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RESEARCH ARTICLE

AFLIBERCEPT PLUS FOLFIRI AS SECOND-LINE THERAPY IN METASTATIC COLORECTAL CANCER (MCRC) DURING PANDEMIC COVID-19: A REAL-WORLD EXPERIENCE

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ABSTRACT: The use of Aflibercept plus Folfiri represents the second-line chemotherapy in patients with metastatic colorectal cancer (mCRC) previously treated with Oxaliplatin. The outbreak of COVID-19 upset the standardized procedure of routinary access to the hospital with a lot of difficulty in administering chemotherapy. For this reason, we conducted this retrospective study on 78 enrolled patients who were diagnosed with mCRC, through the pandemic period. Primary endpoints were quality of life (QoL), progression-free survival (PFS) and overall response rate (ORR) in two patient groups treated before and after the onset of COVID-19, group A and group B, respectively. Secondary endpoints were tolerability profile, prognostic factors and carcinoembryonic antigen (CEA) reduction. The median age in all patients was 58 years old, and the median PFS was 6.2 months (95% CI: 5.1-7.2). A significant correlation was observed between decreased CEA levels and PFS with a P value of 0.63 (P = 0.009), which led to consequent improvement of QoL. The treatment was well tolerated, with good disease control and a manageable toxicity profile. Our survival analysis shows a non-significant difference in PFS in the two groups of patients treated before and after COVID-19 (6.1 versus 6.2 months). Furthermore, our analysis suggests left-side tumor site and wild-type RAS/BRAF status as potential prognostic factors for PFS and ORR. The results showed therapeutic benefits of AFL plus Folfiri as second-line therapy in mCRC patients previously treated with Oxaliplatin. The use of AFL plus Folfiri showed efficacy and safety, although the COVID-19 pandemic has affected the management of patients' care.

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Impact statement: AFL plus Folfiri showed therapeutic benefits in mCRC patients previously treated with Oxaliplatin. AFL influenced patient care management, maintaining good QoL.

Key words: *Aflibercept; chemotherapy; colorectal cancer; pandemic; covid-19; survival; quality of life.*

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INTRODUCTION

The outbreak of the coronavirus disease 2019 (COVID-19) has generated new challenges in cancer patients' care procedures, with a particular impact on the readjustment of the resources and the risk-benefit balance of cancer therapies (1). Cancer centers have developed new strategies and also preventive measures to deal with oncological patients during the COVID-19 pandemic (2). Such measures include the performance of oropharyngeal swabs, the administration of oral therapies instead of intravenous ones, and the spreading of remote multidisciplinary teams (general practitioners, psychologists, health professionals) to reduce the access of patients to the wards at a high risk of contagion (3, 4). The pandemic has called for a review of our daily medical practices, including our approach to colorectal cancer (CRC) management. Even during the COVID-19 pandemic, chemotherapy combined with target therapies remains an effective strategy to treat metastatic colorectal cancer (mCRC) (5, 6). Aflibercept (AFL) plus FOLFIRI (Fluorouracil, Leucovorin, and Irinotecan) has been shown effective in increasing the chances of survival of patients with advanced CRC, after previous treatments including oxaliplatin-based regimens with the addition of anti-VEGF (vascular endothelial growth factor) Bevacizumab monoclonal antibody or anti-EGFR (Epidermal growth factor receptor) Cetuximab or Panitumumab monoclonal antibodies, according to RAS/BRAF gene status (7-9). AFL is a second-generation antiangiogenic with a broader spectrum of action than Bevacizumab, as it can block both VEGF-A and PIGF, inhibiting the activity of VEGFR-1 and VEGFR-2 receptors by blocking tumor neoangiogenesis (10-12). VELOUR phase III randomised controlled trial (ClinicalTrials.gov NCT00561470) analyzed the effect of adding AFL to FOLFIRI, as a second-line option. Compared to FOLFIRI alone, the combination resulted in 1.5 month median overall survival (OS), (13.50 vs.12.06 respectively; HR: 0.817; 95% CI: 0.713-0.937; p = 0.0032) and median 2.2 months in PFS improvements (6.90 vs. 4.67 respectively; HR: 0.758; 95% CI: 0.661-0.869; p = 0.00007) (13, 14). The safety profile of this combination has been proven acceptable and manageable. Based on the results of the VELOUR study, we conducted a mono-institutional retrospective analysis, which embraced both the pre-pandemic and the pandemic periods, to evaluate the safety and efficacy of AFL in combination with FOLFIRI in patients with progressing mCRC previously treated with Oxaliplatin based regimens as routinely used in clinical practice (15, 16).

PATIENTS AND METHODS

Design and Participants

Between June 2016 and March 2022 a total of 78 patients were enrolled in the study. The inclusion criteria were: histologically confirmed diagnosis of mCRC; age ≥18 years old; Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2; measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (17, 18); progressive disease after first-line therapy with Oxaliplatin (according to RAS/BRAF gene status) regular heart function with left ventricular ejection fraction (LVEF) >50% and electrocardiogram (ECG) with sinus rhythm; adequate bone marrow, renal and hepatic functions; computerized tomography and/or magnetic resonance imaging of the central nervous system available for radiological review.

The exclusion criteria were: patient whit hypersensitivity to AFL, its excipients, or any other formulation components; no concomitant anticancer therapies were allowed, and radiotherapy at extracranial sites must have been stopped at least one month before starting the treatment.

Method of Administration

All patients received 4 mg/kg of AFL intravenously according to the treatment assignment, for more than an hour on day 1 every two weeks, immediately followed by the FOLFIRI regimen (Irinotecan 180 mg/m^2 IV for more than 90 minutes, with leucovorin 400 mg/m^2 IV for more than 2 hours, followed by FU 400 mg/m^2 bolus and FU 2400 mg/m^2 continuous infusion for more than 46 hours) (19). Patients were premedicated as indicated in routine clinical practice. Electrocardiogram (ECG) and echocardiogram were performed at baseline and every three months. Treatment was administered until disease progression or development of unacceptable toxicity (20). The outbreak of the COVID-19 pandemic has required a revision of routine medical care to minimize the risk of exposing patients to the virus infection.

Evaluation of Response and Toxicity

Dose interruption was allowed to manage treatment-related adverse events (TRAEs). FOLFIRI TRAEs and side effects were assessed at the end of each cycle and reported according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. G3 or G4 toxic effects were managed with dose reduction or delay, in compliance with clinical practice procedures. Patient characteristics such as performance status, histopathological data, laboratory and radiological data (number of metastatic sites ≥2), and treatment outcomes were collected and reviewed to identify any prognostic factors to assess the best second-line therapy.

Quality of Life

QoL was regularly assessed by the psycho-oncologists, which provided all patients with the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer) questionnaire at the beginning of the treatment and after three months (21). The questionnaire is composed of both single-item and multi-item scales. The scaling is organized into five functional domains (physical, role, cognitive, emotional, and social), three-item symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and six single-item scales (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea and perceived financial impact of the disease). The score is evaluated according to a linear grading scale ranging from 0 to 100. A high score on a functional scale and global health status/QoL represents a high/healthy level of functioning, whereas a high score on a symptom scale/item represents a high level of symptomatology/problems.

Statistical Analysis

All statistical analyses ware performed using Statistical Package for Social Science (SPSS) software version 25. for Mac (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the baseline data of the patients, divided into two groups, respectively cancer treatment before COVID-19 (Group A) and after COVID-19 (Group B), with standard deviation or qualitative data being expressed as percentages. Proportions for categorical variables were compared using Student t tests. ORR is defined as the percentage of patients who achieved complete or partial response after treatment. PFS was calculated from the beginning of the treatment until progression, the PFS curve was assessed using the Kaplan-Meier method and the subgroup analysis of survival curves was performed with the Log-rank test. Bravais-Pearson's (r) linear correlation index was used to define the relation between PFS and CEA with a 95% confidence interval (CI). The statistical significance was defined as a p-value of less than 0.05. The last follow-up was in August 2022.

Endpoints

The main objective was to assess the impact of the COVID-19 pandemic on the management of patients. Primary endpoints were the comparison of the QoL, PFS and ORR in the two patient groups treated before and after the onset of COVID-19, group A and group B, respectively. Tolerability profile, prognostic factors and carcinoembryonic antigen (CEA) reduction were secondary endpoints.

Ethical Aspects

The study, approved by the Local Ethics Committee, Policlinico Palermo 1, was conducted in full compliance with the provisions of the Declaration of Helsinki as well as with the Good Clinical Practice guidelines. All patients provided written informed consent to be included in this study.

RESULTS

Descriptive Patients Characteristics

A total number of 78 patients were enrolled in this retrospective study, divided into two groups. Group A comprised all patients who underwent cancer treatment before the onset of the COVID-19 pandemic, between Jun 2016 and February 2020, while Group B included all those patients who were treated between March 2020 and March 2022. Demographic characteristics of the patients were well-balanced in all two cohorts (**Table 1**), in the Group A (cancer treatment before COVID-19) were 56 patients (29 male and 27 female), with a median age of 58 years old (range 49-68), in the Group B (cancer treatment after COVID-19) were 22 patient (12 male and 10 female) with a median age of 57 years old (range 51-62). All patients were previously treated with an Oxaliplatin first-line regimen. As for the ECOG performance status, in all 78 patients, 25 (32%) patients had ECOG 0, 43 (55%) had ECOG 1, and 10 (13%) had ECOG 2. Patients who had already undergone primary surgery were 65,

Table 1. *Baseline clinical and pathological characteristics (n. 78) divided in two groups (Group A and Group B).*

	GROUP A N = 56 (%)	GROUP B N = 22 (%)	*P* VALUE
Mean age (range)	58 (49-64)	57 (51-62)	0.02
Sex			
Male	29 (52%)	12 (58%)	1.93
Female	27 (48%)	10 (42%)	1.09
ECOG performance status			
0	18 (32%)	7 (31%)	0.78
1	32 (57%)	11 (50%)	1.45
2	6 (11%)	4 (18%)	0.08
Primary tumor location			
Single left-site	21 (38%)	14 (64%)	0.92
Single right-site	34 (61%)	8 (36%)	0.88
Single transverse-site	1 (1%)	-	
K-RAS and B-RAF status			
Wild-type	33 (59%)	16 (72%)	0.78
Mutant	23 (41%)	6 (28%)	0.98
Location of metastasis			
Liver	14 (25%)	8 (36%)	0.16
Lung	9 (16%)	5 (23%)	0.08
Lymph nodes	33 (59%)	9 (41%)	1.51

Group A: cancer treatment before COVID-19; Group B: cancer treatment after COVID-19; ECOG: Eastern Cooperative Oncology Group.

whilst 13 had concurrent hepatic metastasectomy. Anti-EGFR therapies were administered to 49 patients with wild-type RAS tumors, whilst anti-VEGF therapy with Bevacizumab was administered to 29 patients with mutant RAS/BRAF tumors. Furthermore, 17 patients (22%) were treated with FOLFOX and 61 patients (78%) with CAPOX. The primary tumor site was the left side in 35 patients, the right side in 42 patients, and the transverse colon in 1 patient only. The metastatic sites of the disease were the liver, lungs, and peritoneum. 16 patients had pre-treatment CEA values <10 mg/dl and only one metastatic site (liver or lung). **Table 1** shows the main characteristics of the study groups.

Clinical outcomes

On average, patients received 9 cycles of chemotherapy (range: 7-11). AFL plus FOLFIRI was well-tolerated, with a manageable toxicity profile. After a median follow-up of 12.6 months (range: 9.2-13.6) response rates according to RECIST criteria showed 1 (1%) complete response (CR); 15 (19%) partial response (RP); 48 (62%) disease stabilization (SD); 13 (17%) progression disease (PD) and 1 (1%) not evaluable. Accordingly, ORR (CR + PR) was 19.4%, and DCR (CR+PR+SD) was >82% (**Table 2**) summarized results for groups A and B respectively). The median response time in all patients (n = 78) was 6.5

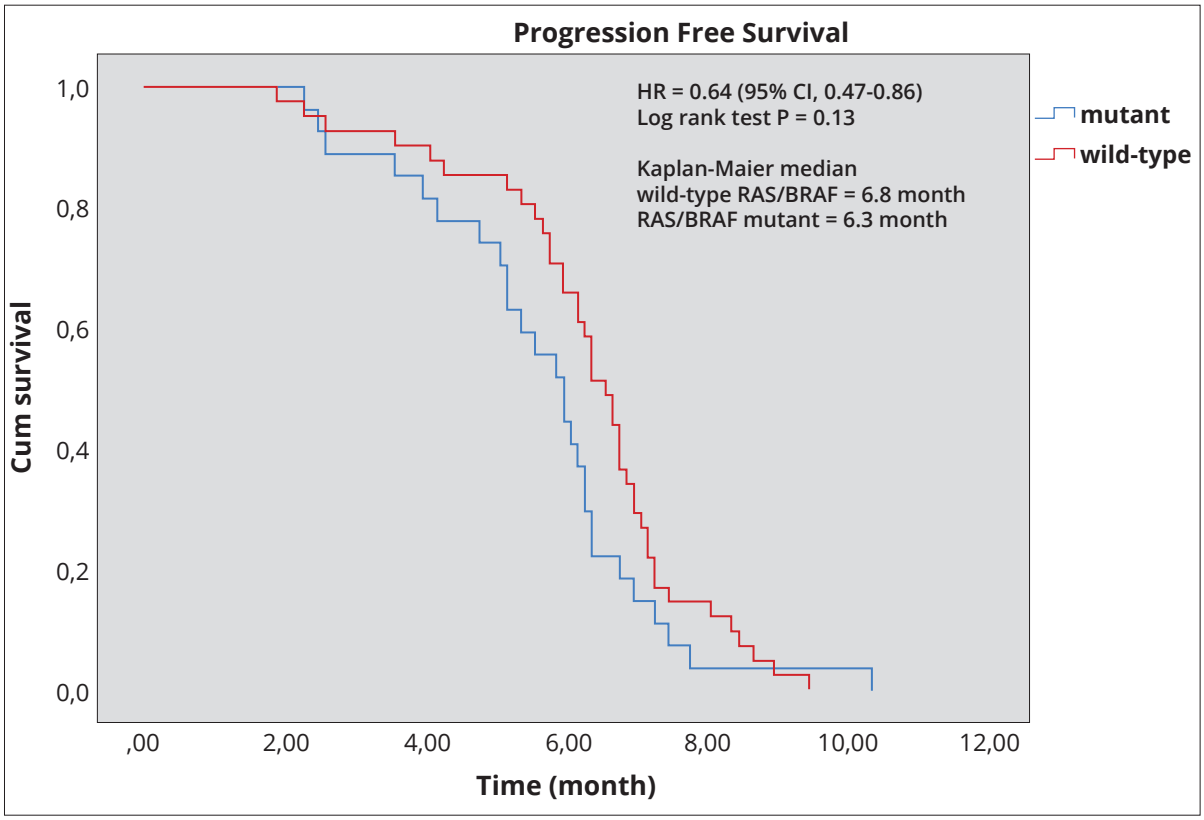

Figure 1. *Log rank test for PFS in wild-type RAS/BRAF (n. 49) and RAS/BRAF mutant (n. 29). PFS: progression-free survival.*

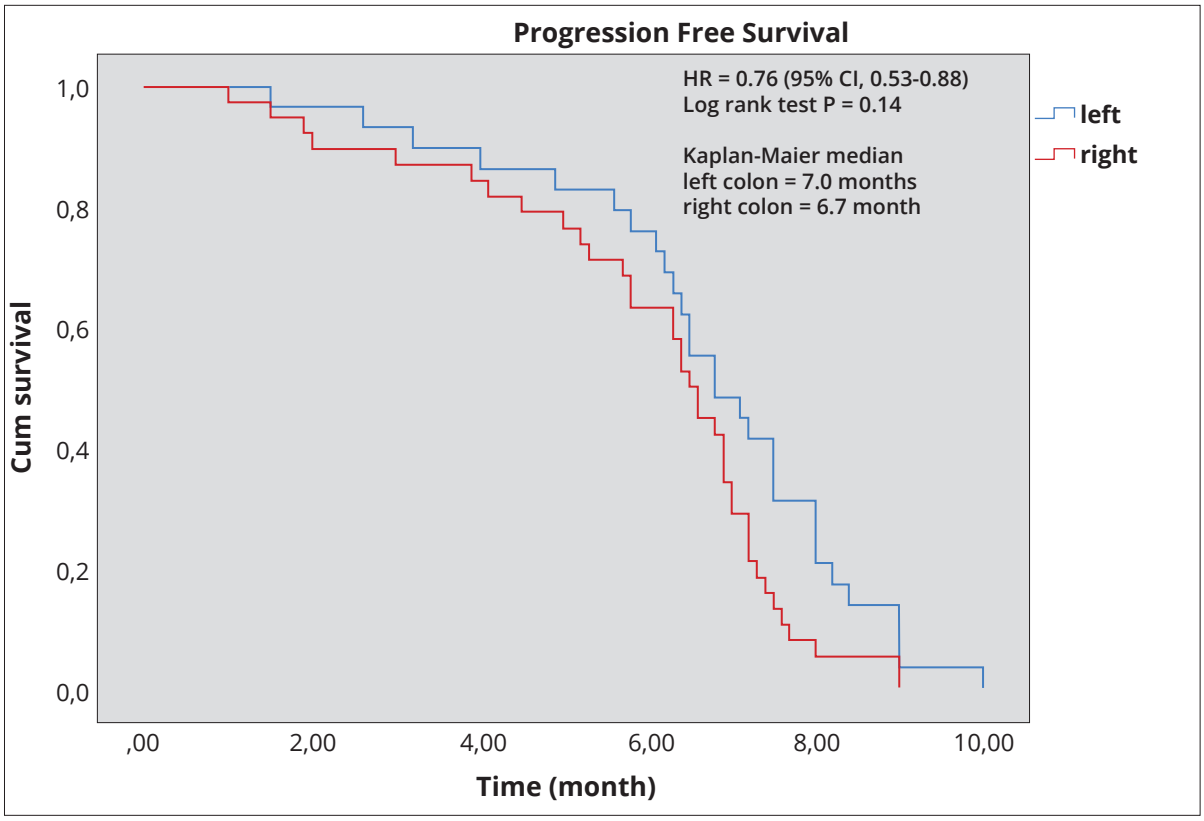

Figure 2. *Log rank test for PFS in primary tumor site in the left colon (n. 35) and primary tumor site in the right colon (n. 42). PFS: progression-free survival.*

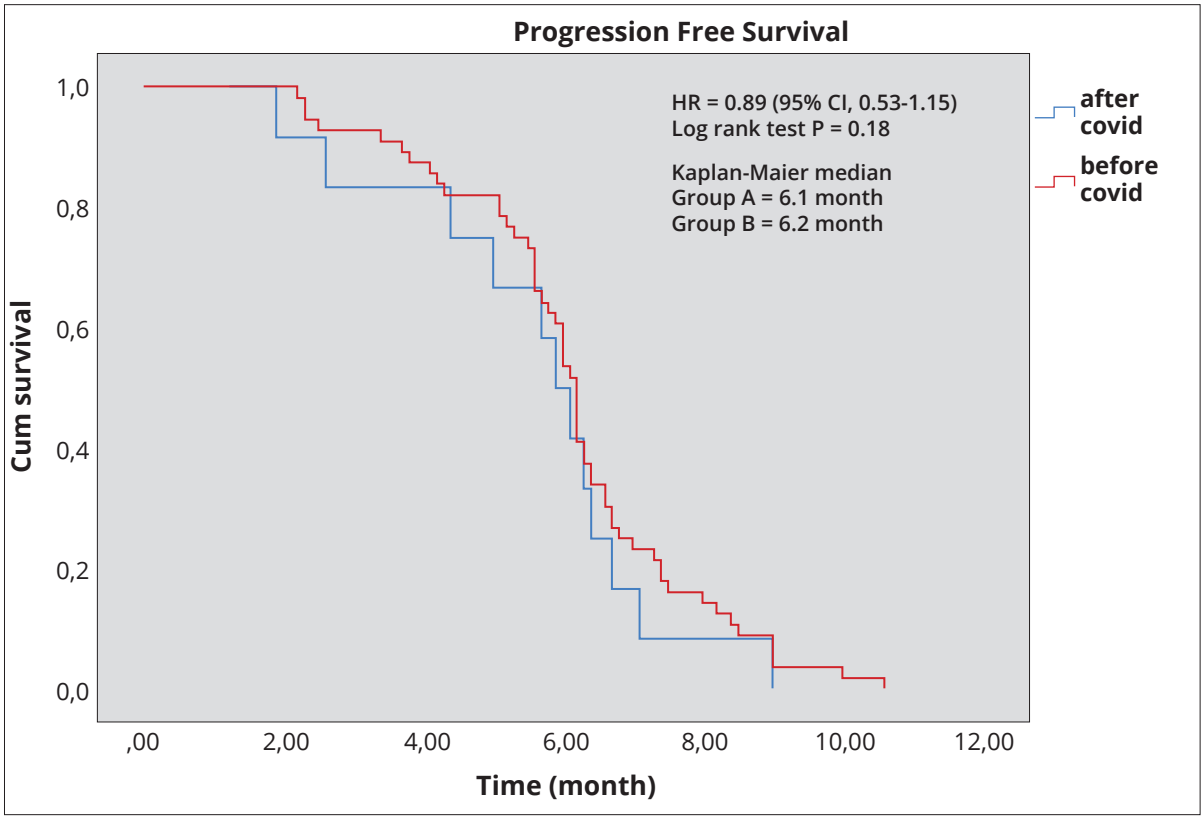

Figure 3. *Log rank test for PFS in patients treated before COVID-19 period (n. 56) and patients treated after COVID-19 period (n. 22). PFS: progression-free survival; Group A: cancer treatment before COVID-19; Group B: cancer treatment after COVID-19.*

Table 2. *Overall Response Rate divided in two groups (Group A and Group B).*

	GROUP A N = 56 (%)	GROUP B N = 22 (%)	*P* VALUE
Complete response	1 (2%)	-	
Partial response	9 (16%)	6 (27%)	0.05
Stable response	36 (64%)	12 (55%)	0.46
Progressive response	9 (16%)	4 (18%)	0.03
Not evaluable	1 (2%)	-	
Overall response rate (CR+PR)	10 (18%)	6 (27%)	0.12
Clinical benefit rate (CR+PR+SD)	46 (82%)	18 (82%)	0.46

Group A: cancer treatment before COVID-19; Group B: cancer treatment after COVID-19; ECOG: Eastern Cooperative Oncology Group; CR: complete response; PR: partial response; SD: stable response.

months (95% CI: 4.9-8.1) with a modest improved QoL. Bravais-Pearson index showed a positive correlation between PFS and CEA reduction, with a correlation coefficient (95% CI:0.31-0.76) value of 0.59, p = 0.009. We observed a mean CEA reduction >50% reflecting an increase in PFS.

Our analysis of the final cohort of patients showed a median PFS of 6.2 months (95% CI:5.1-7.2). According to RAS/BRAF status (WT vs mutant), PFS was 6.8 months versus 6.3 months respectively (**Figure 1**); also sideness (left vs right) did not affect PFS (7.0 months versus 6.7 months respectively) (**Figure 2**); we have recorded a PFS of 6.1 months in Group A versus 6.2 months in Group B with a HR of 0.89 (95%, CI 0.53-1.15), furthermore, in patients with low pre-treatment CEA levels and a low number of metastatic sites, we registered also greater PFS time. **Figure 3** reports the PFS analyses of patients, divided according to the treatment period before COVID-19 (group A) and after COVID-19 (group B). Our analyses showed no statistically significant differences in PFS between the two groups likely due to their small size.

Quality of Life

At baseline (treatment beginning), the EORTC QLQ-C30 questionnaires showed an overall slightly lower QoL outcome (the score for global health status was 57.7 in group A vs 56.3 in the group B). As for the symptom scales, patients reported sleeping disorders (24.3), fatigue (41.6) and nausea/vomiting (50.3) in two groups. Furthermore, the group B shows a worsening in the social area (47.0 group A vs 58.1 group B) and financial area (44.3 group A vs 45.7 group B). At follow-up, QoL had improved with a score of 61.3 for global health status (61.5 group A vs 60.7 group B). In the two groups we observe a reduction in pain symptoms (44.3 group A vs 45.2 group B), (**Table 3**). The reduction of financial impact appeared also relevant. In fact it was at baseline 44.3 in group A and 45.3

Table 3. *The Quality of Life score (n. 78) divided in two groups (Group A and Group B).*

	GROUP A N = 56		GROUP B N = 22		*P* VALUE
	BASELINE	FOLLOW UP	BASELINE	FOLLOW UP	
Global health status	57.7	61.5	56.3	60.7	0.05
Physical	46.1	47.4	46.9	47.0	0.35
Role	41.5	42.5	44.3	44.7	0.78
Cognitive	43.6	43.8	43.9	44.3	1.06
Emotional	51.4	50.6	52.7	51.8	0.58
Social	47.0	48.3	58.1	57.9	0.02
Fatigue	41.4	39.4	41.7	40.6	1.69
Pain	48.6	44.3	48.8	45.2	0.00
Nausea and vomiting	50.3	50.2	50.3	50.1	1.56
Dyspnoea	29.6	28.3	28.4	28.1	1.73
Loss of appetite	19.6	19.5	19.9	18.9	0.07
Insomnia	24.3	24.7	34.6	35.7	0.01
Constipation	18.6	18.8	18.9	18.4	1.83
Diarrhoea	18.6	18.9	17.5	18.2	0.59
Financial impact	44.3	45.7	45.3	48.1	0.06

in group B, respectively, and it became after three months 45. 7 in group A and 48.1 in group B, respectively.

Tolerability

No severe treatment-related hypersensitivity reactions were reported, and no patients died of treatment-related adverse events. The main hematological toxicities related to AFL and FOLFIRI were: neutropenia (all grades: 36%; G3-G4: 12%), febrile neutropenia (all grades: 8%), G2-G3 anemia (22%) G4 anemia (5 patients), and G3 thrombocytopenia (12%). Granulocyte colonies-stimulating factor (G-CSF), antibiotics, erythropoietin, oral steroids, and blood transfusions (3 patients) were used as expected in routine clinical practice. The most frequent major non-hematological toxicities were: asthenia (all grades: 26%); diarrhoea (all grades: 24%; G3-G4: 9%), treated with loperamide as needed; arterial hypertension; G3 hypertension (18%), treated with the dose-adjustment of the pre-existing antihypertensive therapies or with more than one drug; G4 hypertension (only 1 case); G3 proteinuria (6%); palmar-plantar erythro-dysesthesia (in 1-4%- of G2-G3 patients) (**Table 4**). No heart failure, left ventricular ejection fraction (LVEF) reduction, gastrointestinal perforations, or fistulas cases were reported. No significant differences were recorded in both incidence and severity of Ae in the two groups of patients.

Table 4. *Adverse events graded according CTCAE, Version 4.0 (n. 78).*

ADVERSE EVENTS	ALL GRADES	GRADE 3-4
Hematological		
Anemia	22%	6%
Neutropenia	38%	14%
Trombocitopenia	16%	12%
Febbrile neutropenia	13%	13%
Non-hematological		
Nausea	16%	12%
Vomiting	12%	8%
Hypertension	18%	12%
Fatigue	28%	28%
Hyperbilirubinemia	4%	2%
Hand foot syndrome	4%	4%
Peripheral neuropathy	0%	0%
Diarrhoea	48%	13%

CTCAE: Common Terminology Criteria for Adverse Events.

DISCUSSION

The outbreak of the COVID-19 pandemic has interfered with the normal practices of cancer patients' management in both providing and receiving care. This study was carried out before and after the COVID-19 pandemic. As a result of this analysis, AFL combined with FOLFIRI was proven effective and well-tolerated as second-line therapy for mCRC. Patients were previously treated with Oxaliplatin-based regimens as first-line chemotherapy and, in some cases, they also received anti-VEGF or anti-EGFR targeted agents. The pandemic has required new practices in patient management: to reduce the risk of exposition to the virus, preventive measures were introduced to limit access of cancer patients to the hospital. Our results were in line with the VELOUR trial experience (15-22). Although the retrospective design of this study, our results showed AFL effective and well-tolerated, with good disease control and a manageable toxicity profile, with a median PFS of 6.2 months (95% CI: 5.1-7.2). As a consequence, COVID-19 pandemic had probably no impact on PFS for FOLFIRI + Aflibercept treatment.

A significant impact on QoL was observed in most patients (23, 24), the result of this study showed no significant impact due to the onset of COVID-19 pandemic. In the present study, mutations of the RAS / BRAF genes were associated with a lower response rate with a median PFS of 6.3 months, compared to a median PFS of 6.8 months for the wild-type RAS/ BRAF subgroup. Similar trends were observed in the biomarker sub-analyses of the VELOUR study (16). The primary tumor site is an important independent prognostic factor in CRC due to the distinct biological characteristics of right-sided and left-sided tumors. Of interest, right colon cancer is associated with defective repair genes and increased numbers of KRAS / BRAF mutations (25). In our study, no clinically relevant differences were shown according to the localization of the tumor on the left or right side (7.0 months versus 6.7). Finally, a significant correlation was observed between lower pre-treatment CEA values, deceased post-treatment CEA values, increased PFS. Therefore, based on these results, the lack of RAS/BRAF mutations, the localization of the primary tumor, and the pre-treatment CEA levels may represent prognostic factors to achieve greater responses and prolongation of survival.

The results of this study suggest that AFL with FOLFIRI may have specific benefits in patients with the above-mentioned characteristics even during COV-

ID-19 pandemic. Moreover, patients treated with this combination did not experience QoL worsening. On the contrary, thanks to psyconcologist support, the 85% patients enrolled experienced either improvement or stability in QoL. The study confirms that the absence of RAS/BRAF gene mutations, the localization of the primary tumor on the left side, and low pre-treatment CEA levels might be prognostic biomarkers for the treatment with AFL plus FOLFIRI. In addition, a significant correlation between decreased CEA levels increased PFS, and clinical benefits were observed. AFL is an effective antiangiogenic therapy with a manageable tolerability profile that provides significant clinical benefits when combined with FOLFIRI in mCRC after Oxaliplatin with or without biological agents (26). The results obtained showed that AFL is well-tolerated by most patients. AFL does not alter QoL, and its efficacy in terms of survival is confirmed. The results show a good QoL for patients under treatment, without critical consequences in the management of the disease. The physical symptoms were well tolerated without any impact on QoL, however a greater impact was observed on the social area, affecting what were distracting and sociable activities.

CONCLUSIONS

During the recent COVID-19 pandemic, although treatment guidelines remained unchanged, patient management was modified. Nevertheless, the best oncological therapy was performed with a reasonable profile of complications and side effects of chemotherapy due to antiemetics, antiallergics, prophylaxis for immunodeficiencies (G-CSF). A specific patient management was crucial to limit the access of patients to the hospital and, consequently, to drastically reduce the risk of Covid infections in cancer patients (27). The psycho-oncological support, as established by national and international guidelines, is a tool that allows you to improve patients' mood and QoL. This study showed efficacy results for mCRC patients treated with AFL and FOLFIRI in common clinical practice, including patients previously treated with anti-EGFR antibody or bevacizumab during the COVID-19 pandemic (28). AFL plus FOLFIRI has a manageable safety profile, and the results regarding the efficacy and toxicity are consistent with previous studies (29, 30). Limitations of this analysis include the restricted number of patients enrolled as well as the non-randomized sampling. According to the retrospective nature of our analysis and the limited number of patients enrolled, we can suggest that our results can provide valid assumptions for future studies.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

This research received no external funding.

Conflict of interests

The authors have nothing to disclose, and all authors declare no conflict of interest.

Availability of data and materials

All the datasets on which the conclusions of this study rely were displayed in the manuscript.

Authors' contributions

All authors made a significant contribution to the work reported. GC as coordinating investigator, principal investigator and project manager: designed, initiated, managed and coordinated the research; AG, RD, RA, GR, SC and GL: contributed to the study conception and design; RD, AG and GC: performed material preparation and data collection. The final version of the article was approved by all authors for publication.

Ethical approval

Human studies and subjects

The study was conducted in full compliance with the provisions of the Declaration of Helsinki as well as with the Good Clinical Practice guidelines.

Animal studies

N/A.

Publications ethics

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) Weekly Epidemiological Updates and Monthly Operational Updates. In: Situation reports. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed: Apr 4, 2020.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. doi: 10.1056/NEJMoa2001017.
3. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 100. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200429-sitrep-100-covid-19.pdf. Accessed: Mar 21, 2024.
4. Morris EJA, Goldacre R, Spata E, Mafham M, Finan PJ, Shelton J, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. Lancet Gastroenterol Hepatol. 2021;6(3):199-208. doi: 10.1016/S2468-1253(21)00005-4.
5. Stintzing S, Fischer von Weikersthal L, Decker T, Vehling-Kaiser U, Jäger E, Heintges T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. Ann Oncol. 2012;23(7):1693-9. doi: 10.1093/annonc/mdr571.
6. Gong J, Cho M, Fakih M. RAS and BRAF in metastatic colorectal cancer management. J Gastrointest Oncol. 2016;7(5):687-704. doi: 10.21037/jgo.2016.06.12.
7. Afrăsânie VA, Marinca MV, Alexa-Stratulat T, Gafton B, Păduraru M, Adavidoaiei AM, et al. KRAS, NRAS, BRAF, HER2 and microsatellite instability in metastatic colorectal cancer - practical implications for the clinician. Radiol Oncol. 2019;53(3):265-74. doi: 10.2478/raon-2019-0033.
8. Golshani G, Zhang Y. Advances in immunotherapy for colorectal cancer: a review. Therap Adv Gastroenterol. 2020;13:1756284820917527. doi: 10.1177/1756284820917527.
9. Sun W. Angiogenesis in metastatic colorectal cancer and the benefits of targeted therapy. J Hematol Oncol. 2012;5:63. doi: 10.1186/1756-8722-5-63.
10. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44. doi: 10.1200/JCO.2006.09.6305. Corrected and republished in: J Clin Oncol. 2023;41(21):3670-5.
11. Feliu J, Díez de Corcuera I, Manzano JL, Valladares-Ayerbes M, Alcaide J, García García T, et al. Effectiveness and safety of aflibercept for metastatic colorectal cancer: retrospective review within an early access program in Spain. Clin Transl Oncol. 2017;19(4):498-507. doi: 10.1007/s12094-016-1556-3.
12. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499-506. doi: 10.1200/JCO.2012.42.8201.
13. Chong DQ, Manalo M, Imperial M, Teo P, Yong G, Ng M, et al. Safety and efficacy of aflibercept in combination with fluorouracil, leucovorin and irinotecan in the treatment of Asian patients with metastatic colorectal cancer. Asia Pac J Clin Oncol. 2016;12(3):275-83. doi: 10.1111/ajco.12496.
14. Lockhart AC, Rothenberg ML, Dupont J, Cooper W, Chevalier P, Sternas L, et al. Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. J Clin Oncol. 2010;28(2):207-14. doi: 10.1200/JCO.2009.22.9237.
15. Van Cutsem E, Joulain F, Hoff PM, Mitchell E, Ruff P, Lakomý R, et al. Aflibercept Plus FOLFIRI vs. Placebo Plus FOLFIRI in Second-Line Metastatic Colorectal Cancer: a Post Hoc Analysis of Survival from the Phase III VELOUR Study Subsequent to Exclusion of Patients who had Recurrence During or Within 6 Months of Completing Adjuvant Oxaliplatin-Based Therapy. Target Oncol. 2016;11(3):383-400. doi: 10.1007/s11523-015-0402-9.
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur

J Cancer. 2009;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.
17. Cicero G, Lo Re G, DE Luca R, Vernuccio F, Picone D, Midiri M, et al. Role of Densitometric Criteria in Evaluation of Effectiveness of Antiangiogenic Therapies in Metastatic Colorectal Cancer: An Italian Clinical Experience. Anticancer Res. 2017;37(9):5187-92. doi: 10.21873/anticanres.11941.
18. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705. doi: 10.1200/JCO.2009.27.4860.
19. Yusof MM, Abdullah NM, Sharial MM, Zaatar A. Safety and Management of Toxicity Related to Aflibercept in Combination with Fluorouracil, Leucovorin and Irinotecan in Malaysian Patients with Metastatic Colorectal Cancer. Asian Pac J Cancer Prev. 2016;17(3):973-8. doi: 10.7314/apjcp.2016.17.3.973.
20. Snyder CF, Blackford AL, Okuyama T, Akechi T, Yamashita H, Toyama T, et al. Using the EORTC-QLQ-C30 in clinical practice for patient management: identifying scores requiring a clinician's attention. Qual Life Res. 2013;22(10):2685-91. doi: 10.1007/s11136-013-0387-8.
21. Wirapati P, Pomella V, Vandenbosch B, Kerr P, Maiello E, Jeffery GM, et al. Velour trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity. *JCO*. 2017;35(15):3538. doi: 10.1200/JCO.2017.35.15_suppl.3538.
22. Riechelmann RP, Srimuninnimit V, Bordonaro R, Kavan P, Di Bartolomeo M, Maiello E, et al. Aflibercept Plus FOLFIRI for Second-line Treatment of Metastatic Colorectal Cancer: Observations from the Global Aflibercept Safety and Health-Related Quality-of-Life Program (ASQoP). Clin Colorectal Cancer. 2019;18(3):183-91.e3. doi: 10.1016/j.clcc.2019.05.003.
23. You XH, Wen C, Xia ZJ, Sun F, Li Y, Wang W, et al. Primary Tumor Sidedness Predicts Bevacizumab Benefit in Metastatic Colorectal Cancer Patients. Front Oncol. 2019;9:723. doi: 10.3389/fonc.2019.00723.
24. Loupakis F, Hurwitz HI, Saltz L, Arnold D, Grothey A, Nguyen QL, et al. Impact of primary tumour location on efficacy of bevacizumab plus chemotherapy in metastatic colorectal cancer. Br J Cancer. 2018;119(12):1451-5. doi: 10.1038/s41416-018-0304-6.
25. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22(1):23-30. doi: 10.1200/JCO.2004.09.046. Corrected and republished in: J Clin Oncol. 2023;41(19):3461-8.
26. Shen H, Yang J, Huang Q, Jiang MJ, Tan YN, Fu JF, et al. Different treatment strategies and molecular features between right-sided and left-sided colon cancers. World J Gastroenterol. 2015;21(21):6470-8. doi: 10.3748/wjg.v21.i21.6470.
27. Modest DP, Ricard I, Heinemann V, Hegewisch-Becker S, Schmiegel W, Porschen R, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol. 2016;27(9):1746-53. doi: 10.1093/annonc/mdw261.
28. De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010;11(8):753-62. doi: 10.1016/S1470-2045(10)70130-3.
29. Prager GW, Braemswig KH, Martel A, Unseld M, Heinze G, Brodowicz T, et al. Baseline carcinoembryonic antigen (CEA) serum levels predict bevacizumab-based treatment response in metastatic colorectal cancer. Cancer Sci. 2014;105(8):996-1001. doi: 10.1111/cas.12451.
30. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2017;3(2):211-9. doi: 10.1001/jamaoncol.2016.4227.