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Metastatic Colorectal Cancer, Where Were We Fifteen Years Ago?

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Abstract **Original Research Article**

Colorectal cancer, is the third most common cancer. 19% of patients have metastatic disease at the time of diagnosis. Half of the patients have risk of distant metastasis during their lives. New drugs were added in recent years, but it was limited fifteen years ago. In this study demographic parameters, treatment options, effects on overall survival of 172 patients with mCRC followed by Medical Oncology Department were examined. 110 patients(64%) had metastasis at diagnosis, 62(36%) had metastasis thereafter. Liver was the most common site(107 patients %62,2). 16 patients(9,3%) had metastasectomy. 104 patients(59,3%) had one; 49(28,5%) had two and 21(12,2%) had three lines of chemotherapy. Life expectancy was found to be increased as the number of line of chemotherapy increased. 44 patients(25,6%) had FOLFOX therapy, 52(30,2%) had IFL, 39 patients(22,7%) had a combination of bevacizumab and FOLFIRI and 37(%21,5) had XELOX. Overall survival rates were not different when treatment regimes were considered(Log rank:6,668; p:0,083;p>0,05). Most important factor at choosing the chemotherapy regime's the evaluation of possible side effects. This hypothesis is supported with our study in which patients with higher performance status had second and third line treatments.

Keywords: Metastatic, colorectal, cancer, systemic treatment.

INTRODUCTION

Colorectal cancer (CRC) is an important cause of death in worldwide. It is usually seen in the sixth decade, but can be diagnosed in any age. Male and female ratio is equal untill age 40, but relatice risk is increased in males after 40 years of age. [1] Western type of diet, physical inactivity and obesity increases the risk for CRC. An increase in body mass index increases the CRC risk two-fold.

Most common symptoms of CRC are lower gastrointestinal bleeding, change in bowel movements, stomach ache, loss of appetite, weight loss and obstruction. Mass, hemothokezia (left colon or rectum origin), blood on stool (right colon origin).[7] many prognostic factors were defined for CRC, but none is as effective as stage of the disease.

Liver is the most common site for metastases. Other organs were lungs, lymph nodes and peritoneum. For the last years there is a definitive improvement in the treatment of metastatic colorectal cancer (mCRC). Targeted therapies, immunotherapy are some of them. But in the beginning of 2000's sistemic chemoterapeutic agents and vascular endothelial growth factor antibody Bevacizumab were the only choices in Turkey.

In our study, we studied 172 of 473 mCRC patients whose full data were obtained between 1998-2007 in Cerrahpaşa Medical Faculty. The choice for treatment and effect on prognosis were observed.

MATERIAL AND METHOD

In our study, we studied 172 of 473 mCRC patients whose full data were obtained between 1998-2007 in Cerrahpaşa Medical Faculty. The overall survival between patients who had metastases on diagnosis and those who developed metastases later were ezamined. Systemic chemotherapeutic drugs and Vascular Endothelial Growth Factor antibody Bevacizumab were drugs of choice in that time. And with this "majority" patients can have multiple cycles of therapies. The choice for treatment and effect on prognosis were observed. Overall survival was analyzed between these choices. NCSS 2007&PASS 2008 Statistical Software (Utah, USA) programme was used for statistical analysis. Descriptive statistical methods, Kaplan Meier Survival Analysis andLog Rank test was used.

RESULTS

172 of 473 mCRC patients whose full data were obtained between 1998-2007 in Cerrahpaşa Medical Faculty were examinde. Patients were between 26 to 91 years of age. 93 of the patients were female (54,1%) and 79 were male (45,9%) PFS was between 3 days to 74 months (median 18,13±15,78 months) and overall survival ranked between 10 days to 92,17 months (median 24,24±19,16 months). 110 of 172 patients (%64) were stage IV at the time of diagnosis.

44 patient (%25,6) had Oxaliplatin containing FOLFOX4 regimen, 52 (%30,2) had Irinotecan containing IFL regimen, 39 (%22,7) had Irınotecan containing FOLFIRI regimen with VEGFR antibody Bevacizumab and 37 patient (%21,5) had Capacitabine and Oxaliplatin combination of XELOX. At the end of the study 46 patients (%26,7) were alive.

These 172 patients were followed between 10 days to 92 months. Median time of follow up was 17,6 months. Five year survival rate was %17,17±5,10 months and overall survival was 38,32±2,92 months.

According to their performans status patients had 1 to 3 different series of therapies. Patients who had only one serie of therapy had a 5-year survival of %10,42±6,24 with OS of 31,40±3,17 months, while patients had two different series of therapy had a 5-year survival of %22,52±8,23 and an OS of 41,02±5,12 months and patients having three different series of therapies had a 5-year survival of %34,41±13,42 and an OS of 54,38±7,20 months (Log rank: 8,80; p: 0,032; p<0,05). As the number of series of therapies increases so does the survival.

When we analyze the survival according to the therapy regimens given to the patients; 44 patient (%25,6) had Oxaliplatin containing FOLFOX4 regimen, 52 (%30,2) had Irinotecan containing IFL regimen, 39 (%22,7) had Irınotecan containing FOLFIRI regimen with VEGFR antibody Bevacizumab and 37 patient (%21,5) had Capacitabine and Oxaliplatin combination of XELOX. Patients who had FOLFOX regimen had a 5-year survival of %49,79±9,49 and overall survival is 55,13±7,22 months. Patients who had IFL regimen had a 5-year survival of %9,57±6,16 and overall survival is 32,53±3,9 months. Patients who had FOLFIRI and Bevacizumab regimen had a 5-year survival of %27,17±9,0 and overall survival is 32,53±3,9 months. Patients who had Capacitabine containing regimen (XELOX) had a 5-year survival of %23,43±9,98 and overall survival is 40,76±4,86months. Overall survival was statistically insignificant between these groups (Log rank: 6,668; p: 0,083; p>0,05).

DİSCUSSİON

Colorectal cancer is the third most common type of cancer in Western societies and the second leading cause of cancer-related deaths [9]. In the United States, the lifetime risk of developing CRC has been found to be close to 6%. This rate is slightly higher in men than in women. (5.88% vs. 5.49%)1 CRC is most commonly seen in the sixth decade of life, but can be detected at any age. CRC can spread to many regions and can involve one or more organs. The organs where metastases most frequently develop are the liver and lung. In a study conducted on autopsy materials of 1500 patients with CRC, liver metastases were detected in 44% of the cases and lung metastases in 21%.10 Other organs where metastases developed were adrenal glands (7%), bone marrow (6%), spleen (3.4%), pleura (2.8%) and brain (2.5%). In our material, 108 (62.79%) of our patients with metastatic CRC had liver metastases and 31 (18.02%) had lung metastases. 21 of our patients (12.2%) had peritoneal involvement. The number of patients with ovarian metastasis was 5 (2.91%). There was no significant difference in the overall survival times of the patients examined according to their metastasis localization (Log rank: 0.974; p: 0.614; p>0.05). No connection has been shown between metastasis localization and survival in the literature. The results in our material are also consistent with the current literature.

For years the main drug used in treatment was 5-fluorouracil, a fluoropyrimidine. (5-FU). However, over the years, numerous studies have revealed new drugs that are both cytotoxic, targeted, and immune-stimulating as treatment options. 5-FU was the main drug used in the treatment of metastatic CRC in the second half of the twentieth century. They act as an antimetabolite by affecting nucleic acid metabolism during the cell cycle. In the cell, 5-FU is metabolized to fluorodeoxyuridine monophosphate (FdUMP) and forms a complex that inhibits the thymidylate synthase enzyme. This complex reduces thymidylate formation and therefore DNA production [9]. Leucovorin or folinic acid is used as a modulator that stabilizes the FdUMP/thymidylate synthase complex and increases the effect of 5-FU.16

Discovered in the 1980s, irinotecan is a semi-synthetic product of the natural alkaloid camptothecin, which is converted to SN-38 by the carboxylesterase enzyme [19]. Three large phase III trials have investigated the combination of irinotecan with 5-FU as first-line therapy for metastatic disease. Saltz *et al*., randomized 683 patients to receive either irinotecan and 5-FU/leucovorin (IFL) or bolus 5-FU (Mayo) [23]. Patients assigned to the combination irinotecan arm had significantly longer progression-free survival (median 7.0 vs 4.3 months, p=0.004), higher response rates (39% vs 21%, p<0.001), and longer overall survival (median 14.8 vs 12.6 months, p=0.04). More grade III diarrhea was observed in the IFL arm. In the second study of 387 patients, irinotecan was added to some patients who received weekly or biweekly infusion therapy, and not to the others [24]. The patients who received irinotecan had

significantly better response rates (49% vs. 31%, p<0.001), time to progression (median 6.7 vs. 4.4 months, p<0.0001), and overall survival (median 17.4 vs. 14.1 months, p=0.031) than the other group. More diarrhea and bone marrow suppression were observed in the combination arm compared to the monotherapy arm. Based on the results of these two phase III studies, the FDA approved the use of irinotecan and 5-FU/leucovorin combination in the first-line treatment of patients with metastatic CRC. These studies have shown that irinotecan combined with bolus (IFL) or infusional 5-FU (FOLFIRI) therapy has a significant benefit in the treatment of patients with metastatic CRC.

In our study, irinotecan-based chemotherapy was used in the first-line treatment of metastatic CRC patients in 91 (52.90%) patients. However, in order to use irinotecan and bevacizumab in combination in some of these patients and to evaluate the efficacy of bevacizumab, these patients were divided into bevacizumab-receiving and non-bevacizumab-receiving groups. There were 52 (30.23%) patients in the irinotecan-based chemotherapy arm (IFL, FOLFIRI) in which bevacizumab was not used in their treatment. In these cases, the 5-year survival rate was determined as 9.57%+6.16. It was observed that 12 of the 36 patients (23.1%) in this group survived, 40 deaths were observed, and the average overall survival time was 32.53+3.90 months.

Oxaliplatin is a platinum compound that inhibits DNA synthesis. Its major effect is the formation of DNA extensions by the combination of platinum and a specific base sequence [9]. Oxaliplatin has been used as a monotherapy in the first or second line of metastatic CRC treatment, resulting in a response rate of 24% [26]. However, the majority of studies have examined the combination of oxaliplatin with 5-FU-based therapies. A phase III study has tested oxaliplatin with infusional 5-FU therapy (FOLFOX regimen) in the first-line treatment of metastatic CRC [27]. Compared with infusional 5-FU therapy alone, the combination therapy was found to provide better response rates (50.7% vs. 22.3%, p=0.0001) and significantly longer progression-free survival (median 9 vs. 6.2 months, p=0.0003). However, no significant superiority was observed in overall survival. Naturally, oxaliplatin provides significant improvements in response rate and progression-free survival when compared to bolus 5-FU regimens. There are studies comparing oxaliplatin-containing regimens with irinotecan-containing regimens to investigate superiority in treatment. One of these studies compared FOLFOX with IFL in first-line treatment in patients with newly diagnosed metastatic CRC [28]. As a result of this study, FOLFOX treatment was shown to be superior to IFL treatment in terms of progression-free survival and overall survival. However, since the superiority of infusional 5-FU treatment over bolus treatment is already known, it is not possible to deny that it affected the results of the study. Therefore, two separate studies were conducted comparing oxaliplatin and irinotecan given together with infusional treatment. In both studies, no statistically significant superiority was shown in tumor response rate, progression-free survival, or overall survival in either arm [11]. In our study, there were 44 patients (25.58%) who received an oxaliplatin-containing regimen in first-line treatment. The 2-year overall survival rate of these patients was 49.79+9.49%; the 5-year overall survival was 49.79+9.49%; it was determined that 27 patients (61.4%) in this group survived, 17 died, and the mean overall survival was 55.13+7.22 months.

With the increasing importance of targeted therapy in cancer treatment, it was unthinkable that CRC would not be affected by it. Understanding the growth mechanisms of cancer cells, especially the vascularization mechanism of cancer cells, has led to the identification of potential targets in cancer treatment. Bevacizumab is a human monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). In normal tissues, VEGF is a potential proangiogenic factor that plays an important role in angiogenesis. VEGF is closely associated with tumor invasion and poor prognosis in many types of cancer, especially CRC [29]. A phase III study in which bevacizumab was added and not added to first-line IFL treatment in previously untreated metastatic CRC patients showed a significant superiority in the bevacizumab arm in terms of response rate, progression-free survival, and most importantly overall survival (median 20.3 vs. 15.6 months, p<0.001) [30]. The major side effect detected in this study was hypertension. In the subgroup analysis, a significant superiority in overall survival was found in patients who received oxaliplatin-containing regimens in the second-line treatment of bevacizumab group compared to patients who received only 5-FU. Based on the results of this study, bevacizumab has been approved by the FDA for the first-line treatment of metastatic CRC. Since there was no reimbursement for the use of bevacizumab with oxaliplatin-containing regimens in our country during the time period in which our study was conducted, it was possible to combine it only with irinotecan-containing regimens. Therefore, the results of the combination of bevacizumab with irinotecan alone were evaluated in our study. The 5-year survival rate was determined as 7.17%+9.0. There were 39 cases in this group, 20 patients (51.3%) of whom survived, 19 died, and the mean overall survival time was understood to be 27.30+4.39 months.

When these four different combinations used in first-line metastatic CRC treatment are compared, there is no significant difference in overall survival times (Log rank: 6.668; p: 0.083; p>0.05). However, it is noteworthy that the 5-year survival rate and survival time are longer in patients receiving oxaliplatin regimen.

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The optimal duration of metastatic CRC treatment has not been precisely determined. In a study conducted in England, one group of patients who responded to or remained stable after fluoropyrimidine treatment continued treatment until progression, while the others interrupted treatment and started the same treatment when progression occurred. Only 37% of the patients started chemotherapy again after the break. However, no significant difference was found in overall survival between the two groups. However, fewer side effects were seen in the group receiving intermittent chemotherapy compared to the group receiving continuous treatment, and the quality of life of this group was found to be better than the other group [9].

In conclusion, both oxaliplatin and irinotecan are effective when combined with 5-FU. The major difference between the two drugs is their side effect profiles. Therefore, it would be more appropriate to make the selection accordingly in the first-line treatment. Our decision to choose the protocol was determined by the patients' findings, tolerance to side effects, and whether the drugs were available on the market. Tournigand *et al*., compared patients who received FOLFIRI as a first-line treatment and then received FOLFOX as a second-line treatment after progression with patients who received FOLFOX as a first-line treatment and then received FOLFIRI after progression [31]. When the responses to first-line treatment were examined, no significant difference was observed between the two groups. 74% of patients who received FOLFIRI received FOLFOX as a second-line treatment. The rate of receiving FOLFIRI as a second-line treatment was 62% in patients who received FOLFOX as a first-line treatment. In patients who received FOLFIRI as a second-line treatment, a response rate of 4% and a median progression-free survival time of 2.5 months were found, while in those who received FOLFOX, a response rate of 15% and a median progression-free survival of 4.2 months were found. As expected, the side effect profiles that developed in the two groups differed. In patients who received multiple chemotherapy, the choice of second-line treatment should be made for drugs with different side effect profiles than those used in first-line treatment.

As the treatment options available to us increase, patients can be applied third or even fourth-line treatments. However, the most important rule here is that the patient's performance status can tolerate the new treatment. As a result, today we have many options for the treatment of metastatic CRC. Regardless of the current treatment options, the survival times of patients have increased dramatically. However, 15 years ago, opportunities were relatively limited. Despite this, important steps have been taken in the treatment of metastatic colorectal cancer with current treatment methods and the door has been opened to new treatments.

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