UNIVERSITATEA LUCIAN BLAGA DIN SIBIU

Doctoral School of Medicine
Doctoral field: Medicine

DOCTORAL THESIS

ASSESSMENT OF RISKS ASSOCIATED WITH PHARMACOTHERAPY IN PATIENTS WITH COLON CANCER

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SIBIU 2025

“The only thing standing between you and your dream is the will to try and the belief that it is truly possible.” - J. Brown

Thank you...

With a heart full of gratitude and emotion, I reach the end of this scientific journey and I want to thank you from the bottom of my heart for every step you have taken with me.

Mrs. Prof. Univ. Dr. Farm. Felicia Gligor, my doctoral supervisor, I owe you the light that guided every thought and hope. Under your wing, I learned what authentic passion for research, intellectual rigor and unconditional affection mean. Thank you for believing in me when doubts seemed to engulf me and for showing me that every idea, no matter how timid, can take wing.

The research team – Assoc. Prof. Dr. Claudiu Morgovan, Assoc. Prof. Dr. Anca Butucă, Medical Lecturer Dr. Carmen Dobrea, Medical Lecturer Dr. Adina Frum and Assoc. Prof. Dr. Loredana Vonica – you are the soul of this work. Every moment spent together was more than a simple experiment: it was a story of collegiality and trust. Claudiu, with your generosity in sharing knowledge, you transformed each problem into an exciting challenge. Anca and Carmen, your dedication and passion were the beacon which guided me in the darkest moments. Adina, your infectious energy raised the morale of the team even on the most tiring days. Loredana, your attention to detail was the clock that kept the pace of this work at the highest standards.

To the members of the advisory board, Assoc. Prof. Dr. Manuela Pia Pumnea, Assoc. Prof. Călin Cipăian and Assoc. Prof. Dr. Anca Butucă, I thank you for the courage with which you opened new horizons for me. Your observations full of depth and critical spirit were the seeds of the ideas that blossomed in the pages of the thesis. I thank you for your generous time, for the patience with which you polished my arguments and for the academic honesty that taught me to aspire to excellence.

Assoc. Prof. Dr. Manuela Pumnea, thank you not only for your scientific support, but also for the precious chance you gave me to start my university teaching career in the discipline of Physiology. It was a beginning that changed my life and for which I will always be grateful. Thank you for trusting me!

I would like to express my special thanks to my mentor in the field of oncology, Dr. Răzvan Curcă. Under your guidance, I learned what dedication to the patient and to research truly means. The vision, clarity and humanity with which you guided me have shaped me not only as a doctor, but also as a person.

My deepest gratitude goes to my parents and my family, to whom I owe everything I am. You have been my protective umbrella in emotional storms and unwavering support on the arduous path of research. Thank you for instilling in me the courage to dream and the strength to move forward, even when the steps seemed clumsy. Thank you for believing in me when I myself no longer believed. Thank you for all the unspeakable sacrifices, for the nights you did not sleep because of my worry, for the silences in which you were close to me without asking for anything in return. Thank you for your education, for your patience, for your dignity and for your infinite love. You were, are and will remain my heroes.

In particular, I pay tribute to my grandmother, who watched over me from heaven with the same gentle care with which she raised me. I still feel her warm presence in difficult times and her unseen comfort when I need it most. This work is also for her.

My friend, Ana, with you every moment spent away from home had meaning. Thank you for your infinite patience, for the hugs that were my shelter, and for your smile that brightened even the longest nights of writing. Without you, this achievement would not have had the same flavor.

This thesis is the fruit not only of my work, but of a covenant of friendship, trust, and love that has grown every day. Each of you has left a unique imprint on the heart of this work. Thank you for being with me, for making sense of my searches, and for helping me turn hope into reality.

LIST OF PUBLICATIONS:

1. **Razvan Constantin Vonica** , Anca Butuca, Andreea Loredana Vonica Tincu, Claudiu Morgovan, Manuela Pumnea, Remus Calin Cipaian, Razvan Ovidiu Curca, Florina Batar, Vlad Vornicu, Adelaida Solomon, Adina Frum, Carmen Maximiliana Dobrea, Dan Damian Axente and Felicia Gabriela Gligor - The Descriptive and Disproportionality Assessment of EudraVigilance Database Reports on Capecitabine Induced Cardiotoxicity – Cancers 2024, 16, 3847. https://doi.org/10.3390/cancers16223847
   Impact factor: 4.5 (2023); 5 - year impact factor: 4.9 (2023)
   Quartile : 1;
   Publication date : November 2024
   Journal indexed in : Web of Science
   Information from **Study 1** can be found in this article

2. **Razvan Constantin Vonica** , Claudiu Morgovan, Anca Butuca, Manuela Pumnea, Remus Calin Cipaian, Adina Frum, Carmen Maximiliana Dobrea, Andreea Loredana Vonica-Tincu, Aliteia-Maria Pacnejer, Florina Batar, Vlad Vornicu, Steliana Ghibu and Felicia Gabriela Gligor - Real-World Evidence of Bevacizumab and Panitumumab Drug Resistance and Drug Ineffectiveness from EudraVigilance Database - Cancers 2025, 17, 663. https://doi.org/10.3390/cancers17040663
   Impact factor: 4.5 (2023); 5 - year impact factor: 4.9 (2023)
   Quartile: 1;
   Publication date: February 2025
   Journal indexed in: Web of Science
   Information from **Study 2** can be found in this article

3. **Razvan Constantin Vonica** , Anca Butuca, Claudiu Morgovan, Manuela Pumnea, Remus Calin Cipaian, Adina Frum, Carmen Maximiliana Dobrea, Andreea Loredana Vonica-Tincu, Aliteia-Maria Pacnejer, Steliana Ghibu, Florina Batar and Felicia Gabriela Gligor - Bevacizumab—Insights from EudraVigilance Database on the Assessments of the Safety Profile of Monoclonal Antibodies Used as Targeted Cancer Treatment - Pharmaceuticals 2025, 18, 501. Published: 30 March 2025 https://doi.org/10.3390/ph18040501
   Impact factor: 4.3 (2023); 5 - year impact factor: 4.6 (2023)
   Quartile : 2;
   Publication date : March 2025
   Journal indexed in : Web of Science
   Information from **Study 3** can be found in this article

Contents

INTRODUCTION

Colon cancer currently represents a major public health problem, with an increasing incidence and a significant impact on the quality of patients' life [1] . Medicine has made significant progress in the field of oncology, regarding diagnosis, treatment, and supportive medication, however, numerous clinical challenges remain, especially regarding the balance between therapeutic efficacy and the occurrence of adverse effects [2] .

Technological and therapeutic progress proposes individualized treatments. Thus, modern therapy does not follow a standardized model, but a process adapted to each patient. An important aspect is highlighted by the continuous, careful and rigorous evaluation of the response to treatment [3] . Another area of interest is the identification, monitoring, prevention or mitigation of adverse reactions, which may occur following modern therapy or chemotherapy [4] .

Clinical and pharmacovigilance studies provide a direct picture of symptoms, treatment tolerance, and general condition, through direct interaction with the patient. Paraclinical methods include laboratory analyses, imaging investigations, and increasingly, molecular tests that provide objective and quantifiable data, which are useful in therapeutic adjustment [5] .

The reason for choosing the topic of the paper lies in the need to identify and implement objective and standardized methods for evaluating oncological treatments for patients diagnosed with colon cancer. The context of treatment-associated adverse effects remains a major cause of morbidity, decreasing therapeutic adherence and quality of life. The integration of clinical and paraclinical methods provides the premises for a safe, effective and personalized approach.

This paper proposes a broad analysis of how integrated clinical and paraclinical assessment can contribute to optimizing the treatment of patients with colon cancer. It aims to highlight the role of these methods in the anticipation, early identification and reduction of adverse effects, in order to outline a safer and more effective therapeutic model.

In the first part of the study, a descriptive analysis of adverse reactions related to resistance and ineffectiveness of drugs such as panitumumab and bevacizumab was performed, these being the most used targeted treatments depending on the molecular profile and tumor location in patients with colon cancer. The review of

pharmacovigilance reports determined the frequency of reporting of adverse reactions related to drug resistance and ineffectiveness associated with the proposed medications. Subsequently, a disproportionality analysis was performed, which compared the frequency of reporting of adverse reactions associated with resistance and ineffectiveness of these molecules with the frequency of reporting of the same adverse reactions associated with other modern drugs for colon cancer.

In the second part of this work, descriptive and disproportionality analysis of reports from the EudraVigilance database on capecitabine-induced cardiotoxicity were performed. It was shown that treatment with fluoropyrimidines is associated with cardiovascular adverse reactions, especially myocardial infarction, heart failure and cardiomyopathies. Also, an important objective of the work was to identify resistance and ineffectiveness to bevacizumab and panitumumab based on the data uploaded to the EudraVigilance database. Another topic of interest is the evaluation of the safety profile of monoclonal antibodies used as targeted therapy for colon cancer.

In the last part of the doctoral thesis, a retrospective cohort study was conducted in which several important aspects regarding the drug therapy administered to patients diagnosed with colon cancer were monitored: demographic data, stage of the disease, therapeutic line, type of treatment, but also the correlation of these data with the paraclinical evaluation through the study of the blood count and biochemical analyses reported between 2019 and 2024 obtained at the Oncohelp Timișoara Oncology Center.

Through the studies conducted, this work aimed to highlight some of the complex interactions between the use of antitumor molecules and the risk of adverse reactions, but also of inefficiency and resistance to colon cancer treatment..

PART I

CURRENT STATE OF KNOWLEDGE

Colorectal cancer is the most common malignancy of the gastrointestinal tract, and reducing its burden depends crucially on population-based screening and early detection [6] . In the last two decades, advances in biology and genomics have allowed for fine-grained risk stratification (including RAS/RAF, MSI/MMR, HER2 profiles), better prognosis estimation, and more rational selection of therapies [7] . Although the global burden remains substantial, standardized incidence and mortality have declined in many regions due to prevention, polypectomy, and treatment modernization; however, there is an increase in cases in young adults, parallel to a decrease in the elderly [8] .

The etiology is multifactorial: hereditary syndromes (familial adenomatous polyposis, Lynch syndrome, serrated polyposis) confer very high risks; environmental and lifestyle factors (diet rich in red meat and ultra-processed foods, high alcohol consumption, smoking, sedentary lifestyle, obesity, diabetes) amplify the risk, while fiber, calcium intake and certain dietary habits seem protective. Chronic intestinal inflammation and iatrogenic exposures (e.g. some antibiotics, in relation to dysbiosis) contribute additionally [9] .

Pathophysiologically, carcinogenesis frequently follows the adenoma–carcinoma sequence, with APC inactivation, KRAS activation, and TP53 alterations; alternative pathways include microsatellite instability (dMMR/MSI-H) or CpG methylation phenotype, often with BRAF mutations [8] . Tumor–microenvironment communication (exosomes, microRNAs) modulates invasion, metastasis, and immune evasion [10] .

Clinically, many cases are asymptomatic until advanced stages; when they appear, the most common manifestations are iron deficiency anemia, rectal bleeding, abdominal pain, and persistent transit disorders, with particularities related to tumor location [11] . The increase in incidence under 50 years of age requires diagnostic vigilance in the face of apparently trivial symptoms.

Screening aims at prevention by identifying and resecting premalignant lesions and detecting curable cancer: colonoscopy (preferred standard) alternatively with fecal tests (FIT/fecal DNA) or imaging (CT-colonography). The age of initiation is usually 45–50 years in the average-risk population, with adaptations for high-risk groups [12] .

Molecular testing is mandatory in advanced disease: extended RAS/RAF profile, MSI/MMR status, HER2 assessment and, selectively, NTRK/RET fusions or

POLE/POLD1 mutations [13] These results guide the use of anti-EGFR, BRAF ± EGFR inhibitors, HER2 blockade, and immunotherapy [14] .

Diagnosis and staging integrate endoscopy (modern classifications of superficial lesions, endoscopic resection for selected pTis/pT1) and anatomical and functional imaging (ultrasound, CT/MRI, PET-FDG). The TNM system (UICC/AJCC) remains the lingua franca for therapeutic decisions and prognosis estimation [15] .

Treatment is multimodal and personalized. In non-metastatic disease, surgery with free margins (R0) is curative, supplemented, according to risk, by adjuvant chemotherapy based on fluoropyrimidines ± oxaliplatin; neoadjuvant immunotherapy becomes an option in dMMR/MSI in stages II–III. In the metastatic stage, cytotoxic combinations (FOLFOX, CAPOX, FOLFIRI) are associated with anti-VEGF (bevacizumab/alternatives) or, in wild-type RAS/BRAF with favorable sidedness, with anti-EGFR; in MSI-H/dMMR, PD-1 inhibitors (± CTLA-4) are the standard; the BRAF V600E, HER2-positive or NTRK-fusion subgroups have dedicated options [13] .

Surveillance after curative treatment is focused on the first five years (clinical controls, periodic thoraco-abdomino-pelvic CT, colonoscopy at 1, 3 and 5 years), aiming at early detection of relapse/metachronous events. Prevention combines screening with lifestyle interventions (physical activity, weight control, alcohol limitation and smoking cessation, diet rich in vegetables and fiber) and, selectively, chemoprevention (e.g., aspirin in appropriate cohorts). Overall, the integration of therapeutic advances with rigorous patient monitoring allows maximizing efficacy and reducing toxicity, prolonging survival and maintaining quality of life [16] .

PART II

PERSONAL INPUT

Study 1. Descriptive and disproportionate assessment of reports from the EudraVigilance database on capecitabine-induced cardiotoxicity

Purpose and objectives

The aim of this study is to evaluate the cardiovascular safety profile of CAP, based on pharmacovigilance data from the EV database, used in the treatment of CRC, through descriptive and disproportionality analysis of reported adverse reactions.

The objectives of this study are:

- identification and characterization of cardiac adverse reactions associated with CAP in relation to other antitumor drugs used in the same pathology;
- comparing the frequency and typology of cardiac reactions, including myocardial infarction, arrhythmias, heart failure and cardiomyopathies;
- analysis of the disproportionality of reported signals, with the aim of developing clinical cardiovascular monitoring protocols and optimizing therapeutic management in oncological patients.

Colorectal cancer is among the top ten most common malignancies, accounting for approximately 12% of all cancer cases diagnosed annually worldwide. According to GLOBOCAN 2022 estimates, there will be nearly 20 million new cases of cancer and 9.74 million deaths, highlighting the significant burden of this pathology. In the United Kingdom, the annual incidence of colon cancer is approximately 40,000 cases. The etiology is multifactorial, including environmental factors (diet high in red and processed meat, low fiber intake, smoking, alcohol), associated pathologies (obesity, diabetes, inflammatory bowel diseases) and genetic predispositions (Lynch syndrome, familial adenomatous polyposis).

Prevention and screening strategies have had a favorable impact in countries with strengthened health systems, reducing incidence and mortality. Regarding treatment, until the 1990s, the standard option was 5-fluorouracil (5-FU). Subsequently, the therapeutic palette has diversified, including cytotoxic agents (oxaliplatin, irinotecan), oral fluoropyrimidines (capecitabine), biological therapies (bevacizumab, panitumumab) and modern immunotherapies (pembrolizumab,

nivolumab). The introduction of anti-angiogenic agents (aflibercept, regorafenib) has strengthened the therapeutic arsenal.

Capecitabine (CAP), a prodrug of 5-FU, is widely used, including in combination regimens such as CAPOX, FOLFOX, or FOLFIRI. However, the administration of fluoropyrimidines is associated with significant adverse reactions, of which cardiac toxicity is one of the most severe. Manifestations of cardiotoxicity include angina pectoris, myocardial infarction, arrhythmias, heart failure, and, rarely, sudden death. Symptoms often occur during the first cycles of treatment, as early as 12–48 hours after 5-FU infusion or within the first few days of CAP administration. Coronary vasospasm is considered the main pathophysiological mechanism.

Pharmacovigilance analyses, such as those in the EudraVigilance (EV) database, constitute an important resource for assessing the safety of oncology therapies. In EV, by July 2024, almost 38,000 cases had been reported for CAP, comparable to those for 5-FU but fewer than for bevacizumab and oxaliplatin. The majority of adverse reactions reported for CAP (over 93%) were classified as severe, and their distribution revealed a preponderance of cardiac and gastrointestinal disorders.

The results show that myocardial infarction is the most frequently reported cardiac adverse reaction associated with CAP, followed by heart failure, arrhythmias and cardiomyopathies. The proportion of fatal events was relatively low for myocardial infarction (approximately 2%), but significantly higher for arrhythmias and heart failure, where almost a quarter of the cases had a fatal outcome. A notable element is that adverse reactions to CAP are reported more frequently in women than in men, an aspect that can be explained by pharmacokinetic and pharmacodynamic differences, but also by reporting factors.

Disproportionality analysis confirmed that fluoropyrimidines (CAP and 5-FU) are associated with a higher likelihood of reporting serious cardiac events compared with other anticancer agents (irinotecan, oxaliplatin, bevacizumab, panitumumab). CAP also had a higher risk of cardiomyopathy, while 5-FU was more frequently associated with arrhythmias. These differences suggest possible mechanistic variations between the two fluoropyrimidines.

From a clinical perspective, these findings highlight the importance of rigorous cardiac monitoring during CAP or 5-FU treatment, especially in patients with cardiovascular risk factors. Surveillance includes ECG, echocardiography, biomarkers (troponins, BNP) and, if necessary, coronary angiography. In case of

acute cardiotoxicity, immediate treatment interruption and multidisciplinary collaboration (including cardio-oncology) are essential to reduce mortality.

In addition to monitoring, pharmacovigilance plays a central role in optimizing patient safety. By analyzing safety signals, updating guidelines, and developing clinical protocols, the management of adverse reactions can be improved. However, spontaneous reports have inherent limitations: underreporting, incomplete data, lack of information about patient history or concomitant therapies.

In conclusion, capecitabine remains an essential agent in the treatment of colorectal cancer, but its use carries the risk of severe cardiovascular events. Rigorous risk assessment, careful monitoring, and adaptation of the therapeutic protocol are indispensable measures to reduce the negative impact on patients. The development of cardio-oncology as a subspecialty and the integration of modern pharmacovigilance tools constitute essential pillars for the personalization and safety of modern oncology treatments.

Study 2. Real-world evidence of drug resistance and drug ineffectiveness to bevacizumab and panitumumab from the EudraVigilance database

Purpose and objectives

Purpose: to assess the risk, resistance and ineffectiveness of treatment with BEV and PAN, based on real data from EudraVigilance, in patients with metastatic colorectal cancer.

The objectives of this study are:

- determining the frequency of RA reported as ineffectiveness/resistance for PAN and BEV;
- conducting a disproportionality analysis regarding the inefficiency/resistance of BEV/PAN compared to other systemic, targeted and immunotherapies used in mCRC;
- interpreting clinical implications for patient monitoring and personalizing treatment.

Classical chemotherapy, although essential in oncology, has important limitations such as narrow therapeutic index, major toxicity and high risk of drug resistance. These shortcomings have stimulated the development of innovative therapies – immunotherapies, prodrug therapies, monoclonal antibodies and combinations with antiangiogenic agents – aimed at increasing efficacy and reducing side effects. In colorectal cancer (CRC), RAS gene mutations play a central role in the choice of treatment: patients with mutant RAS usually receive bevacizumab (BEV), and those with wild-type RAS benefit from panitumumab (PAN) or cetuximab, associated with chemotherapy.

Bevacizumab is a widely used anti-VEGF monoclonal antibody with antiangiogenic activity, but adaptive resistance limits its long-term efficacy. The mechanisms involve activation of alternative signaling pathways (FGF, PDGF, ANGPT2), remodeling of the extracellular matrix and induction of hypoxia, which favors tumor progression and metastasis. Hypoxia also stimulates metabolic reprogramming through the Warburg effect and the use of fatty acids or glutamine. Recent studies have identified the CD5L protein as an important mediator of anti-VEGF resistance, which opens new therapeutic directions, such as the use of RNA aptamers or specific antibodies.

On the other hand, panitumumab, an anti-EGFR monoclonal antibody, is indicated exclusively for patients with wild-type RAS. Although initially effective, acquired resistance occurs in most patients, through secondary mutations in KRAS/NRAS, MET or HER2 amplification, epithelial-mesenchymal transformation and the influence of the tumor microenvironment (CAF, HGF). In addition, the emergence of mutations detectable by liquid biopsies of circulating tumor DNA (ctDNA) provides an explanation for therapeutic failure and suggests the usefulness of dynamic molecular monitoring.

Pharmacovigilance data from EudraVigilance confirm the low but clinically relevant incidence of adverse reactions related to resistance and ineffectiveness. By December 2024, almost 60,000 cases had been reported for BEV and over 7,000 for PAN, with a higher proportion of ineffectiveness reported for PAN (2.3% vs. 1.4% for BEV). Disproportionality analysis revealed a higher likelihood of reporting resistance to both drugs compared to other therapies (e.g., the immunotherapies nivolumab and pembrolizumab), and ineffectiveness of PAN was more frequently reported than that of BEV.

Interpretation of these results suggests mechanistic differences between the two therapies: BEV is initially effective but vulnerable to adaptive mechanisms of angiogenesis, while PAN has a strongly genetically conditioned profile, being effective only in molecularly selected patients, but susceptible to secondary mutations. The clinical implications emphasize the need for periodic biomarker testing (RAS mutations, VEGF levels), the use of combination therapies, and strict patient monitoring for early detection of inefficiency.

In conclusion, resistance to anti-VEGF and anti-EGFR targeted therapies represents a major challenge in metastatic colorectal cancer. Identifying molecular mechanisms and using combination approaches – antiangiogenics, immunotherapies and multiple signaling pathway inhibitors – may increase the chances of disease control. Pharmacovigilance remains an essential tool for detecting signals of ineffectiveness and guiding future clinical strategies.

Study 3. Bevacizumab - Insights from the EudraVigilance database on safety profile assessments of monoclonal antibodies used as targeted cancer therapy

Purpose and objectives

Aim: to evaluate the safety profile of BEV in CRC by descriptive and disproportionality analysis compared to chemotherapy, targeted therapy and immunotherapy based on EudraVigilance reports.

The objectives of this study are:

- characterization of the type, severity of adverse reactions and distribution by MedDRA/SOC classes and demographics;
- comparison of reporting probability (ROR, 95% CI) for BEV versus targeted systemic therapy and immunotherapy;
- identifying clinical implications for patient monitoring and treatment personalization.

In the last two decades, the treatment of colorectal cancer (CRC) has undergone significant evolution, with the median survival of patients with metastatic disease increasing to over 30 months due to multimodal therapies. Beyond chemotherapy, molecular agents targeting VEGF and EGFR receptors have contributed to prolonging life and improving its quality. Bevacizumab (BEV), an anti-VEGF monoclonal antibody, is widely used in the treatment of CRC, being particularly important in patients with RAS mutations, where administration in combination with chemotherapy increases tumor sensitivity and therapy efficacy.

However, the widespread use of BEV has brought to light a number of adverse reactions (ARs). The most common include hypertension, thromboembolic events, proteinuria, delayed wound healing, and gastrointestinal complications. Rare but severe cases, such as intestinal perforations, pulmonary hemorrhages or neurological toxicities, have also been reported. In addition to BEV, cytostatic chemotherapy remains associated with variable adverse reactions (hematological, digestive, neurological or cardiac), while immunotherapy with immune checkpoint inhibitors (ICI) has changed the therapeutic paradigm, but is effective only in a limited subset of patients (those with high microsatellite instability – MSI-H).

Methodologically, a retrospective analysis of individual safety reports (ICSRs) submitted to EV until December 1, 2024 was performed. Data included demographic variables (age, gender), geographical origin and category of reporter

(healthcare professional or patient). The terms used for coding RA were organized according to the MedDRA classification into 27 system organ classes (SOC). Disproportionality analysis was performed according to EMA recommendations, using ROR.

The results showed that by the end of 2024, almost 60,000 BEV-associated cases had been reported. The majority of patients belonged to the age groups 18–64 years (39.4 %) and 65–85 years (34.1%). The share of women was slightly higher (49.8 % compared to 41.7% men), which also reflects the use of BEV in gynaecological or breast cancers. Over two-thirds of the reports came from outside the European Economic Area, and almost 94% were completed by medical professionals, suggesting a high degree of accuracy.

The most frequently reported SOC categories for BEV were gastrointestinal disorders (12.6 %), general and administration site conditions (12.5%), and vascular disorders (6.8%). Disproportionate analysis indicated a higher likelihood of reporting vascular, hematological, and ocular reactions compared to other oncology treatments. In contrast to systemic chemotherapy, BEV was associated with a lower incidence of hematological toxicity, but with a higher risk of vascular and ocular events. Compared to other targeted agents (e.g. panitumumab, regorafenib), BEV was notable for its increased frequency of cardiovascular and infectious disorders. Compared to immunotherapy (pembrolizumab, nivolumab, dostarlimab), BEV had a distinct profile, characterized by more frequent vascular and ocular RAs but fewer immunological toxicities.

Discussion of these results emphasizes that the choice of therapeutic regimen should be tailored to the patient profile. Elderly patients, with cardiovascular or gastrointestinal comorbidities, are at higher risk of complications, requiring rigorous monitoring. In particular, hypertension and thromboembolic events are major side effects, reported more frequently in patients over 70 years of age. Gastrointestinal perforations and bleeding may also occur, especially in patients with a history of abdominal surgery or inflammatory bowel disease. Other notable effects include proteinuria and the risk of nephrotic syndrome, as well as rare neurological events such as posterior reversible encephalopathy syndrome (PRES).

Based on these observations, clinical management of patients treated with BEV should include: assessment and control of blood pressure, monitoring of proteinuria and renal function, surveillance of thromboembolic risk, and screening

for gastrointestinal and neurological complications. In addition, the use of inflammatory biomarkers and imaging tests may contribute to the early detection of severe adverse reactions.

The overall conclusion is that BEV remains an essential agent in the treatment of colorectal cancer, bringing clear benefits in survival and quality of life, especially in combination with chemotherapy. However, its specific safety profile requires careful monitoring and personalized therapeutic approaches. Compared to other therapies, BEV is distinguished by an increased incidence of vascular and infectious reactions, but with lower hematological toxicity.

The limitations of the study derive from the nature of the EV database, where reporting is voluntary and may be incomplete, inconsistent, or influenced by external factors (geographical differences, risk perception). The disproportionality analysis does not establish causality, but only highlights significant associations, which need to be validated by prospective clinical trials.

In conclusion, pharmacovigilance confirms the importance of continuous monitoring of patients treated with BEV and underlines the need for a multidisciplinary approach to the prevention and management of adverse reactions. Integrating safety data with personalized therapeutic strategies will allow for the optimization of treatment and reduction of associated risks.

Study 4. Evaluation of the effectiveness and safety of treatment of patients with colon cancer.

Purpose and objectives

The aim of this study is to evaluate the influence of oncological treatment and some biological parameters on the survival of patients diagnosed with colon cancer, in order to identify factors associated with prognosis and risk of death in clinical practice.

Objectives of this study are:

- Analysis of correlations between biological parameters in oncology patients;
- Evaluation of the survival of patients with colon cancer depending on the type of oncological treatment administered;
- Analysis of the dynamic evolution of hemoglobin depending on oncological treatment;
- Analysis of platelet evolution over time depending on treatment;
- Analysis of leukocyte evolution over time depending on treatment;
- Analysis of bilirubin evolution over time depending on treatment;
- Analysis of creatinine evolution over time according to treatment;
- Analysis of the evolution of neutrophils over time according to treatment;
- Analysis of the evolution over time of some biochemical parameters of TGO/AST values over time depending on treatment;

Colorectal cancer is one of the leading causes of oncological mortality, and its prognosis depends fundamentally on the stage of the disease at the time of diagnosis. In stage IV, treatment has a predominantly palliative role, aimed at prolonging survival, improving quality of life and reducing symptoms. In current practice, therapeutic regimens include combinations of fluoropyrimidine-based chemotherapies, oxaliplatin and irinotecan, frequently associated with targeted therapies (anti-VEGF or anti-EGFR monoclonal antibodies). However, the response to treatment is variable and influenced by the biological particularities, general condition and individual tolerance of the patient.

A major aspect is the monitoring of hematological and biochemical biological parameters during therapy. Anemia, thrombocytopenia, changes in transaminases, bilirubin and creatinine levels can affect treatment tolerance and lead to premature interruptions of therapy. From this perspective, longitudinal evaluation of biological

markers provides useful data both for optimizing personalized therapy and for identifying prognostic factors in the survival of patients with advanced colon cancer.

The paper is based on a retrospective observational study, conducted at the OncoHelp Center in Timisoara, on a group of 100 patients diagnosed with metastatic colorectal cancer between 2022–2024. Patients were included based on histopathological confirmation and the availability of clinical and biological data. Statistical analysis was performed using robust methods for longitudinal data (GLMM, Kaplan-Meier, log-rank test), with a significance threshold of $p < 0.05$.The studied group had an average age of 64 years, predominantly men (62%). The distribution of patients by treatment type showed the frequent use of regimens based on 5-FU and bevacizumab, with or without irinotecan/oxaliplatin. Overall survival was 12%, with notable differences between regimens: the best results were recorded for treatments A and B, while regimen F was associated with the worst survival curves.

The analysis of biological parameters revealed significant correlations between hemoglobin and hematocrit, between leukocytes and neutrophils, as well as between the liver enzymes AST and ALT, confirming the expected pathophysiological relationships. Dynamically, hemoglobin showed significant variations depending on the treatment, with treatments A and D being associated with better values compared to regimen F. Regarding platelets, treatment A caused significant decreases, while regimens D and F had more stable profiles. Leukocytes and neutrophils showed differences between treatments, with treatment B being associated with increased values, suggesting a more pronounced inflammatory or immune reaction.

Biochemical analysis revealed that total bilirubin was highest in treatment E, suggesting an increased liver risk, while treatment D was associated with lower values. Serum creatinine indicated a possible higher renal load under treatments A and D, with the best profile for treatment F. Regarding liver enzymes, AST was significantly increased under treatment D, suggesting hepatotoxicity, while ALT did not show significant variations between groups.

The results confirm that the type of treatment influences both the survival of patients with advanced colorectal cancer and the evolution of biological parameters. Schemes A and B were associated with higher survival rates and a more favorable hematological profile, compared to scheme F, which had the worst prognosis. Analysis of biological markers suggests that careful and continuous monitoring of these is indispensable, since hematological and biochemical changes can provide essential information regarding the tolerability, safety and efficacy of the treatment.

In conclusion, the study emphasizes the need for a personalized approach to the oncological patient, based on the integration of clinical and biological data, to maximize therapeutic benefits and minimize risks. The results can contribute to improving practice protocols and underpinning therapeutic decisions adapted to the individual profile of each patient.

GENERAL CONCLUSIONS

The doctoral thesis makes an important contribution to the field of oncology, with a particular emphasis on optimizing the pharmacological therapies currently used in the treatment of CRC. The present work highlights, by integrating clinical, paraclinical, and pharmacovigilance analyses, the need for a personalized approach, aiming to balance therapeutic efficacy with reducing the risks of ADRs.

The studies conducted in this thesis are conducted with real-world data, namely from the EudraVigilance database and clinical and paraclinical data from the Oncohelp Oncology Center Timișoara. The study provides a complex perspective on the impact of CAP, BEV and PAN in the treatment of CRC.

One of the objectives of the thesis was to evaluate the cardiotoxicity induced by CAP treatment, a fluoropyrimidine frequently used in the treatment of CRC. Both descriptive and disproportionality analysis of case reports from the EudraVigilance database demonstrate a significant incidence of cardiovascular adverse reactions, in particular: MI, HF and cardiomyopathies. Compared to 5-FU, in the case of CAP, ARs are reported with a higher frequency, suggesting an important cardiovascular risk profile.

These results emphasize the need for rigorous cardiac monitoring in patients treated with CAP, especially in the context of pre-existing risk factors, such as advanced age or cardiovascular comorbidities.

The paper studies the resistance and therapeutic inefficiency associated with BEV and PAN, two monoclonal antibodies mainly used in metastatic CRC. The disproportionality analysis for resistance to BEV and PAN revealed that from the reporting point of view, these ARs are very varied depending on the molecular profile of the tumor and its location, such as right colon vs. left colon.

These findings suggest that mutations in genes such as *KRAS* , *NRAS* , or *BRAF* may influence therapeutic response, necessitating extensive molecular testing before initiating treatment with anti-EGFR or anti-VEGF antibodies, as recommended by the ESMO and NCCN guidelines.

The study, conducted from data collection from the Oncohelp Timisoara Oncology Center, between 2022 and 2024, retrospectively analyzed demographic characteristics, disease stage, therapeutic lines and paraclinical results (hematology and biochemical analyses). This analysis highlights significant correlations between clinical parameters and therapeutic response. Patients with advanced stages (stage

IV) had a higher incidence of severe adverse reactions, such as anemia or thrombocytopenia, observed in the hemogram, which influenced treatment adherence.

These data emphasize the importance of regular paraclinical monitoring to adjust therapeutic regimens and reduce morbidity.

The results of the thesis bring to the fore direct implications for clinical practice, but also the need for pharmacovigilance data and the integration of clinical and molecular assessment. In the case of the analysis of CAP-induced cardiotoxicity, the implementation of pre-treatment cardiovascular screening protocols is suggested, especially for high-risk patients.

Regarding PAN and BEV, identification of resistance mechanisms, such as *HER2 amplification or PIK3CA* mutations , may guide the selection of combination therapies,

such as encorafenib-cetuximab for *BRAF* -mutated cases.

The thesis proposes several directions for further research. Mainly, the need to deepen the molecular mechanisms of resistance in PAN and BEV, such as the role of extracellular vesicles in immunosuppression, thus facilitating the development of adjuvant therapies. Another important aspect highlights the identification of predictive biomarkers for capecitabine cardiotoxicity, such as DPD levels, which could improve the safety of the treatment.

This doctoral thesis represents an essential contribution to optimizing the therapeutic management of CRC, highlighting the risks associated with CAP, BEV and PAN.

Through detailed analyses from EudraVigilance and clinical data from Oncohelp Timișoara, the paper demonstrates that integrated monitoring of adverse reactions and therapeutic resistance can significantly improve the safety and efficacy of treatment.

The results obtained encourage the development of personalized therapeutic strategies, based on the molecular profile of the tumor and the clinical characteristics of the patient, thus contributing to improving the prognosis and quality of life of patients with colon cancer.

Finally, expanding retrospective studies to larger cohorts and longer time periods could validate the clinical observations in this paper.

ORIGINALITY AND INNOVATIVE CONTRIBUTIONS OF THE RESEARCH

The doctoral thesis entitled "Assessment of risks associated with pharmacotherapy in patients with colon cancer " contributes in a significant and original way to current research in the field of colorectal oncology. By addressing the risks associated with oncological treatments, with the purpose of reducing adverse effects and optimizing treatment, this work aims to highlight the importance of personalized therapy.

This research highlights a multidimensional perspective on the efficacy and safety of therapeutic regions used in CRC. It is based on a retrospective analysis of clinical data obtained at the Oncohelp Timisoara Oncology Center during 2022–2024 and on a complex pharmacovigilance analysis based on data extracted from EudraVigilance.

The originality of the study is demonstrated by its interdisciplinary methodology and the detailed study for specific drugs: CAP, BEV, PAN. The data obtained are correlated with the specialized scientific literature, but also with clinical practice.

The following lines detail the main aspects of originality and innovative contributions of the research:

The integrated clinical-paraclinical and pharmacovigilance approach, as central and original elements of this thesis; the integration of clinical data obtained from longitudinal monitoring of biological parameters (e.g. blood count, liver and kidney function), with disproportionality analysis from the EudraVigilance database.

This dual approach highlights the assessment of risks associated with pharmacotherapy, combining direct clinical observations with pharmacovigilance data at the European level.

This paper provides a corroborative synthesis of hematological and biochemical adverse effects observed in clinical practice with widely reported signals. The study thus contributes to a deeper understanding of the safety profile of oncological treatments.

Another perspective of the research studies specific adverse effects which are less explored in the specialized literature: capecitabine-induced cardiotoxicity and

vascular and renal risks associated with bevacizumab. Thus, the present research makes an essential contribution through publications in prestigious journals such as Cancers (Q2, IF 4 ,4) and Pharmaceuticals (Q1, IF 4,8), which validate the relevance and novelty of the results.

This statement is supported by the fact that 5-FU and bevacizumab-based therapeutic regimens in prolonging overall survival, combined with the need for strict toxicities monitoring, may influence and inform therapeutic decisions in metastatic CRC. In addition, the identified limitations, such as the absence of molecular data (e.g. KRAS/NRAS mutations, MSI status) and quality of life assessments, open new directions for research.

The proposal of prospective, multicenter studies integrating genetic analyses and quality of life data represents an innovative contribution, with the role of guiding future investigations in colorectal oncology.

This study encourages the need to implement personalized treatment strategies and careful knowledge of patient characteristics, which can only be achieved through a holistic approach by a multidisciplinary team consisting of oncologists, pathologists, geneticists, clinical pharmacologists, pharmacists, and laboratory personnel.

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List Figure

List Tables