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Assessment of Oral Capecitabine in Elderly Patients with Stage 2 Colon Cancer: Toxicity, Tolerability, and Survival Outcomes

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ABSTRACT

Introduction: Adjuvant chemotherapy, particularly oral capecitabine, is often considered for stage 2 colon cancer despite its controversial use in elderly patients with comorbidities. This study aimed to assess the toxicity, tolerability, and survival outcomes of oral capecitabine in elderly patients diagnosed with T4N0, stage 2 colon cancer.

Methods: This retrospective study included 52 patients aged >70 years who were diagnosed with T4N0M0 colon cancer and received adjuvant capecitabine. Treatment toxicities were graded according to the National Cancer Institute of Canada Common Toxicity Criteria v4. Overall survival (OS) was analyzed.

Results: The study revealed that 86% of patients experienced treatment-related adverse events, with 29% exhibiting grade 3 and 23% grade 4 toxicities. Common severe adverse events include diarrhea and nausea. Despite starting treatment at lower doses, a significant proportion of patients required further dose reductions due to side effects, with only seven patients completing the full eight cycles of capecitabine. The median follow-up was 48 months, with disease-free survival and relapse-free survival rates of 61.6% and 67%, respectively. The 5-year OS rate was 71%.

Conclusion: In stage 2 colon cancer, administering adjuvant capecitabine to elderly patients aged >70 years poses challenges due to significant toxicity and tolerability issues. However, our study found that even with dose reductions, adjuvant therapy remains crucial for elderly patients, with a 71% 5-year OS rate similar to that of younger populations.

Keywords: Colon neoplasms, chemotherapy, adjuvant, aged, capecitabine

Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy globally, affecting both sexes. According to GLOBOSCAN data, an estimated 1.9 million new cases and 1 million deaths were recorded in 2020. The majority of diagnoses are manifest in individuals aged 65 years (1,2). Notably, the critical determinant influencing patient survival in colon cancer postoperatively revolves around the disease stage at diagnosis. For stage 2 tumors, the 5-year disease-specific survival rate ranges from 60% to 86% (3,4).

According to TNM staging, T4N0 tumors fall within stages 2B and 2C, with the distinction hinging on the tumor's invasion pattern. T4a signifies penetration of the visceral peritoneum surface, while T4b denotes direct invasion or histological adherence to structures or other organs (5,6). Although negated, lymph node involvement does not guarantee a favorable prognosis. Interaction of T4 tumors with other organs increases the risk of recurrence and metastasis.

The potency of adjuvant chemotherapy is most pronounced in stage 3 (node-positive disease). Nevertheless, several trials have indicated the benefit of adjuvant chemotherapy for high-risk patients with stage 2 disease, such as T4 (7,8). Given the roadblocks posed by comorbidities and suboptimal performance scores in elderly patients, the administration of adjuvant chemotherapy becomes constrained. Moreover, the customization of chemotherapy for older patients, particularly oxaliplatin-containing regimens, remains a subject of debate. The recommended postoperative chemotherapy regimen for elderly patients is oral capecitabine or a fluoropyrimidine regimen (9,10).

This study aimed to assess the toxicity, tolerability, and survival impact of oral capecitabine in patients aged >70 years diagnosed with T4N0

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colon cancer following complete mesocolic excision with lymph node dissection.

Methods

The ethics approval of the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-04-16, date: 24.06.2024).

Patients

The research design was a retrospective cross-sectional study. The study involved the analysis of patient files from 180 individuals diagnosed with early-stage colon cancer who underwent surgery between 2014 and 2019. Specifically, 52 patients meeting the criteria of T4N0M0 according to TNM staging and aged over 70 years were included in the study after excluding those unable to receive adjuvant capecitabine. The eligible patients received at least one course of adjuvant capecitabine (1000 mg/m^2 twice daily for 14 days, followed by a 7-day rest period). Data on the patients' demographic and pathological characteristics were retrieved from patient files and the hospital database. Retrospective treatment toxicities and tolerances were evaluated based on patient records.

Furthermore, treatment-related adverse events were retrospectively compiled from patient data files. Adverse effects, such as hand-foot syndrome, fatigue, alopecia, diarrhea, laboratory abnormalities, nausea, vomiting, and stomatitis, were graded by the National Cancer Institute of Canada Common Toxicity Criteria v4. Progression-free survival was defined as the duration from the commencement of the first chemotherapy treatment to disease progression. In contrast, overall survival (OS) was defined as the duration from the initiation of the first chemotherapy treatment until death (Figure 1).

Statistical Analysis

Statistical analyses were conducted using the SPSS version 22.0 for Windows. Categorical and continuous data were analyzed using the chi-squared test, while continuous data were analyzed using the Student's t-test. Survival analysis was performed using the Kaplan-Meier test. Results were assessed using a 95% confidence interval with a significance level set at $p<0.05$.

Results

A total of 52 elderly patients were included in our study database between 2014 and 2019. The median age at the time of colon cancer diagnosis was 77.9 years (range, 70-87 years). The gender distribution was almost equal, with a male-to-female ratio of 1.17:1. Table 1 shows the detailed demographic characteristics, data, and pathological features of all patients.

In treated patients, 86.0% experienced adverse events related to capecitabine, with 29% and 23% of the patients encountering grade 3 or 4 treatment-related adverse events, respectively (Table 2). The most common grade 3 or 4 capecitabine-related adverse events were diarrhea and nausea. As a result of capecitabine-related adverse events, 86% of the patients (n=45) had to discontinue treatment, some due to low-grade side effects.

Eight patients developed capecitabine-related hand-foot syndrome, with three cases classified as grade 3-4 severity. For grade 1-2 adverse effects, local treatments and maintenance of capecitabine dosage were employed, whereas treatment was discontinued in patients experiencing persistent toxicity from grade 3-4 side effects.

Table 1. Baseline demographics, clinical, and pathologic characteristics of patients

Characteristic	n (%)
Age, median (range)	77.9 (range, 70-87)
Gender	
Male	28 (54%)
Female	24 (46%)
Comorbidities	
None	4 (8%)
1-2	31 (60%)
>2	17 (32%)
Smoking status	
Current smoker	12 (23%)
Former smoked	27 (52%)
Never smoked	13 (25%)
ECOG performance-status-score	
0	9 (17%)
1	32 (61%)
2	11 (22%)
Primary tumor locations	
Left site	33 (64%)
Right site	16 (30%)
Other site	3 (6%)
Lymphovascular invasion	
Present	42 (80%)
Absent	10 (20%)
Perineural invasion	
Present	40 (77%)
Absent	12 (23%)
Grade	
Well-differentiated	37 (71%)
Moderately differentiated	10 (20%)
Poorly differentiated	5 (9%)

Table 2. Capecitabine-related adverse events

Treatment-related adverse events	Grade 1-2 (n)	Grade 3-4 (n)
Nausea	20	3
Vomiting	28	4
Diarrhea	12	1
Fatigue	3	1
Stomatitis	7	1
Neutropenia	6	13
Hand-foot syndrome	5	3
Increased creatinine	6	2
Hyperbilirubinemia	2	1

Neutropenia was the most common laboratory abnormality caused by capecitabine, with 8 and 5 patients experiencing grade 3-4 neutropenia, respectively. Capecitabine-induced creatinine elevation led to acute renal failure in 8 patients, with two cases attributed to fluid loss from diarrhea. Intravenous fluid replacement was administered, and the dose was reduced in these patients. Ultimately, capecitabine was discontinued in 6 of these patients.

All patients initially received a daily dose of 2000 mg of capecitabine, which was adjusted in the second cycle according to tolerance. Despite starting with a lower dose during the first cycle, eight patients exhibited poor tolerance, preventing any dose increase. Ultimately, 28 patients required dose reductions because of side effects, whereas only seven completed eight cycles of capecitabine. Gastrointestinal intolerance, particularly nausea and vomiting, was the most common reason for the early discontinuation of capecitabine (Table 3).

Table 3. Treatment modifications in patients

Average number of cycles	5 (10%)
Patients who completed full cycles of capecitabine	7 (13%)
Patients with treatment delay	34 (65%)
Patients with reduced dose	28 (53%)
Patients who stopped treatment	45 (86%)

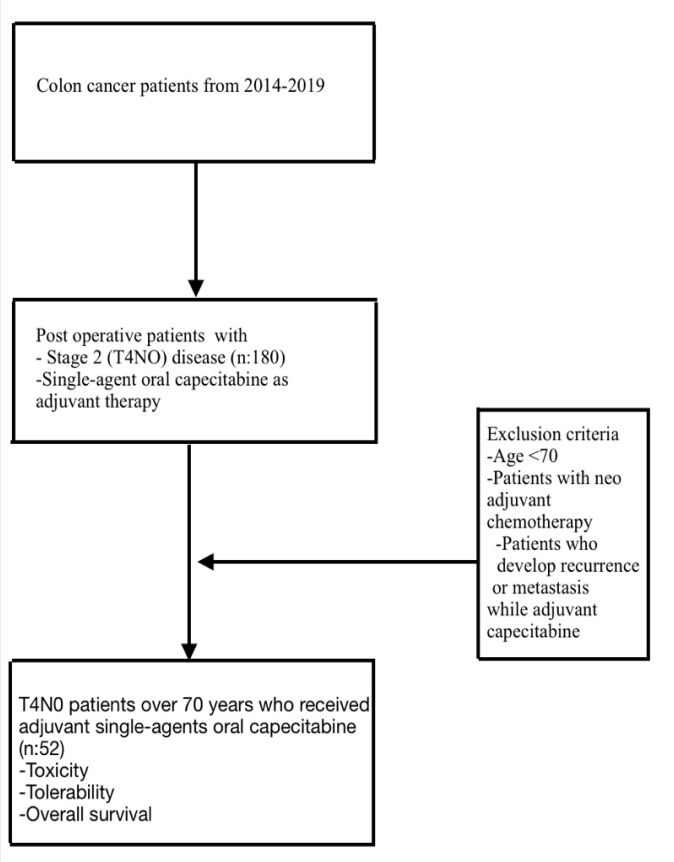

Figure 1. Flow of patient

Survival Outcomes

The median follow-up duration was 48 months. Four patients died because of unrelated health conditions, and there were no recurrences of CRC. The disease-free survival (DFS) rate was 61.6% (n=32), and the relapse-free survival (RFS) rate was 67% (n=35) for all patients. The 5-year OS rate was 71% (n=37) (Figure 2).

Discussion

Based on the available data, the prognosis of stage 2 colon cancer is variable due to various factors, with pathological changes being a significant determinant. Notably, stage 2b and 2c colon cancers, which are characterized by T4 tumors, exhibit a higher incidence of postoperative residual tumors compared with stage 3 tumors, resulting in poorer prognoses and lower 5-year survival rates (11). Effective adjuvant treatment for T4 tumors is therefore crucial. Nevertheless, administering practical nursing oncological treatments at appropriate doses can be a complex challenge, particularly for elderly patients.

Clinical studies have shown that the addition of oxaliplatin to capecitabine in adjuvant therapy does not provide survival benefit for patients over 65 (12). However, it is important to note that oral capecitabine alone can cause numerous side effects in elderly patients. The variability in response to and toxicity of capecitabine is influenced by several factors, including ethnicity. For instance, studies have reported variations in the tolerability and toxicity of capecitabine among different ethnic groups (13,14). Notably, there are no clinical studies that directly demonstrate the toxicity of capecitabine in Turkish patients, but existing studies suggest that the Turkish group may exhibit lower tolerability (15,16).

In our study involving patients aged >70 years, a maximum dose of 1000 mg/m^2 of capecitabine twice daily was administered, with cautious initial dose escalation to assess tolerability. Despite these precautions, the occurrence of drug-related toxicity was high, with a notable proportion of patients experiencing grade 3 and 4 toxicity. This is consistent with the established role of genetic variations

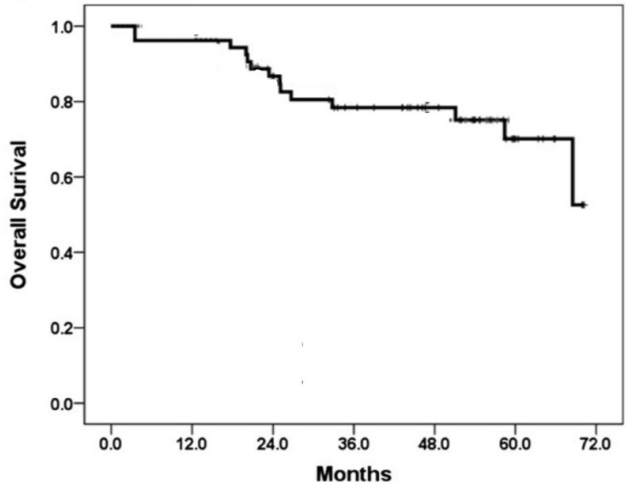

Figure 2. Overall survival of all patients

in capecitabine-related toxicity, specifically the well-documented association between dihydropyrimidine dehydrogenase (DPD) genetic variations and predisposition to fluoropyrimidine-induced toxic effects (17,18). Deficiencies in DPD activity cause severe, life-threatening drug-related toxicities in capecitabine-treated patients.

In routine oncology practice, DPD enzyme activity should not be assessed before initiating capecitabine treatment. However, it is advisable to assess it in patients experiencing severe toxicity (19). Unfortunately, since DPD enzyme activity tests cannot be performed in our oncology center, we lack information on our patients' genetic polymorphisms. We suspect that *DPD* gene polymorphisms and similar genetic variations may be present in a significant proportion of patients who experience grade 3 or 4 side effects.

Our study observed a high treatment discontinuation rate due to side effects, with a small percentage of patients completing the recommended eight cycles of adjuvant capecitabine at the total dose. In addition, more than half of the patients required dose reduction. Similar observations have been reported in other studies, suggesting the challenges associated with tolerability and the necessity of dose adjustments in elderly patients receiving capecitabine-based therapy (20,21). Notwithstanding the challenges, our study demonstrated a 3-year DFS rate of 61.6%, an RFS rate of 67%, and a 5-year OS rate of 71%, which are comparable to the existing literature. These findings indicate that adjuvant capecitabine may improve survival rates, regardless of age, for patients with stage 2 colon cancer. Additionally, the occurrence of side effects and dose reductions during treatment implies that these challenges may also be relevant in younger patient populations. Notably, our study revealed no significant difference in survival rates between the two age groups in the context of colon cancer.

Study Limitations

The study presented herein is subject to several limitations that warrant consideration. Primarily, the restricted number of patients included in the study limits the ability to draw definitive conclusions. Furthermore, the retrospective nature of the analysis may have introduced biases, potentially leading to deficiencies in the evaluation of retrospective side effects. Additionally, although the comorbidities of the patients were known, the medical treatments administered for these coexisting conditions were not comprehensively documented. Consequently, the evaluation of toxicity may not fully capture the potential interactions of these treatments with capecitabine.

Conclusion

Our study is the first to demonstrate elevated toxicity and challenging tolerability of adjuvant single-agent capecitabine in Turkish patients aged >70 years. Despite these challenges, the survival outcomes were comparable to those of the younger population. This finding highlights the significance of adjuvant treatment in the geriatric population, even with dose reduction.

Ethics Committee Approval: The ethics approval of the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-04-16, date: 24.06.2024).

Informed Consent: Retrospective study.

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