FOLFOX. Disease progression and mortality rates were higher in those receiving FOLFOX than those receiving CAPOX. However, no significant difference was found between the two chemotherapy regimens in terms of survival.[14] In our study, when the effects of FOLFOX and CAPOX were examined at the level of cancer markers, FOLFOX was found to be more effective. This result pointed that it has the potential to have a positive effect on disease progression and survival.

Souglakos *et al*. investigated whether there was a significant difference between 3rd month and 6th FOLFOX and CAPOX application in 3-year disease-free survival in high-risk stage 2 and stage 3 colon cancer patients. Patients who received FOLFOX or CAPOX treatment for 3 months and patients who received one of these chemotherapy for 6 months, were selected. Of the 1115 patients who participated in the mentioned study, 413 were high-risk stage 2 colon cancer patients and 702 were high-risk stage 3 colon cancer patients. As a result of the study, 3-year disease-free survival rates were found to be 77.2% after 3 months of chemotherapy and 77.9% after 6 months of chemotherapy. The 3-year disease-free survival rate of high-risk stage 2 patients receiving FOLFOX was 76.7% after 3 months of administration; while it was 79.3% after 6 months of application; the rates of patients receiving CAPOX after 3 months of application were 85.4%, and 83.8% after 6 months of application. The disease-free survival rate of patients with stage 3 colon cancer who received FOLFOX after 3 months of application was 71.5%, and 77.3% after 6 months of application. It was found that those who recieved CAPOX were 74.5% after 3 months of application and 74,7% after 6 months of application. The results of the study indicated that the 3-year survival rate was associated with the chosen adjuvant chemotherapy regimen.[15] Consistent with Souglakos' study, our data showed the effectiveness of FOLFOX was to be higher than CAPOX.

Loree *et al*., compared the use of CAPOX and FOLFOX in terms of toxicity in patients with advanced colon cancer. 93 patients who received FOLFOX and 83 patients who received CAPOX. As a result, it was observed that the patients who received CAPOX showed lower toxicity than the patients who received FOLFOX.[16]

Sobrero *et al*., investigated whether reducing the treatment time of FOLFOX and CAPOX could affect treatment efficacy. Stage 2 or stage 3 colon cancer patients who received FOLFOX or CAPOX treatment for

3 month and 6 month periods participated in the study. 3759 patients from 130 Italian hospitals participated in the study. Of these, 64% received FOLFOX and 36% received CAPOX. 2/3 of them are stage 3, 1/3 of them are stage 2 cancer patients. The study could not completely show the effect of treatment duration since the results varied according to the type of adjuvant chemotherapy received. For CAPOX, the 3-month treatment period was as effective as the 6-month treatment period. For FOLFOX, the 6-month treatment period provided extra benefits. The low-risk patient group benefited more from 6 months of treatment than the high-risk patient group. The choice of treatment type and adjuvant type should be based on patient characteristics.[17]

A statistically significant decrease was observed in the CEA and CA 19-9 levels in the 3rd month of the patients who received FOLFOX chemotherapy, compared to T0. In conclusion, our data suggests the effect of FOLFOX on CEA was more significant than CA 19-9. The effect of CAPOX on CEA and CA 19-9 levels was found to be mathematically significant, but not statistically significant. In order to expand the study, it is planned to increase the population we work on.

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