Original Article

First-line treatment choices of Turkish medical oncologists in metastatic colorectal cancer: A survey study

Ismail Beypinar¹, Murat Araz¹, Mukremin Uysal¹, Suayib Yalcin²

¹Afyon Kocatepe University, Department of Medical Oncology, Afyonkarahisar, Turkey; ²Hacettepe University, Institute of Cancer, Department of Medical Oncology, Ankara, Turkey.

Summary

Purpose: Colorectal cancer is one of the most common malignancies in the World. RAS-BRAF mutational status and primary tumor location are also important factors for the selection of optimal combinations therapies. In this study, we aimed to evaluate the Turkish oncologists' treatment decisions depending on tumor location and mutational status in metastatic colorectal cancer.

Methods: An online survey link was sent to the medical oncologists who are registered to Turkish Society of Medical Oncology via e-mail and mobile applications.

Results: Ninety-four oncologists (85.5%) reported that tumor localization affects their treatment modality. In RAS-BRAF wild type left colon tumors, Turkish oncologists mostly use chemotherapy and anti-EGFR therapy (90.1%) for the first-line treatment, while on the right side, oncologists favored anti-VEGF therapy in combination with chemotherapy (65.5%). BRAF-mutant tumors in left colon had nearly the same rates of treatment tendency with both anti-VEGF and anti-EGFR antibodies in combination with chemotherapy, while in right-sided tumors the main treatment selection of the participants was anti-VEGF-based treatment (83.6%). In RAS-mutant patients, a great number of oncologists selected anti-VEGF-based treatment. On the right and left colon tumors, anti-VEGF treatment options ratios were 91.7 and 92.7%, respectively. Maintenance treatment is usually preferred by oncologists in both anti-VEGF and anti-EGFR-based treatment.

Conclusion: Turkish oncologists are considering tumor sidedness as an indicator for treatment individualization of patients. The selection of monoclonal antibodies is being affected by tumor localization and mutation status.

Key words: colorectal cancer, oncologists preferences, tumor sidedness, RAS mutation, BRAF mutation

Introduction

Colorectal cancer is one of the most common malignancies in the World. Nearly half of the patients either have metastasis at the time of diagnosis or later develop metastatic disease during follow up [1]. Addition of irinotecan or oxaliplatin to fluoropyrimidine-based chemotherapy is the backbone of treatment [2,3]. The new targeted agents like vascular endothelial growth factor antagonist (anti-VEGF) and epidermal growth factor receptor antagonist (anti-EGFR) monoclonal antibodies have opened a new era in the treatment of metastatic colorectal cancer. The combination of targeted agents and chemotherapy have extended life expectancy of metastatic colorectal cancer patients over 30 months [4,5]. But, optimal combination regimens as first-line treatment are still controversial. Extended RAS mutation evaluation is a key factor for the selection of the anti-EGFR agents because these drugs are effective only in RAS-wild type patient population. BRAF mutational status and primary tumor location are also important factors for the selection of optimal combinations.
therapies [6–9]. Retrospective analyses of studies showed that left-sided colon cancer patients achieve long-term survival benefit with anti-EGFR combination therapies [10]. Still, treatment suggestions for metastatic colorectal cancer differ from guidelines to guideline due to tumor location. While National Comprehensive Cancer Network (NCCN) guidelines restrict anti-EGFR agents in right-sided tumors in the first-line setting, however, there are no suggestions for the treatment of colon cancer depended on tumor sidedness by European Society of Medical Oncology (ESMO) guidelines yet. There are also some studies which investigate the treatment choices and guideline adherence of oncologists in the adjuvant setting of colorectal cancer, but there is no study for advanced disease [11,12]. In this study, we aimed to evaluate the Turkish oncologists’ treatment decisions depending on tumor location and mutational status in metastatic colorectal cancer.

Methods

Participants
An online survey link was sent to the medical oncologists who are registered to Turkish Society of Medical Oncology via e-mail and mobile applications. A total number of 599 oncologists were invited to fill in a questionnaire. The e-mail invitation and mobile application messages were sent two times in a week for increasing the response rates. The survey started on 22nd December 2017 and ended on 8th January 2018.

Survey
The online survey form was established via Google Surveys. The survey was taken voluntarily by oncologists. There were no promotions or gifts to increase participation. The questionnaire was containing 16 questions which were designed to understand the participants’ experience, working conditions, and colorectal cancer treatment decisions. Information about the experience in oncology practice, academic status and the type of hospital was obtained from the participants. The accessibility of genetic tests for RAS and BRAF and the type of hospital was obtained from the participants. The participants were the second group with 31 participants (28.2%). Most of the participants were working in university hospitals and educational state hospitals (39.1 and 29.1%, respectively). Other features of the study population are shown in the Table 1.

Most of the participants (72.7%) had genetic laboratories at their hospitals to make RAS and BRAF tests. The rest of the oncologists needed asistance of other facilities. A great number of oncologists (35.5%) answering the survey. Oncology specialists were the second group with 31 participants (28.2%). Most of the participants were working in university hospitals and educational state hospitals (39.1 and 29.1%, respectively). Other features of the study population are shown in the Table 1.

Results
One hundred and 10 oncologists (18% of all members) responded the survey invitation. Most of the oncologists (44.5%) who responded the questionnaire had 6- to 10-year experience in oncology. Associate professors were the largest population (35.5%) answering the survey. Oncology specialists were the second group with 31 participants (28.2%). Most of the participants were working in university hospitals and educational state hospitals (39.1 and 29.1%, respectively). Other features of the study population are shown in the Table 1.

Most of the participants (72.7%) had genetic laboratories at their hospitals to make RAS and BRAF tests. The rest of the oncologists needed assistance of other facilities. A great number of oncologists (77.5%) had the results in 2-week time.

The results for treatment choices were evaluated individually in all questions. In second evaluation the results were grouped into 4 categories as only chemotherapy, chemotherapy plus anti-EGFR, chemotherapy plus anti-VEGF and multiple choices.

Ninety-four oncologists (85.5%) reported that tumor localization affects their treatment option.

In RAS-BRAF wild left colon tumors, Turkish oncologists mostly used chemotherapy and anti-EGFR therapy (90.1%) for the first-line treatment. Chemotherapy backbone was (fluorouracil/capecitabine, leucovorin, oxaliplatin) FOLFOX/XELOX and FOLFIRI (fluorouracil, leucovorin, irinotecan) (64.5 and 47.3%, respectively). Only 4.5% of oncologists tended to use anti-VEGF combined with doublet
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Table 1. Oncologists’ experience, working conditions and academic status

<table>
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<tr>
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Table 1. Oncologists’ experience, working conditions and academic status

Figure 1. The chemotherapy backbone and targeted agent selection of oncologists in RAS-BRAF wild type tumors.

chemotherapy. Four oncologists had chosen more than 1 treatment option and one answered to use only chemotherapy in RAS-BRAF wild-type left colon cancers. On the right side colon cancers with RAS-BRAF wild-type, oncologists favored anti-VEGF therapy in combination with chemotherapy (65.5%). Nine oncologists chose more than one treatment modality while four reported only use of chemotherapy without monoclonal antibodies. The chemotherapy regimens most used were FOLFOX/XELOX, FOLFIRI, and FOLFOXIRI in combination with anti-VEGF antibodies (57.3, 26.4 and 11.8%, respectively) (Figure 1). A small subset of oncologists (6.4%) reported that they will use FOLFOXIRI plus anti-EGFR therapy. The medical oncologists working at an academical setting significantly preferred to use anti-EGFR antibodies in this group of patients (p=0.02). In the RAS-BRAF wild-type tumors localized to the transverse colon, the participants chose anti-EGFR treatment in combination with chemotherapy (59.1%). FOLFOX/XELOX backbone regimen was the most preferred option in this setting (52.7%). Chemotherapy plus anti-VEGF treatment was selected by 30 oncologists (27.3%). Anti-EGFR treatment choice decreased significantly from left to right colon (left: 90.9%, transverse: 59.1%, right: 22.7%, p<0.001). Thirteen participants had chosen more than one treatment option (11.8%). The oncologists who were working in university hospitals tended to use less anti-EGFR-based treatment in transverse colon tumors (University hospitals 47%, non-university hospitals 68%, p=0.03).
RAS wild and BRAF mutant tumors in the left colon had nearly the same rates of treatment tendency with both anti-VEGF and anti-EGFR antibodies in combination with chemotherapy (46.4 and 43.6%, respectively, p=0.68). In both arms, FOLFOX/XELOX backbone chemotherapy was the first option (anti-EGFR: 25.5%, anti-VEGF: 31.8%) (Figure 2). FOLFOXIRI was the second most selected option in front of FOLFIRI (22.7 and 20.9%, respectively) among medical oncologists who preferred to use an anti-VEGF agent plus chemotherapy. In rightsided tumors with RAS-wild type and BRAF mutant genetic profile, the use of anti-EGFR treatment was very low (6.4%). The main treatment selection of the participants was anti-VEGF-based treatment (83.6%). In this group, the choices of backbone chemotherapies were FOLFOX/XELOX, FOLFOXIRI, and FOLFIRI (55.5, 34.5 and 23.6%, respectively).

Figure 2. The chemotherapy backbone and targeted agent selection of oncologists in BRAF mutant tumors.

Figure 3. The chemotherapy backbone and targeted agent selection of oncologists in RAS mutant tumors.
In BRAF mutant patients with right-sided tumors oncologists preferred in significantly higher rates anti-VEGF than anti-EGFR-based treatment (83.6% and 46.4%, p<0.001).

In RAS mutant patients, a great number of oncologists selected anti-VEGF based-treatment. On the right and left colon tumors, anti-VEGF treatment options ratios were 91.7 and 92.7%, respectively. There was no statistical difference between these groups (p=0.63). As a second option, the oncologists preferred more than one option which was consisted of chemotherapy with or without a biologic agent (Figure 3). The selection of this option was higher in left-sided tumors (5.5%, 4.6%). Only chemotherapy and chemotherapy in combination with anti-EGFR agents were rarely selected (Table 2). The maintenance treatment was usually preferred by oncologists in both anti-VEGF and anti-EGFR-based treatment. The maintenance treatment rates were higher in the anti-VEGF group which was statistically significant (81.8 and 58.2%, p<0.001). The oncologists who had experience more than 10 years, used significantly less maintenance treatment with anti-EGFR antibodies (p=0.008). Also, anti-EGFR maintenance therapy was significantly less preferred in university hospitals (p=0.03).

Discussion

In this study, we investigated the guideline adherence and first-line treatment choices of Turkish oncologists in metastatic colorectal cancer. We reached 110 oncologists and had a sufficient representative sample of Turkish oncologist population. Most of the participants (85.5%) make their treatment choices according to tumor location. The retrospective analyses of phase 3 trials dependent on tumor location affected the treatment choices of Turkish oncologists in both chemotherapy regimens and targeted agents. In the retrospective analyses of FIRE-3 and CRYSTAL trials, while left-sided RAS wild colon tumors achieved great benefit from chemotherapy with or without anti-EGFR treatment, right-sided tumors had not benefited from the addition of anti-EGFR agents [13]. In our study participants chose mostly chemotherapy plus anti-EGFR treatment regimens in left-sided RAS wild type tumors. Turkish medical oncologists preferred FOLFOX/XELOX at a higher rate than FOLFIRI in combination with anti-EGFR agents. The FOLFOX/XELOX preference of participants can be based on the CALBG trial which showed the same response rate as FOLFIRI [14].

In our survey the selection of anti-EGFR agents decreased from left to right colon in RAS wild type colon cancer. In most studies, the transverse colon was excluded and there is no clear data about treatment effectiveness of these tumors. The participants mostly preferred chemotherapy plus anti-VEGF combinations. In RAS-mutated patients anti-EGFR-based treatment was very low in our survey on both sides of colon cancers by Turkish oncologists (1%, 1%).

The RAS mutation is very frequent in both right and left colon cancer and associated with anti-EGFR treatment resistance and even detrimental effects [16,17]. Both NCCN and ESMO guidelines do not recommend anti-EGFR-based treatment in this group of patients. Also in our survey, most of the oncologists preferred anti-VEGF-based treatments in both right and left-sided tumors (91.7 and 92.7%, respectively) with RAS mutant tumors. The other options were mostly composed of chemotherapy alone or both chemotherapy and anti-VEGF combinations. In RAS-mutated patients anti-EGFR-based treatment was very low in our survey on both sides of colon cancers by Turkish oncologists (1%, 1%).

The BRAF V600E mutation is the second most frequent mutation in colorectal cancer and rarely overlapping RAS mutations. BRAF mutation is seen in most right-sided tumors in association with tu-
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The authors declare no conflict of interests.

References


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Appendix. The questionnaire

Please do not consider reimbursement conditions while answering questions.
Please consider the patients’ ECOG performance status 0-1 while answering questions.
Anti-VEGF: Bevacizumab, Anti-EGFR: Cetuximab, Panitumumab

1. How long have you been working in Medical Oncology? (years)
   - 0-5
   - 6-10
   - 11-15
   - 16-20
   - 21-30
   - 31-40

2. What is your academic status in Medical Oncology?
   - Professor
   - Associate Professor
   - Assistant Professor
   - Specialist
   - Fellow

Continued on the next page
Please do not consider reimbursement conditions while answering questions. 
Please consider the patients’ ECOG performance status 0-1 while answering questions.

**Anti-VEGF:** Bevacizumab, **Anti-EGFR:** Cetuximab, Panitumumab

### 3. What kind of hospital are you working for?
- Government University Hospital
- Education and Research Hospital
- State Hospital
- Private Hospital
- Foundation University Hospital

### 4. Are your treatment decision influenced by the tumor sidedness in first-line treatment of metastatic colorectal cancer?
- Yes
- No

### 5. Do you have an opportunity of analyzing the KRAS-BRAF status of colorectal cancer in your hospital?
- Yes
- No

### 6. What is your estimated time of receiving results of KRAS-BRAF mutation analyze?
- 1 week
- 2 weeks
- 3 weeks
- 4 weeks
- More Than 4 weeks

### 7. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
- FOLFOX/XELOX
- FOLFIRI
- FOLFOX/XELOX+anti-EGFR
- FOLFIRI+anti-EGFR
- FOLFOX/XELOX+anti-VEGF
- FOLFIRI+anti-VEGF

### 8. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
- FOLFOX/XELOX
- FOLFIRI
- FOLFOXIRI
- FOLFOX/XELOX+anti-EGFR
- FOLFIRI+anti-EGFR
- FOLFOXIRI+anti-EGFR
- FOLFOX/XELOX+anti-VEGF
- FOLFIRI+anti-VEGF
- FOLFOXIRI+anti-VEGF

### 9. What are your first line palliative treatment choices in a patient who has TRANSVERSE COLON LOCATED TUMOR and RAS-BRAF WILD type? (More than one can be chosen)
- FOLFOX/XELOX
- FOLFIRI
- FOLFOXIRI
- FOLFOX/XELOX+anti-EGFR
- FOLFIRI+anti-EGFR
- FOLFOXIRI+anti-EGFR
- FOLFOX/XELOX+anti-VEGF
- FOLFIRI+anti-VEGF
- FOLFOXIRI+anti-VEGF

Continued on the next page
Please do not consider reimbursement conditions while answering questions.  
Please consider the patients’ ECOG performance status 0-1 while answering questions.  
Anti-VEGF: Bevacizumab, Anti-EGFR: Cetuximab, Panitumumab

10. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS WILD-BRAF MUTANT type? (More than one can be chosen)  
- FOLFOX/XELOX  
- FOLFIRI  
- FOLFOXIRI  
- FOLFOX/XELOX+anti-EGFR  
- FOLFIRI+anti-EGFR  
- FOLFOXIRI+anti-EGFR  
- FOLFOX/XELOX+anti-VEGF  
- FOLFIRI+anti-VEGF  
- FOLFOXIRI+anti-VEGF

11. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS WILD-BRAF MUTANT type? (More than one can be chosen)  
- FOLFOX/XELOX  
- FOLFIRI  
- FOLFOXIRI  
- FOLFOX/XELOX+anti-EGFR  
- FOLFIRI+anti-EGFR  
- FOLFOXIRI+anti-EGFR  
- FOLFOX/XELOX+anti-VEGF  
- FOLFIRI+anti-VEGF  
- FOLFOXIRI+anti-VEGF

12. What are your first line palliative treatment choices in a patient who has LEFT-SIDED TUMOR and RAS MUTANT type? (More than one can be chosen)  
- FOLFOX/XELOX  
- FOLFIRI  
- FOLFOXIRI  
- FOLFOX/XELOX+anti-EGFR  
- FOLFIRI+anti-EGFR  
- FOLFOXIRI+anti-EGFR  
- FOLFOX/XELOX+anti-VEGF  
- FOLFIRI+anti-VEGF  
- FOLFOXIRI+anti-VEGF

13. What are your first line palliative treatment choices in a patient who has RIGHT-SIDED TUMOR and RAS MUTANT type? (More than one can be chosen)  
- FOLFOX/XELOX  
- FOLFIRI  
- FOLFOXIRI  
- FOLFOX/XELOX+anti-EGFR  
- FOLFIRI+anti-EGFR  
- FOLFOXIRI+anti-EGFR  
- FOLFOX/XELOX+anti-VEGF  
- FOLFIRI+anti-VEGF  
- FOLFOXIRI+anti-VEGF

14. Do you use maintenance treatment with anti-VEGF agents?  
- Yes  
- No

15. Do you use maintenance treatment with anti-EGFR agents?  
- Yes  
- No

16. What is your guideline preference in colorectal cancer treatment?  
- NCCN  
- ESMO  
- Other