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Real-World Toxicity Profile, Treatment Compliance, and Dose Intensity of CAPOX Chemotherapy in Gastric and Rectal Cancers: A Prospective Observational Study

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Abstract

Background: Capecitabine–oxaliplatin (CAPOX) is a commonly used chemotherapy regimen in gastric and colorectal malignancies. Although its efficacy has been well established in randomized trials, real-world evidence regarding toxicity patterns, treatment compliance, and dose intensity remains limited. ***Objectives:*** To evaluate the toxicity profile of CAPOX chemotherapy, assess treatment compliance and dose modifications, and identify early clinical predictors of significant adverse events in patients with gastric and rectal cancers. ***Methods:*** This prospective observational study included 60 patients with histologically confirmed gastric (n = 35) or rectal cancer (n = 25) treated with CAPOX chemotherapy. Treatment-related toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment compliance, dose delays, reductions, and relative dose intensity were systematically recorded. ***Results:*** The median age was 54 years, with male predominance. Overall, 46 patients (76.7%) completed all planned cycles of CAPOX, with higher completion rates observed in rectal cancer compared with gastric cancer (84% vs 71%). The most frequent toxicities were peripheral neuropathy (45%), nausea/vomiting (38.3%), diarrhea (30%), hand–foot syndrome (26.7%), and anemia (41.7%). Grade ≥2 peripheral neuropathy occurred in 18.3% of patients and correlated with cumulative oxaliplatin exposure. Early Grade 1 neuropathy within the first two cycles independently predicted subsequent dose reduction. Relative dose intensity ≥85% was maintained in 68% of patients, particularly among those receiving early, individualized dose adjustments. ***Conclusion:*** CAPOX chemotherapy demonstrates acceptable tolerability and good compliance in routine clinical practice. Early low-grade neuropathy, baseline nutritional status, and symptom clustering may serve as clinically useful markers for anticipating cumulative toxicity and optimizing individualized treatment delivery.

Keywords: ***CAPOX, gastric cancer, rectal cancer, chemotherapy toxicity, treatment compliance.***

Introduction

Gastric and colorectal cancers remain major contributors to global cancer-related morbidity and mortality, accounting for a substantial proportion of cancer-related deaths worldwide, particularly in low- and middle-income countries [1]. In India and other developing regions, delayed presentation, poor nutritional status, and limited access to healthcare resources further complicate disease management and adversely affect treatment outcomes. As a result, optimizing systemic therapy delivery in real-world settings remains a critical clinical priority.

Systemic chemotherapy constitutes a cornerstone of management for both gastric and rectal cancers across curative and palliative settings, including neoadjuvant, adjuvant, and metastatic disease [2]. Fluoropyrimidine–platinum combinations have long served as standard regimens owing to their proven efficacy and manageable toxicity profile. The capecitabine–oxaliplatin (CAPOX) regimen has emerged as an effective alternative to in fusional fluorouracil-based combinations, offering comparable oncologic outcomes while providing the practical advantage of oral drug administration and reduced need for central venous access [3-5].

Despite these advantages, CAPOX is associated with a distinct and sometimes treatment-limiting toxicity spectrum. Oxaliplatin-induced peripheral neuropathy is cumulative and dose-dependent and represents one of the most common causes of treatment modification or discontinuation [6]. Capecitabine-related toxicities, including hand–foot syndrome, diarrhea, mucositis, and fatigue, can significantly impair quality of life and adherence to oral

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therapy [7]. Hematological toxicities such as anemia and neutropenia further contribute to treatment delays, dose reductions, and increased healthcare utilization [8].

Evidence derived from randomized controlled trials has been instrumental in establishing the role of CAPOX; however, trial populations are often highly selected and may not accurately reflect patients treated in routine clinical practice. In real-world settings, patients frequently present with compromised nutritional status, baseline anemia, comorbid conditions, and socioeconomic barriers that influence treatment tolerance and compliance [9,10]. Consequently, toxicity patterns, dose intensity, and compliance observed in everyday oncology practice may differ substantially from those reported in clinical trials.

Real-world evidence evaluating CAPOX chemotherapy in gastric and rectal cancers remains limited, particularly from developing countries. Moreover, there is a paucity of data identifying early clinical predictors of cumulative toxicity that could enable proactive treatment modification and improve treatment continuity. Understanding such predictors is essential for individualized patient management, especially in settings where supportive care resources are constrained.

In this context, the present prospective observational study was undertaken to comprehensively evaluate the real-world toxicity profile, treatment compliance, and relative dose intensity of CAPOX chemotherapy in patients with gastric and rectal cancers. Particular emphasis was placed on identifying baseline and early treatment-related factors that may predict clinically significant toxicity and influence treatment delivery.

Aims and Objectives

Primary Aim

a) To assess the incidence and severity of CAPOX-related toxicities in patients with gastric and rectal cancers.

Secondary Objectives

a) To evaluate treatment compliance and cycle completion rates.
b) To analyze the frequency and causes of dose delays, dose reductions, and treatment discontinuation.
c) To identify baseline and early treatment-related predictors of clinically significant toxicity.

Materials and Methods

Study Design and Setting

This was a prospective observational study.

Study Population

Patients aged ≥18 years with histologically confirmed gastric or rectal cancer planned for treatment with CAPOX chemotherapy were enrolled.

Eligibility Criteria

Inclusion criteria: ECOG performance status 0–2 and adequate baseline organ function.

Exclusion criteria: Prior exposure to oxaliplatin or capecitabine, uncontrolled comorbid illness, or baseline Grade ≥2 peripheral neuropathy.

Treatment Protocol

CAPOX chemotherapy consisted of oxaliplatin 130 mg/m² administered intravenously on Day 1 and oral capecitabine 1000 mg/m² twice daily on Days 1–14, repeated every 21 days.

Assessment and Data Collection

Toxicities were evaluated at each cycle using CTCAE version 5.0. Treatment compliance, dose delays, dose reductions, relative dose intensity, and unplanned hospital visits were prospectively recorded.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and toxicity patterns. Associations between clinical variables and toxicity outcomes were explored using appropriate statistical tests, with $p < 0.05$ considered statistically significant.

Results

Patient Characteristics

A total of 60 patients were prospectively enrolled, including 35 patients (58.3%) with gastric cancer and 25 patients (41.7%) with rectal cancer. The median age of the cohort was 54 years (range, 32–72 years), with a male predominance (63.3%). Most patients had good baseline performance status, with 86.7% having an ECOG performance status of 0–1.

Baseline anemia (hemoglobin <10 g/dL) was present in 31.7% of patients and was more frequent among those with gastric cancer (40.0%) compared with rectal cancer (20.0%). Hypoalbuminemia was observed in 28.3% of patients, again more commonly in the gastric cancer subgroup, reflecting compromised nutritional status at presentation (**Table 1**).

Table 1: Baseline Patient Characteristics (n = 60)

Characteristic	Overall (n=60)	Gastric Cancer (n=35)	Rectal Cancer (n=25)
Median age, years (range)	54 (32–72)	55 (34–72)	52 (32–68)
Male sex, n (%)	38 (63.3)	23 (65.7)	15 (60.0)
ECOG PS 0–1, n (%)	52 (86.7)	29 (82.9)	23 (92.0)
Baseline anemia, n (%)	19 (31.7)	14 (40.0)	5 (20.0)
Hypoalbuminemia, n (%)	17 (28.3)	12 (34.3)	5 (20.0)

Treatment Compliance and Delivery

Overall, 46 patients (76.7%) completed all planned cycles of CAPOX chemotherapy. Treatment completion was higher in patients with rectal cancer compared with those with gastric cancer (84% vs 71%). Treatment delays of one week or more occurred in 28.3% of patients, primarily due to treatment-related toxicities and hematologic abnormalities.

Oral capecitabine non-compliance, defined as missed doses for three or more consecutive days, was documented in 15.0% of patients and was mainly attributed to gastrointestinal toxicity, hand–foot syndrome, and fatigue.

Toxicity Profile

Treatment-related toxicities are summarized in Table 2. Peripheral neuropathy was the most frequently observed non-hematologic

toxicity, occurring in 45.0% of patients. Grade ≥2 peripheral neuropathy was observed in 18.3%, while Grade ≥3 neuropathy was relatively uncommon (6.7%).

Gastrointestinal toxicities were also frequent, with nausea and/or vomiting reported in 38.3% and diarrhea in 30.0% of patients. Hand–foot syndrome occurred in 26.7% of patients, though severe manifestations were rare. Among hematologic toxicities, anemia was the most common (41.7%), followed by neutropenia (28.3%) and thrombocytopenia (15.0%). Overall, Grade ≥3 toxicities were infrequent and were more commonly observed in patients with gastric cancer (**Table 2**).

Table 2: Treatment-Related Toxicity Profile of CAPOX Chemotherapy

Toxicity	Any Grade n (%)	Grade ≥2 n (%)	Grade ≥3 n (%)
Peripheral neuropathy	27 (45.0)	11 (18.3)	4 (6.7)
Nausea / vomiting	23 (38.3)	7 (11.7)	2 (3.3)
Diarrhea	18 (30.0)	6 (10.0)	2 (3.3)
Hand–foot syndrome	16 (26.7)	5 (8.3)	1 (1.7)
Anemia	25 (41.7)	9 (15.0)	3 (5.0)
Neutropenia	17 (28.3)	6 (10.0)	2 (3.3)
Thrombocytopenia	9 (15.0)	3 (5.0)	1 (1.7)

Dose Modifications and Relative Dose Intensity

Dose reductions were required in 14 patients (23.3%), most commonly due to peripheral neuropathy and hand–foot syndrome. Treatment delays were observed in 17 patients (28.3%). Despite these modifications, a relative dose intensity (RDI) of ≥85% was maintained in 68.0% of patients, reflecting effective individualized dose adjustments (**Table 3**).

Table 3: Treatment Compliance, Dose Modifications, and Relative Dose Intensity

Parameter	n (%)
Completed all planned cycles	46 (76.7)
Treatment delays ≥1 week	17 (28.3)
Dose reductions required	14 (23.3)
Oral capecitabine non-compliance	9 (15.0)
Relative dose intensity ≥85%	41 (68.0)

Predictors of Treatment Modification

Early-onset Grade 1 peripheral neuropathy occurring within the first two cycles was significantly associated with subsequent dose reduction, indicating its potential role as an early clinical predictor of cumulative neurotoxicity. Additionally, patients presenting with baseline anemia or hypoalbuminemia experienced higher rates of Grade ≥2 toxicities and were more likely to require treatment delays or dose modifications.

An analysis of early toxicity patterns revealed a symptom cluster comprising gastrointestinal toxicity, fatigue, and hand–foot syndrome. The presence of this cluster during the initial treatment cycles was associated with later treatment intolerance and the need for dose adjustment.

Impact of Baseline Nutritional and Hematologic Status

Patients with baseline anemia (hemoglobin <10 g/dL) and hypoalbuminemia demonstrated significantly higher rates of clinically relevant toxicities, particularly Grade ≥2 gastrointestinal and hematologic adverse events. These patients experienced more frequent treatment delays and dose reductions compared with those with normal baseline parameters. Baseline nutritional compromise was also associated with reduced treatment tolerance, highlighting its influence on chemotherapy delivery and continuity in real-world practice.

Symptom Clustering and Maintenance of Relative Dose Intensity

A distinct early symptom cluster comprising gastrointestinal toxicity, fatigue, and hand–foot syndrome was identified during the first two cycles of CAPOX chemotherapy. Patients exhibiting this cluster were more likely to develop cumulative toxicity, leading to subsequent dose modifications. Despite this, patients in whom early, proactive dose adjustments were implemented were able to maintain adequate treatment delivery. Overall, a relative dose intensity of ≥85% was preserved in 68% of patients, without an increase in Grade ≥3 toxicities, underscoring the effectiveness of individualized dose management strategies in sustaining treatment intensity while minimizing severe adverse events.

Discussion

The present prospective observational study provides a detailed real-world evaluation of CAPOX chemotherapy in patients with gastric and rectal cancers, focusing on toxicity patterns, treatment compliance, and relative dose intensity. The findings offer valuable insights into the feasibility of CAPOX in routine clinical practice and highlight clinically relevant predictors of cumulative toxicity.

One of the most important observations of this study is the identification of early-onset low-grade peripheral neuropathy as a predictor of subsequent dose reduction. Oxaliplatin-induced neuropathy is well recognized as cumulative and dose-dependent; however, early clinical indicators that reliably forecast later clinically significant neuropathy are rarely emphasized in real-world studies [11]. Early recognition of neuropathic symptoms may allow timely intervention through dose modification, treatment spacing, or supportive measures, thereby preserving overall treatment feasibility.

The overall treatment completion rate of 76.7% observed in this cohort compares favorably with previously published real-world data on oxaliplatin-based chemotherapy regimens [12]. Higher completion rates among rectal cancer patients may reflect better baseline nutritional status and lower prevalence of upper gastrointestinal symptoms compared with gastric cancer patients.

These findings emphasize the need for site-specific supportive care strategies when administering CAPOX.

Baseline nutritional and hematologic status emerged as important determinants of treatment tolerance in this study. Patients with anemia and hypoalbuminemia experienced higher rates of clinically significant toxicity and treatment interruptions. These findings are particularly relevant in developing countries, where malnutrition and anemia are common among cancer patients and often underappreciated during treatment planning [13]. Proactive nutritional assessment and optimization may therefore play a crucial role in improving chemotherapy tolerance.

An additional novel and clinically relevant finding is the identification of early symptom clustering as a predictor of later treatment intolerance. The co-occurrence of gastrointestinal toxicity, fatigue, and hand–foot syndrome early during treatment may represent an integrated marker of systemic treatment stress and impaired drug tolerance. Recognizing such symptom clusters in early cycles may enable clinicians to anticipate cumulative toxicity and intervene proactively [14].

The concept of maintaining relative dose intensity while minimizing severe toxicity is central to effective chemotherapy delivery. In this study, early individualized dose modification allowed maintenance of adequate dose intensity without increasing Grade ≥3 adverse events, challenging the traditional perception that dose reduction necessarily compromises treatment efficacy. Instead, a flexible, patient-centered dosing strategy may enhance overall treatment continuity and outcomes [15].

The study has limitations, including its single-center design and modest sample size, which may limit generalizability. Nevertheless, the prospective assessment of toxicity, uniform treatment protocol, and detailed documentation of compliance and dose modifications strengthen the validity and clinical relevance of the findings. Future multicenter studies with larger cohorts are warranted to validate these observations and further refine predictive models for CAPOX-related toxicity [16].

Conclusion

CAPOX chemotherapy is feasible and well tolerated in real-world clinical practice when supported by vigilant toxicity monitoring and individualized dose management. Early identification of neuropathy, baseline nutritional deficits, and symptom clustering may allow clinicians to anticipate cumulative toxicity and optimize treatment delivery.

Declarations

Ethical Approval

The study was approved by the Ethical Committee.

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Conflict of Interest

None

Funding

None

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