Journal of Medical Care Research and Review
Received 12 Sep 2021 | Revised 15 Oct 2021 | Accepted 15 Nov 2021 | Published Online 21 Dec 2021

DOI: https://doi.org/10.52845/MCRR/2021-4-12-2
JMCRR 4(12), 1167–1173 (2021)

ISSN (O) 2589-8949 | (P) 2589-8930 IF:1.6


**RESEARCH ARTICLE**

# THE USE OF GENE THERAPY THROUGH BEVACIZUMAB IN THE TREATMENT OF COLORECTAL CANCER AN INTEGRATIVE REVIEW

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Abstract

Colorectal cancer is a pathology that affects the individual's gastro-intestinal tract, affecting from the large intestine to the anus. The treatment of this cancer consists of surgical procedure, chemotherapy and radiotherapy. Currently, the combination of bevacizumab with traditional chemotherapy for CRC (colorectal cancer) has been used, since bevacizumab is a monoclonal antibody whose mechanism of action is to inhibit the growth of new blood vessels that would carry nutrients to the tumor. Treatment through gene therapy associated with bevacizumab has shown to be very promising in the treatment of colorectal cancer, seeking to reduce recurrences, mortality and toxicities caused by the treatment. The present study aimed to evaluate how the use of bevacizumab associated with gene therapy has shown promise in the treatment of colorectal cancer. For data collection, an integrative literature review was carried out, where through consultations in the databases, PubMed, SciELO (Scientific Electronic Library Online) and VHL(Virtual Health Libraries), articles published in the last 5 years were selected (period from 2016 to December of 2021). After selecting articles and data obtained, it is observed that gene therapy is able to make changes in specific genes, with the aim of decreasing the level of tumor growth, and can be used in conjunction with bevacizumab, thus increasing the percentage of survival of patients affected by this disease.
Keywords: GENE THERAPY THROUGH BEVACIZUMAB IN THE TREATMENT OF COLORECTAL CANCER

## 1 | INTRODUCTION

Cancer is the term used to describe more than 100 types of malignant diseases that have in common the disordered growth of cells (INCA, 2020), having its origin from mutations in deoxyribonucleic acid (DNA), thus altering the cell cycle, promoting a uncontrolled cell proliferation thus generating tumours (HAUSMAN, 2019). Colorectal cancer is one of the more than 100 diseases that comprise cancer, it is a pathology that affects the intestinal tract and can affect from the large intestine (colon) to the anus. According to data from INCA (National Cancer Institute) (2021), CRC (Corectal Cancer) was ranked as the third that most affects men and second among women, the most common form of this cancer, adenocarcinoma, with a percentage of 96% of cases (AMERICAN CANCER SOCIETY, 2020).

CRC has several risk factors, such as: age over 50 years, history of familial polyposis adenomatosis, previous history of colorectal cancer itself, recurrence of any other cancer such as breast, ovary or endometrium, inflammatory bowel diseases, such as chronic ulcerative colitis and Crohn's disease (PACHEGO et al, 2019). The precedent for the development of CRC is mutations that target oncogenes, tumor suppressor genes, and genes related to the deoxyribonucleic acid (DNA) repair mechanism. Depending on the origin of the mutation, carcinomas of the colon and rectum can be classified as sporadic (70%), inherited (5%) and familial (25%) (MÁRMOL, 2017).

Some clinical manifestations are related to CRC, such as the presence of blood in the stool, weight loss, abdominal pain and swelling, and change in bowel habits. Most of the time these symptoms are not caused by the cancer, so an investigation is important, especially when the symptoms last for days. However, this cancer may initially have no symptoms, so screening is essential for early diagnosis, bringing a greater chance of cure (INCA, 2021).

Screening is carried out through laboratory tests, such as a blood count to assess whether you have an anaemic condition, which may be related to abdominal bleeding, as well as some tumour markers such as CEA (carcinoembryonic protein) (PELIZZER et al., 2016). CEA was discovered in 1965 and is still considered the most effective tumour marker for the diagnosis of patients with CRC. Elevated concentrations of this marker are rarely identified in stage I of the disease; in addition, it does not differentiate between malignant and benign polyps. Some authors such as Lech (2016) apudWeissenberger and Chen (2005) report that high CEA concentrations in stages II and III were considered to be potential indicative of more aggressive types. Lech (2016) apudZhong (2015) and Nicolini (2010), still report that the combination of CEA, CA19-9, CA 72-4, CA 242 and CYFRA21-1 markers improve the diagnostic accuracy when compared to the separate analysis of these biomarkers.

CRC is treated by surgery, combined with chemotherapy and chemotherapy and radiation, however, therapeutic success depends on the ideal therapeutic modality for each patient. (RIVEIRA, 2021). A therapeutic approach is bevacizumab, a monoclonal antibody that entered clinical practice more than 15 years ago and was one of the first targeted therapies and the first approved angiogenesis inhibitor, being used in association with conventional chemotherapy treatment, which acts by inhibiting the growth of new blood vessels that carry nutrients to the tumour (GARCIA et al, 2020).

As gene therapy is a treatment based on the introduction of healthy genes using recombinant DNA techniques, its use through bevacizumab has shown to be very promising in the treatment of CRC. Therefore, drug gene therapy is a treatment option that promises to reduce mortality, side effects and relapses, in order to help patients have faster results compared to other conventional treatments of gene therapy against cancer will reduce costs compared to conventional treat-

**Supplementary information** The online version of this article (https://doi.org/10.52845/MCRR/2021-4-12-2) contains supplementary material, which is available to authorized users.

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ments, because in addition to reducing the length of hospital stay of patients, the chances of regression will be minimal. Thus, there will be a significant reduction in costs for the public coffers, since in Brazil, it is a treatment basically financed by the Unified Health System (SUS), which greatly burdens the government's budget sheet (SHEN et al, 2020).

The present study aimed to analyze how the use of bevacizumab associated with chemotherapy can help in the survival of patients with CRC, defining the main genes to receive necessary modifications to have a satisfactory effect in cancer treatment, exemplifying the methods used in its treatment with the use of gene therapy, comparing the drugs used in the treatment of this type of cancer with bevacizumab and describing the main benefits that patients will have with the use of this therapy.

## 2 | MATERIALS AND METHODS:

For the elaboration of this article, an integrative literature review was carried out, which proposes to reach a survey of scientific productions related to the use of pharmacogenetics through bevacizumab in colon and rectal cancer. For this, the following health databases were consulted: PubMed, Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL). Scientific publications from the last 5 years (period from 2016 to 2021), related to the application of pharmacogenetics with bevacizumab in colorectal cancer, were selected. The health descriptors that were researched are: "bevacizumab" (from English "bevacizumab"), "pharmacogenetics" (from English "pharmacogenetic"), "cancer colon and rectum", "cancer of colon and rectum", "colon and rectal cancer", "colorectal", "colorectal", "colorectal". These descriptors were used in a combined and isolated way, being selected for their current use in the literature and represent the structured vocabulary for the indexing of scientific publications elaborated by the Latin American and Caribbean Center on Health Sciences Information (BIREME).

To determine which articles were not relevant and later excluded, some references obtained from the electronic search were initially examined and then duplicated, as well as articles that addressed other pharmacogenetic treatments other than the use of bevacizumab , as well as any scientific work that has not been published as of 2016. In order to determine which articles are relevant to the present study, the title and a table with author, year, title, abstract were read. and objective of the articles and results found.

This reading was guided by basic inclusion criteria: (1) publications in the period from 2016 to December 2021; (2) writing the text in Portuguese, Spanish or English; (3) publication available in full; and (4) thematic that addresses a comparative study of conventional pharmacogenetic treatments with the use of this ally to bevacizumab in the practice of combating colon and rectal cancer.

The selected articles were submitted to a complete and detailed reading by the authors of this study. The information obtained from the reading was organized in order to compose the literature review with relevant content regarding the proposed theme for this research.

## 3 | RESULTS AND DISCUSSION:

Through electronic search, eight articles were selected to compose this integrative literature review study. These were evaluated in terms of title, author, year, objective and results, as shown in table 1 of the main approaches to the use of bevacizumab in the treatment of CRC.

From the bibliographic searches it was identified that gene therapy is defined as the treatment by administering therapeutic genes or gene-induced cells to patients, whereas colorectal cancer is defined as a pathology that affects the gastrointestinal tract that seems to be preceded by an accumulation of somatic mutations and other genetic changes that affect cell division checkpoints and result in abnormal cell growth and eventually tumorigenesis. Therefore, the most logical gene therapy is the complete repair of all these mutations, however, our knowledge and technology has not yet reached the level necessary to perform this definitive gene therapy (HASBULLAH; MUSA, 2021). In the last decade, significant advances have been observed in gene therapy for

**TABLE 1: to the use of bevacizumab in the treatment of CRC.**

| TITLE | AUTHOR/YEAR | GOALS | RESULTS |
|---|---|---|---|
| IL-8 andeNOSpolymorphismsp linebevacizumab-basedtreatment in patientswith RAS mutantmetastaticcol-orectalcancer. | DISALVATOREet.al. 2017 | Determine whether IL-8 and eNOS SNPs may have a role as predictive biomarkers for the efficacy and toxicity of bevacizumab | In the bevacizumab group, carriers of IL-8 c.-251TA + AA alleles showed PFS (P= 0.002) and OS (P = 0.03) shorter compared to the TT alleles. |
| The relevanceofprimary tumor location in patientswithmetastat-iccolorectalcancer: a meta-analysisoffirst-lineclinicaltrials | HOLCHet.al. 2017 | Evidencing that the location of the primary tumor has a prognostic importance and is related to the response to therapy aimed at the treatment of colorectal cancer. | In 13 first-line randomized controlled trials and one prospective pharmacogenetic study, CR was associated with a significantly worse prognosis compared to LC (hazard ratio [HR] for overall survival: 1.56; 95% confidence interval [CI]: 1.43-1.70; P<0.0001). A meta-analysis of the PRIME study and CRYSTAL suggests that PTL was predictive of survival benefit of adding anti-EGFR antibody to standard chemotherapy in wild-type RAS tumor patients (overall survival, HR for LC: 0.69; 95% CI: 0.58 -0.83; P<0.0001 and HR for RC: 0.96; IC95%: 0.68-1.35; P = 0.802). |
| DPYD and UGT1A1 geno-typingtopredict adverse eventsduringfirst-line FOLFIRI or FOLFOXIRI plusbevacizumab in metastaticcolorectal-cancer | CREMOLINI et.al. 2017 | Evaluate the individual association of three DPYD single nucleotide polymorphisms (SNPs), whose relationship to 5-FU-related toxicity is more robust. | The most frequent chemotherapy-related toxicities included neutropenia (37%), diarrhea (15%), febrile neutropenia (8%) and stomatitis (7%). Among the clinical characteristics investigated, age, sex, and treatment group had a significant impact on the occurrence of general treatment-related AEs of grade 3 or higher in univariate analysis. Female |

translational purposes in the treatment of various types of cancer. This includes the development of vectors as delivery vehicles. Despite the optimism around gene therapy aimed at cancer treatment, it also has several limitations, such as the lack of availability of related technology, the high cost of the procedures involved and ethical issues, however, even in the face of difficulties, many strategies for CCR gene therapy were explored, including the most used technique which is the use of benvacizumab, in chemotherapy, targeting the pathways of epidermal vessel growth factor (VEGF), associated with conventional gene therapy with FOLFOX or FOLFIRI, being perceived that this is very promising, bringing better prognosis to patients (HASBULLAH; MUSA, 2021).

After the process of selection and analysis of articles that met the inclusion criteria, the study by Papachristos et. al. (2020) and Di Salvatore et. al. (2017), who agree that although the standard position in the treatment of metastatic colorectal cancer is to add bevacizumab to the chemotherapy framework, the benefits of it are still modest and clinical outcomes are highly variable with some patients responding remarkably well while others not. as the predictive biomarkers of efficacy and toxicity of bevacizumab have not yet been validated or investigated, as well as the effect of certain covariates on population parameters, including genetic variants of VEGF-A and ICAM-1genes, age, sex, weight, co - treatment and dosage schemes.Each NP has characteristics that specializes itstheranostic applicability, from the delivery of drugs in a more efficient and less toxic way to their use as imaging agents. In table 1, it is possible to observe that even being part of the same group of NP, whether metallic or organic, they have differences between them, allowing their use in multiple approaches.

In the studies by Papachristos et. al. (2020) and DI Salvatore et. al. (2017), both proved that bevacizumab can have variable clinical outcomes, however in the study by Papachristos et. al. (2020) the authors characterized the pharmacokinetic and pharmacodynamic properties (CF and DF) of bevacizumab in patients with CRC, demonstrating how results of variants of genes that regulate angiogenesis can affect the CF and DF characteristics of bevacizumab, possibly influencing clinical outcomes, already DI Salvatore et. al. (2017) evaluated the predictive biomarkers of efficacy and toxicity of bevacizumab, showing that IL-8 and eNOS SNPs may have a role as predictive biomarkers for the efficacy and toxicity of bevacizumab.

Bignucolo et.al. (2017), reported in their study that systemic chemotherapy is usually the main treatment for advanced RCC and in the last two decades it has advanced a lot in the treatment of this cancer, a significant progress with the introduction of new target agents used alone or, more frequently , in combination with conventional chemotherapeutics, improving the management of patients with CRC, that is, a combination of Fluorouracil, Leucovorin and Oxaliplatin (FOLFOX), Fluorouracil, Leucovorin and Irinotecan (FOLFIRI), with molecules targeted to the factor, epidermal growth factor (EGF) pathways (ie, cetuximab, panitumumab) and the epidermal vessel growth factor (VEGF) pathways (ie, bevacizumab, ziv-aflibercept, regorafenib, and ramucirumab) improve clinical practice in the treatment of this cancer.

In the research by Cremoline et. al. (2018), as well as in the study by Bignucolo et.al. (2017), demonstrate that based on the efficacy results of recent randomized trials of FOLFOXIRI (5-FU, oxaliplatin, and irinotecan) plus bevacizumab, they are now held to be the gold standard for all major guidelines as a starting regimen for selected cancer patients colorectal, however, unlike Bignucolo et. al. (2017) and Cremoline et. al. (2018), demonstrated that even though it is feasible, its use is associated with an increase in grade 3/4 neutropenia, diarrhea and stomatitis, advocating the development of tools capable of predicting the probability of developing potentially serious toxicities, as they would be interesting to select better candidate patients and adequately manage the treatment.

Ranier et. al. (2021), demonstrated through their study that bevacizumab-FOLFOX4 with the addition of DEHY, as a first-choice treatment for colorectal cancer, caused a retention of the drug at the tumor site and consequently a delay in the elimination of the medication, thus presenting a high control in the progression of the disease and increasing the effectiveness of the treatment, as well as showing a

good result in terms of toxicity and manifestations of reactions, where they were determined as mild.

Mattia et. al. (2020), concluded through their study some important factors on the insertion of the antigen bevacizumab against colorectal cancer using some genetic markers such as GADD34, PPP1R15A, and ANXA11 to enhance these results, demonstrating how effective and promising when it is taken in Considering the treatment and the patient's survival, however, it is still possible to improve significantly because some patients still do not demonstrate a significant improvement in the treatment with the insertion of these medications.

## 4 | CONCLUSION:

The use of bevacizumab associated with chemotherapy, shows good responses with a significant increase in the survival of patients with colorectal cancer, presenting itself as a promising and innovative alternative in the treatment of this cancer. The study carried out proved through literature searches that bevacizumab associated with conventional treatment has been shown to be more effective in the treatment of CRC compared to when the combination with this drug was not used.

However, despite the great benefits brought by bevacizumab, it was noticed that it still has great chances of generating toxicities to the patient, requiring further studies to analyze its specificities, which can cause health risks/compromises. In this way, developing tools to reduce levels of toxicity of bevacizumab in the treatment of CRC is a beneficial alternative, with the possibility of bringing more positive clinical results for its use, as some studies have already shown, and ensuring greater safety in the use of this drug in patients with colorectal cancer and consequently allow an increase in patient survival.

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**How to cite this article:** Mendes T.S., Souza dos Santos A.B., L.S.O., Salvi M., Cardoso M.V. THE USE OF GENE THERAPY THROUGH BEVACIZUMAB IN THE TREATMENT OF COLORECTAL CANCER AN INTEGRATIVE REVIEW. Journal of Medical Care Research and Review. 2021;1167−1173. https://doi.org/10.52845/MCRR/2021-4-12-2