ISSN (print): 2589-9120
ISSN (online): 2589-9139

International Journal of Medical Science and Applied Research (IJMSAR)

Available Online at: https://www.ijmsar.com

Volume – 3, Issue –6, November – December - 2020, Page No. : 44 – 49

Impact On Progression-Free Survival By Mutational Profile Of KRAS In Advanced Colon Cancer With Bevacizumab In Mexican Population

[1]Dr. Guzmán - Casta Jordi, Department of Clinical Oncology, Instituto Nacional de Enfermedades Respiratorias "Dr. Ismael Cosío Villegas", Ciudad de México and Health Pharma Professional Research, Ciudad de México, México.

[2]Dr. Riera-Sala Rodrigo Fernando, Department of Clinical Oncology, Instituto Nacional de Enfermedades Respiratorias "Dr. Ismael Cosío Villegas", Ciudad de México and Health Pharma Professional Research, Ciudad de México, México.

[3]Rubio-Cordero Jairo Aaron, Department of Clinical Oncology, Hospital General de México "Dr. Eduardo Liceaga", Ciudad de México, México.

[4]Dr. Téllez-Campos Lucía, Department of Clinical Oncology, Hospital General de México"Dr. Eduardo Liceaga", Ciudad de México, México.

[5]Dr. Martínez-Nutes Hector, Department of Clinical Oncology, Hospital General de México"Dr. Eduardo Liceaga", Ciudad de México, México.

[6]Dr. Escobar-Gómez Mario, Department of Clinical Oncology, Hospital General de México"Dr. Eduardo Liceaga", Ciudad de México, México.

[7]Dr. Carrasco - Cara Chards Sonia, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, México.

[8]Dr. Guzmán-Huesca Jorge, Bonita Community Health Center, Internal Medicine, Bonita Springs, Florida, United States

[9]Martínez-Vega Rocío Pamela, Nutritional Department, Hospital General de México "Dr. Eduardo Liceaga" Ciudad de México, México

[10]Dr. González-Araujo Andrea. Resident of Primary Care, Instituto Mexicano del Seguro Social "IMSS", Guanajuato, México

[11]Dr. Hernández-DehesaItzel Ariadna, Department of Radiology, Hospital Ángeles Acoxpa, Ciudad de México

[12]Dr. Domínguez Ayala Adriana, Department of Radio oncology, Centro Médico Naxcional 20 de Noviembre "ISSSTE", Ciudad de México, México

[13]Dr. Correa-Cano Rafael, Centro Médico Hospital ABC Santa Fé, Ciudad de México, México.

[14]Dr. Elvira-Fabián Karina, Resident of Clinical Oncology, Centro Médico Nacional Siglo XXI "IMSS", Ciudad de México, México.

[15]Dr. López -Vrátný Claudia, Health Pharma Professional Research, Ciudad de México, México.

Corresponding Author: Dr. Guzmán - Casta Jordi, Department of Clinical Oncology, Instituto Nacional de Enfermedades Respiratorias "Dr. Ismael Cosío Villegas", Ciudad de México and Health Pharma Professional Research, Ciudad de México, México.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Objective

To determine progression-free survival by KRAS status in patients with metastatic colorectal cancer in a Mexican population at the General Hospital of Mexico.

Methods

This is a descriptive, retrospective and cross-sectional study performed through a review of 71 clinical charts of patients between 2015-2020 with the diagnosis of Colorectal Cancer Metastasic in treatment with chemotherapy plus Bevacizumab in first line.

Results

In the results to sex, we observed that it was more prevalent in men than in women, with the mutational state, with 28 men with mutated KRAS and 20 with KRAS wild type, in women 17 patients with mutated KRAS and only 5 wild type, regarding There was no difference in progression-free survival in both sexes, but there was a trend in the use of Bevacizumab in patients with mutated KRAS.

Conclusion

No distinction was observed in progression-free survival between men and women, but a non-significant trend was observed in patients with mutated KRAS using Bevacizumab versus KRAS wildtype.

Introduction

Colorectal cancer is the third most common cancer neoplasm in Western society and the second leading cause of cancer-related death in North America. It presents as a heterogeneous disease at the molecular level. Many studies have evaluated the molecular subtypes, pathological classification and determining clinical characteristics in prognosis and treatment **(1,2).**

The most common forms of presentation are sporadic (> 85%) or associated with Lynch syndrome (hereditary nonpolyposis CRC). Most cases occur as a consequence of sporadic methylation of hMLH1 (95-97%). The MSI-H phenotype is a hallmark of CRC associated with Lynch syndrome, which is diagnostic **(3,4,5).**

Consensual Molecular Classification

In 2015, The Consensus Molecular Subtypes of Colorectal Cancer was published, in which four molecular subtypes were identified. The 18 data sets used in the characterization and subtyping studies included 4,151 patients. The authors divided the cohort into two equivalent groups for validation. The four consensus subtyping groups included 3104 samples; 858 (13%) did not correspond to any subtype and, therefore, were described as unclassifiable. **(6)**

Molecular consensus subtype 1 (CMS1)

14% of the cohort corresponded to this subtype, which shows microsatellite instability, IMS +, MICpG-H, hypermuted phenotype and numbering mutations in BRAF. The immune subtype of IMS was characterized by increased expression of genes associated with immune infiltrates and strong activation of immune evasion pathways. These tumors were frequent in women, on the right side, presenting in later stages and with worse survival after relapse.

Molecular consensus subtype 2 (CMS2)

37% of the cohort classified in this canonical-epithelial subtype. CMS2 had the highest copy number gains and losses; Furthermore, it had high expression of Wnt and MYC downstream targets. These tumors commonly occur on the left side. The patients had better survival rates after relapse compared to CMS1.

Molecular consensus subtype 3 (CMS3)

13% of the cohort classified in this subtype. Most of the tumors presented mixed IMS, mainly MICpG-L, and had a low frequency of copy number alterations. Mutations in KRAS were common.

Consensus molecular subtype 4 (CMS4)

23% of the cohort classified in this mesenchymal subtype, characterized by prominent activity of the transforming growth factor-β, stromal invasion and angiogenesis. It had a high frequency of gains and losses in the number of copies. Tumors tend to be diagnosed at a later stage and show the greatest relapse and the least overall survival.

Different Antineoplastic Agents And Schemes Approved In CRC Metastatic Left Colon Or Right Colon Which Is The Best Option?

For many years, systemic treatment of mCRC was based almost exclusively on 5-FU and leucovorin. Despite the fact that many drugs were combined with 5-FU, the results did not improve until in the late 1990s irinotecan and oxaliplatin were added to 5-FU and leucovorin and increased survival to 14-16 months. **(7)**

The use of these agents created the already popular regimens known as FOLFIRI or ILF when they contain irinotecan and FOLFOX for oxaliplatin. These schedules are not fixed since they represent combinations that allow different doses and application intervals of its components. **(8)** In turn, 5-FU can be substituted for oral fluoropyridimidine, capecitabine, achieving a similar therapeutic efficacy but with a profile toxicity, mainly at the expense of the hand-foot syndrome that occurs more frequently with capecitabine. **(9)** Regarding the selection of irinotecan or oxaliplatin, the side effects of each of these agents are also largely the which determines the preference for any of them in each particular patient.Regarding the toxicity profile of these two agents, the risk of neuropathy and allergy with oxaliplatin and diarrhea and interactions with other drugs, particularly those metabolized by CYP3A4, such as ketoconazole, with irinotecan should be taken into account. **(10)**

Other options have been added to the previous alternatives, as a result of the development of monoclonal antibodies. The first of these was bevacizumab, which represents the first monoclonal antibody approved by the FDA to inhibit angiogenesis. The inclusion of bevacizumab increased survival by another five months or more **(11),** making the median survival of patients with mCRC now at least 21 months. **(12)**

The next monoclonal antibody approved for the treatment of patients with mCRC was cetuximab, an agent that targets the epidermoid growth factor receptor. Results with cetuximab plus irinotecan administered without prior patient selection were superior in progression-free survival to irinotecan. **(13)** However, when K-ras mutated patients were found to have a minimal chance of responding to cetuximab, patients with wild-type K-ras experienced greater progression-free survival and overall survival. **(14-16)**

An important aspect regarding the use of monoclonal antibodies in mCRC is the fact that "much more is not better". That is, the combination of bevacizumab plus cetuximab **(17)** or bevacizumab plus panitumumab **(18)** were not more effective and if more toxic than the use of one of them alone.Regarding the choice of bevacizumab or cetuximab as part of the first-line treatment in patients with wild-type K-ras, bevacizumab is generally recommended as the first option.

In the past decade, there has been considerable debate as to whether bevacizumab or cetuximab should be the preferred first-line biological therapy for treatment of patients with KRAS wild-type metastatic colorectal cancer. Two large randomised studies, the CALGB/SWOG 80405 study **(19)** (referred to throughout as the CALGB study) and the FIRE-3 study,**(20)**were done to clarify this question. However, the studies reached opposing conclusions. The CALGB study found that the median overall survival was identical for the two biological therapies,**(21)** whereas the FIRE-3 study found a significant overall survival benefit for patients who were given cetuximab compared with

bevacizumab as first-line therapy.**(22)**In subgroup analyses of the overall survival data according to tumour sidedness, both studies found that cetuximab was more effective than bevacizumab for leftsidedtumours, whereas bevacizumab was preferable for right-sided tumours

Our hypothesis was first tested by referring to the differences in overall survival observed in patients classified in the same CMS group who received the same biological therapy, as reported by the two studies**(20-21).** We examined the discrepancy in overall survival found by the FIRE-3 and CALGB studies for firstline cetuximab in the CMS1 and CMS4 tumour subtypes. In the CALGB study, according to our working hypothesis, first-line cetuximab coupled with oxaliplatin probably had an antagonistic effect in patients with CMS1 and CMS4 microenvironments, which would explain the reduced overall survival of 11·7 months (95% CI 10·9−18·0) in the CMS1 subgroup and 30·8 months (24·4−43·5) in the CMS4 subgroup.

By contrast, in the FIRE-3 study, the synergistic combination of cetuximab with irinotecan would provide a greater overall survival benefit, which would explain the improved overall survival of 17·9 months (95% CI 7·1−28·7) in the CMS1 subgroup and 40·1 months (20·3−59·9) in the CMS4 subgroup. Thus, in patients with the same tumour microenvironments who received the same first-line biological therapy (Cetuximab), a different overall survival was observed depending on the first-line chemotherapy backbone. In a clinical setting, the overall survival associated with first-line cetuximab or first-line bevacizumab is actually representative of cumulative overall survival obtained after first-line treatment, second-line treatment, and other treatment lines for each group. Our hypothesis can also explain the discrepant results of the studies with regards to first-line bevacizumab in patients with tumours classified as CMS1 and CMS4.

Compared with the FIRE-3 study, the CALGB study found an improved overall survival with first-line bevacizumab in the CMS1 and CMS4 subgroups. The CALGB study used a sequence of two synergistic combinations for patients with CMS1 and CMS4-defined tumour microenvironments: first-line bevacizumab-oxaliplatin and second-line cetuximab irinotecan (administered to some of the patients; which resulted in a cumulative overall survival of 22·5 months (95% CI 15·9−32·6) for the CMS1 subgroup and 32·7 months (26·3−37·5) for the CMS4 subgroup.

By contrast, in the FIRE-3 study, after the overall survival benefit obtained following the synergistic first-line bevacizumab-irinotecan, 41% of the patients crossed over to secondline cetuximaboxaliplatin,2 which probably had an antagonistic effect in patients classified as CMS1 and CMS4. This effect would reduce the contribution of the secondline cetuximab-oxaliplatin to the cumulative overall survival of patients who received first-line bevacizumab in the FIRE-3 study,and could explain the worse median overall survival of 13·1 months (95% CI 8·5−17·6) in the CMS1 subgroup and 21·1 months (14·8−27·3) in the CMS4 subgroup, compared with 22·5 months (15·9−32·6) and 32·7 months (26·3−37·5), respectively, in the CALGB study.

Results

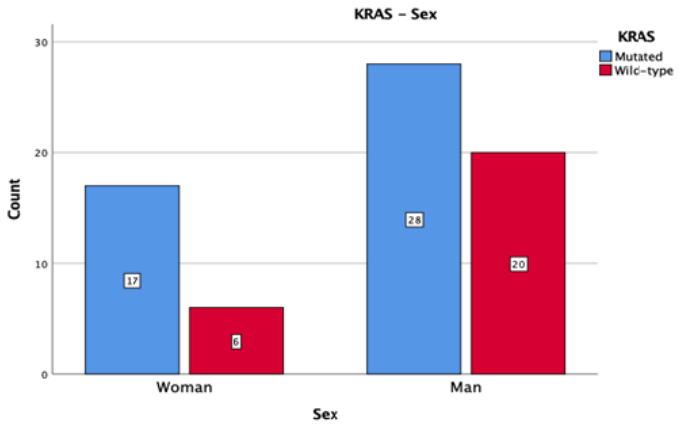

Table 1 - Incidence of sex on KRAS mutational status

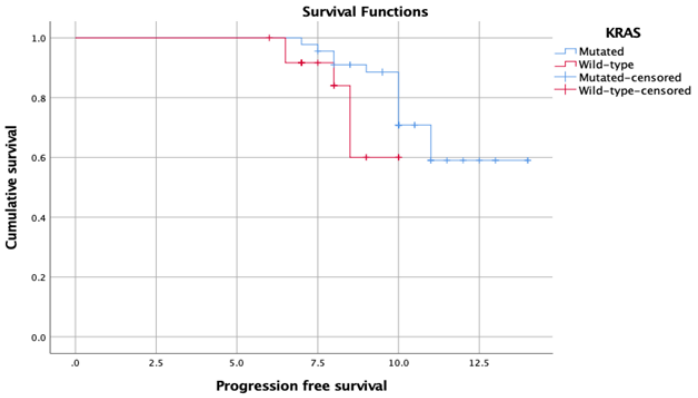

Table 2 - Progression-free survival depending on KRAS mutational status

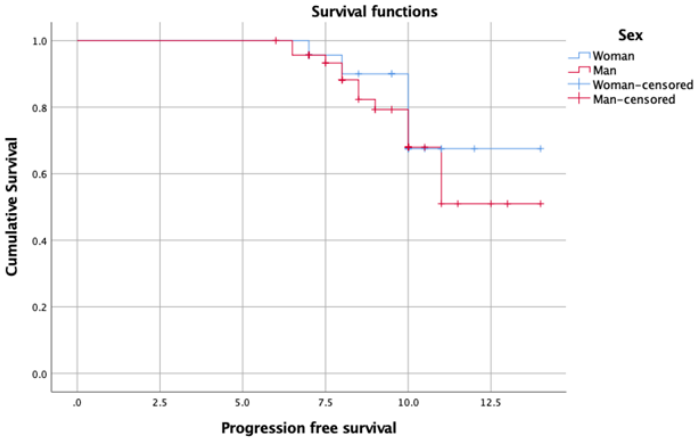

Table 3 - Progression-free survival depending on sex

Discussion

In our study, the real impact that adding Bevacizumab had in patients with metastatic colorectal cancer depending on the KRAS mutational status was determined, which has been debated by several studies already pointed out mainly by CALGB / SWOG and FIRE3 where it is It is evident that despite regardless of the state, the use of Bevacizumab is beneficial both in terms of progression-free survival and overall survival, in our case there was no difference in both sexes and without a slight difference in favor of KRAS mutated with the use of the antiangiogenic .

References

1. Christine M. Ribic, M.Sc., Daniel J. Sargent, Ph.D., Malcolm J. Moore, M.D. Stephen N. Thibodeau, Ph.D et al. Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer. Christine M. Ribic, M.Sc., Daniel J. Sargent, Ph.D., Malcolm J. Moore, M.D. Stephen N. Thibodeau. N Engl J Med 2003;349:247-57.
2. Dr. Boland CR, Dr.Goel A. Microsatellite Instability in Colorectal Cancer GI Cancer Research Laboratory, Division of Gastroenterology, Department of Internal Medicine, Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, Texas GASTROENTEROLOGY 2010;138:2073–2087
3. Zeinalian M, Hashemzadeh-Chaleshtori M, Salehi R, Emami MH. Clinical Aspects of Microsatellite Instability Testing in Colorectal Cancer. Adv Biomed Res 2018; 7:28.
4. Emily y. he,a Nicholas j. Hawkins,bGabrielmak,a Felicia Roncolato,c David Goldstein,AwinstonLiauw,d Philip Clingan,e Melvin Chin,a Robyn l.Warda,b The Impact of Mismatch Repair Status in Colorectal Cancer on the Decision to Treat With Adjuvant Chemotherapy: An Australian Population-Based Multicenter Study. The Oncologist 2016; 21:618–625
5. Kohzoh Imai MD and Hiroyuki Yamamoto MD Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis vol.29 no.4 pp.673–680, 2008
6. Guinney J, Dienstmann R, Wang X, De-Reynies A, Schlicker A, Soneson C, et al. The Consensus Molecular Subtypes of Colorectal Cancer. Nat Med. 2015;21(11):1350-1356.
7. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. New EngJ Med2005;352:476-87.
8. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil - leucovorin,

irinotecan and oxaliplatin in the course of treatment. J Clin Oncol 2004;22:1209

9. Arkenau HT, Arnold D, Cassidy J, et al. Effificacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal Cancer:A pooled analysis of randomized trials. J Clin Oncol 2008;26:5910
10. KehrerDiederik FS, Mathijssen Ron HJ, Verweij J,et al. Modulation of Irinotecan Metabolism by Ketoconazole. J Clin Oncol 2002;20:3122
11. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus iriniotecan, fluorouracuil and leucovorin for metastatic colorectal cancer. New Eng J Med 2004;350:2335
12. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. New Eng J Med 2005;352:476-87.
13. Cunningham D, Humblet Y, Siena S, et al. Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer New Eng J Med 2004;351:337
14. Van Cutsem, E, Kohne, CH, Hitre, E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New Engl J Med 2009; 360:1408.
15. Bokemeyer, C, Bondarenko, I, Makhson, A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009; 27:663.
16. Karapetis, CS, Khambata-Ford, S, Jonker, DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. New Engl J Med 2008; 359:1757.
17. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab and cetuximab in metastatic colorectal cancer. New Eng J Med 2009;360:563
18. Hecht JR, Mitchell E, Chidiac T, et al. A randomized IIIb trial of chemotherapy, bevacizumab and panitumumab compared to chemotherapy and bevacizumab alone for metastatic colorectalcancer. J Clin Oncol 2009;27:672
19. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA 2017; 317: 2392–401.
20. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 1065–75.
21. Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Proc Am Soc Clin Oncol 2014; 32 (suppl): LBA3 (abstr).
22. Heinemann V, von Weikersthal LF, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). Proc Am Soc Clin Oncol 2013; 31 (suppl): LBA3506 (abstr).