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Capecitabine as Maintenance Therapy for High-Risk, Resected Colorectal Cancer

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Keywords
Capecitabine · Event-free survival · High-risk colorectal cancer · Maintenance therapy

Abstract
Introduction: In 2020, colorectal cancer will be the fourth most frequently diagnosed malignant neoplasm and the second leading cause of site-specific, cancer-related deaths in the USA. Notably, 80% of the new cases are, by staging criteria, potentially curable even those with completely resected stage 4 disease. If slightly more than half the losses can be attributed to metastatic disease at presentation, then the remaining portion of deaths may be linked to disease relapse after surgery and, if applicable, adjuvant chemotherapy. The inference that these therapies are not curative for a significant number of subjects poses a role for maintenance therapy. ***Objective:*** To assess event-free survival (EFS) of patients who received capecitabine as maintenance therapy following treatment according to current guidelines. ***Methods:*** Clinical outcomes data were collected for 35 subjects treated with capecitabine as maintenance therapy. Descriptive statistical analyses were conducted on collective data related to duration of maintenance therapy and disease or clinical status from surgery to initial event. Kaplan-Meier method and log-rank test were used to analyze EFS and overall survival. ***Results:*** Of the entire cohort, 26 subjects have no evidence of disease (NED), a median of 5.5 years from surgery. Kaplan-Meier analyses indicated a 5-year EFS rate of 74% (95% CI: 60–90%). Eighteen of these 26 patients received capecitabine ≥30 months. Eight of the 17 subjects treated with capecitabine therapy for <30 months developed progressive disease; the majority of the relapses occurred within 20 months of surgery. The difference between the two groups was statistically significant. Six subjects died, only two of who had metastatic disease at the time of death; the other four had NED at least 4 years from surgery. Five patients with resected stage 4 disease who received capecitabine as maintenance therapy were alive >5 years from surgery. ***Conclusion:*** The findings and analyses of this cohort of patients suggest that maintenance capecitabine therapy reduces the risk of disease progression and cancer-related death.

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Introduction

An estimated 334,000 malignant tumors of the digestive system will be diagnosed in the USA in 2020 [1]. Although this figure represents only 18% of all new cancer diagnoses, this percentage is still higher than any other

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system-related cancer. Further assessment of these cases indicates that site-specific colorectal cancers (CRCs) account for nearly one-half and one-third of all the digestive system tumors and deaths, respectively.

Based on staging criteria alone, the 5-year relative survival rates for stages 1 and 2A colon cancer are 93% and 72%, respectively; the 5-year survival rate for stage 3A with systemic adjuvant therapy is 73%. However, these survival figures are not observed among all subsets of stage 2 and 3 tumors. While improved survival is usually associated with early stage, one anomaly exists with stages 2B and 2C where the 5-year survival rates have been reported to be 51.6% and 32%, respectively [2]. Similarly, the survival figures are 45% and 33% for patients with stage 3B and 3C disease, respectively.

Since surgery alone had been the standard of care for stage 2 colon cancer, it is conceivable that a consequential number of patients relapsed and died because of distant disease. With the introduction of molecular testing for genetic and/or gene-encoded protein aberrations, adjuvant chemotherapy may also be considered in subjects with stage 2B or 2C disease as well as stage 2A [3]. Furthermore, a small, but potentially significant, proportion of patients with stage 3B and 3C disease will not be cured with surgery plus standard adjuvant chemotherapy.

Recent estimates indicate 150,000 new cases and 50,000 CRC-related deaths in 2020 [1]. Inherent, but not apparent, in these figures is the observation that approximately 80% of the new diagnoses are classified as stages 1–3 or resectable stage 4 and, therefore, potentially curable. If slightly more than half the loss is attributable to metastatic disease at presentation, then the remaining portion of deaths may be linked to disease relapse after surgery and, if applicable, adjuvant chemotherapy. The inference that these therapies are not curative for a significant number of subjects poses a role for maintenance therapy.

Although clinical trials of maintenance therapy have been conducted with variable results, it is important to emphasize that these trials included only patients with metastatic colon cancer [4–9]. The inconsistent findings of previous reports are likely related to a number of factors including differences in tumor biology as well as the therapeutic agent(s) used. However, tumor burden, at the time maintenance therapy was initiated, may partially account for the disparate results. Because of the latter possibility, it is conceivable that application of maintenance therapy could have clinical benefit in early-stage, high-risk disease. And, considering the elements of cost, route of administration, side effect profile, and quality of life, an oral fluoropyrimidine prodrug could be an appropriate treatment option. The primary aim of this paper is to report preliminary results related to the use of capecitabine as maintenance therapy after standard treatment in a cohort of patients with high-risk, surgically resected CRC.

Patients and Methods

The majority of patients included in this report had, at the time of diagnosis, pathologically staged 2C, 3A, 3B, or 3C cancer involving the colon or rectum. All subjects in these subsets with colon cancer underwent surgery followed by standard adjuvant chemotherapy; patients with rectal cancer received neoadjuvant chemoradiation therapy followed by surgery and adjuvant chemotherapy. Five additional patients were diagnosed with stage 4 tumors, 2 of who had extrahepatic metastases. The 3 subjects with liver metastases received neoadjuvant radiofrequency ablation (RFA); and one of these patients was also treated with intrahepatic arterial (IHA) infusion of floxuridine (FUDR). All 5 subjects had no measurable disease following RFA +/− FUDR as mentioned, neoadjuvant chemotherapy, surgery, and systemic adjuvant therapy.

All of the subjects were informed that their disease had characteristics considered high risk for relapse and that the option of further chemotherapy was not considered standard of care. Still, all of the subjects in this report expressed that they wanted to try anything that could possibly prevent disease relapse. In order to fulfill this desire, patients were provided with a description of the proposed intervention, the importance of the individual's role in decision-making, a summary of the standard alternative, and a review of risks associated with the proposed intervention; possible reduction in risk of relapse was mentioned but not magnified. All of these discussion points form the basis of respect for persons, beneficence, and justice taken from the Belmont Report [10]. All patients gave verbal informed consent (which was witnessed by G.M.H. in addition to M.L.A., and documented in their medical records) to be treated with capecitabine as maintenance therapy with the understanding that treatment would be continued till disease progression, intolerable toxicity, or patient or physician decision to stop, whichever came first.

Study Design

Following adjuvant therapy, the prescribed treatment dose of capecitabine was 1,500–2,000 mg/m^2/day in divided doses for 1 week, every other week. A priori adjustments to this dosage were based on patient age, comorbidities, and performance status. Kidney function did not influence drug dose though patients with calculated creatinine clearances <30 mL/min were not involved; body surface area was capped at 2 m^2. The planned course of maintenance therapy was 60 months with the stipulation related to stopping mentioned previously. The primary objective of this report was to assess event-free survival (EFS) of patients who received capecitabine as maintenance therapy.

Statistical Analyses

Descriptive statistical analyses were performed on the entire cohort to summarize data related to time from surgery to last as-

Table 1. Composite data of subjects treated with maintenance capecitabine

Variables	*N* (%)
Gender	
F	12 (34.3)
M	23 (65.7)
Stage (in detail)	
2C	2 (5.7)
3A	2 (5.7)
3B	14 (40)
3C	12 (34.3)
4	5 (14.3)
Disease status at time of data collection	
NED	26 (74.3)
Stable	3 (8.6)
Metastatic	6 (17.1)
	Median (range)
Age	64 (40, 87)
SEER 5-year survival rate	0.33 (0.13, 0.73)
Duration of capecitabine, months	30 (3, 60)
Time from surgery to last assessment, years	5.5 (1.33, 17.8)

NED, no evidence of disease.

sessment, disease status at the time of this report, and EFS, including summary tables, waterfall plot, median, and standard deviations. Kaplan-Meier method and log-rank test were used to analyze EFS and overall survival.

Results

Thirty-five subjects included in this report were, or continue to be, treated with capecitabine as maintenance therapy. Numbers of colon and rectal cancer cases were 20 and 15, respectively. A summary of key data is shown in Table 1.

Duration of follow-up is shown in Figure 1. Of the entire cohort, 26 subjects have no evidence of disease (NED) when last seen in the clinic, a median of 5.5 years from surgery. The Kaplan-Meier method indicated a 5-year EFS of 74% (95% CI: 60–90%) (Fig. 2). Eighteen of these 26 patients received capecitabine ≥30 months. In comparison, 8 of the 17 subjects who received maintenance capecitabine therapy for less than the median duration (i.e., 30 months) developed progressive disease; the majority of the relapses occurred within 20 months of surgery. Overall, when all 35 patients were dichotomized by the median duration of capecitabine therapy, the difference of EFS between the two groups was statistically significant (Fig. 3). In particular, the 5-year EFS is 100% in patients with capecitabine duration ≥30 months compared to 43% in patients with capecitabine duration <30 months. In addition, the Kaplan-Meier estimate of the 5-year overall survival rate was 78% (95% CI: 63–96%).

A total of six subjects died, only two of who had metastatic disease at the time of death. The other four had NED at least 4 years from surgery. Five patients with stage 4 disease at diagnosis received capecitabine as maintenance therapy following neoadjuvant induction chemotherapy, surgery, and systemic adjuvant therapy; all 5 are

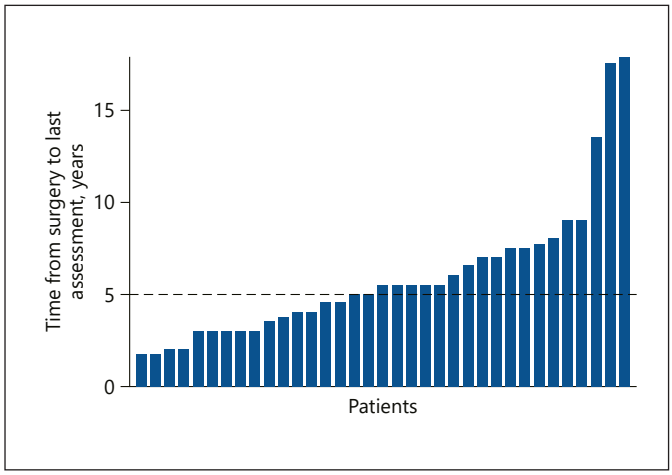

Fig. 1. Waterfall plot of time from surgery to last assessment (median 5.5 years).

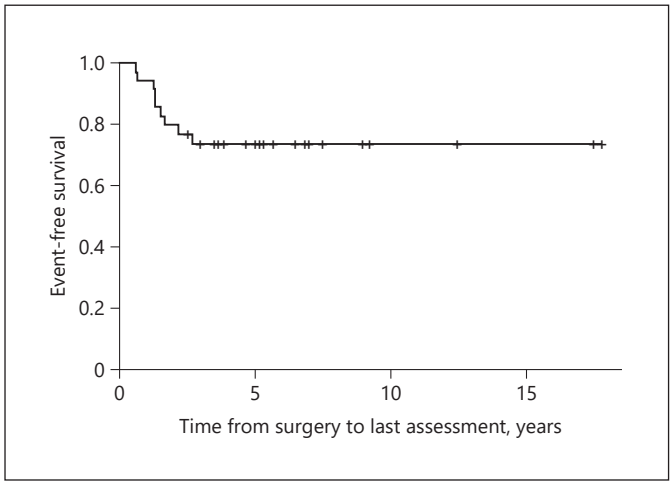

Fig. 2. Kaplan-Meier plot of EFS, 74% (95% CI: 60–90%). EFS, event-free survival.

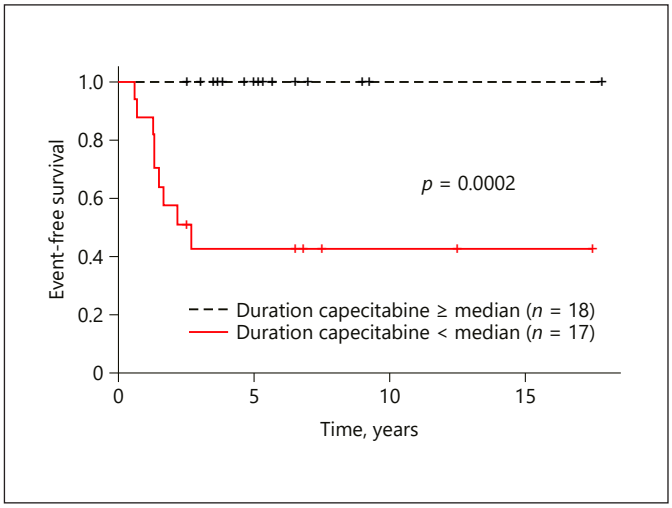

Fig. 3. Kaplan-Meier plot of EFS by duration of capecitabine therapy (median 30 months, *p* value = 0.0002 from the log-rank test). EFS, event-free survival.

alive >5 years from surgery. Four of the subjects have been on maintenance capecitabine for >4 years with NED.

The most common side effect observed was grade 1/2 hand-foot syndrome which occurred in nearly all of the subjects. The relatively low-grade toxicity responded to, or resolved with, dose reduction (500 mg of the total daily dose).

Discussion

Notwithstanding the availability of screening tests, the mortality rate of CRC is still more than twice that of breast cancer in their respective incident populations. Part of the reason for the latter observation is related to the absence of key predictive markers to guide therapy. Even *K-RAS* appears to be, at best, only marginally important because it may not be a major tumor driver. Indeed, response to cetuximab or panitumumab treatment is observed in <10% of patients with metastatic CRC (mCRC) who exhibit wild-type *K-RAS*, and disease progression will occur in the majority of these patients [11, 12].

It has been clearly shown that addition of adjuvant systemic therapy has improved disease-free and overall survival in patients with operable breast and CRCs [13–16]. One striking difference between the two tumor types relates to the *duration* of adjuvant therapy, particularly in patients with hormone receptor-positive, HER2-negative early breast cancer. Furthermore, patient age, anatomic stage, tumor size, lymphovascular invasion, extent of nodal involvement, tumor grade, and genomic signature are used to identify women with ER-positive tumors, some of who will benefit from addition of chemotherapy. In addition to these considerations, obstruction of the lumen and genetic instability have been associated with relapse risk among patients diagnosed with early-stage CRC [17, 18].

Data in this report appear to support the belief that some patients will gain additional benefit by extending the duration of systemic therapy beyond 6 months (of adjuvant therapy). Of particular interest is the median 5-year EFS rate of 74% for the entire group of patients reported herein. This relatively good outcome is consistent with the SEER Database estimate for patients with stage 3A disease; only 2 subjects in this study's cohort had stage 3A tumors at diagnosis.

Equally noteworthy were the five patients with mCRC at diagnosis who received maintenance capecitabine following RFA with or without IHA infusion of FUDR (in those with liver metastases) and induction FOLFOX followed by surgery and adjuvant chemotherapy. Despite the small number, it is important to emphasize that median overall survival of patients with mCRC is approximately 30 months [19]. That all 5 are alive, 4 of who have NED for >5 years from surgery suggest that this finding may be partially attributable to maintenance therapy.

Although a formal quality of life tool was not utilized, none of the subjects developed side effects that necessitated treatment discontinuation. One other concern of maintenance therapy relates to nascent bone marrow abnormalities. A single institution reported a small number of patients treated for CRC who were subsequently diagnosed with acute leukemia or myelodysplasia [20]. However, limited data precluded any statement regarding a causal relationship between prior therapy and incident hematologic malignancies. Instead, the authors speculated that incorporation of oxaliplatin, rather than fluorouracil, may be the link between anticancer therapy and latent marrow aberrances. Adding further credence to their notion regarding the lack of culpability of the fluoropyrimidine is the absence of any reported premalignant marrow findings or leukemogenic effect associated with capecitabine therapy.

When assessing the significance of clinical data, especially findings that were retrospectively collected, there is an inherent obligation to address study limitations. First, using medical records to source data is frequently associated with the inability to assess all facets of patient outcomes. However, all subjects in this report were patients of only one oncologist. As such, the accuracy of the data

collected is supported by meticulous recording of histories related to date of and stage at diagnosis, all anticancer treatments received by the patients, and detailed notes on follow-up visits. Despite the diligent record keeping, some information was not retrievable such as the cause of death of 4 subjects. However, all of these patients had been followed for >3 years and when last seen, none had any evidence of recurrent disease. Second, data collected included only patients who (a) were deemed to be high risk for relapse at diagnosis and (b) provided verbal consent to be treated with capecitabine as maintenance therapy. While these subjects were "selected" according to the above criteria, the findings were not biased by selection based primarily on "best" individual outcomes. Third, the duration of follow-up for half of the entire population was <5 years from surgical resection, typically an event-free endpoint which approximates cure. However, all patients in this particular subset were followed over 2 years following surgery, an important figure because the majority of the subjects with disease progression relapsed within 24 months of tumor resection. Fourth, the dose of capecitabine used was lower than the FDA-approved dose. A priori attenuation of the dosage was justified based on clinical experience that few subjects have been able to tolerate the recommended starting dose of 2,500 mg/m^2/day. Furthermore, a dose-response relationship has not been established for capecitabine; and lower doses may be associated with a better therapeutic index [21]. Fifth, the small sample size precludes making any statement regarding therapeutic effectiveness as statistical inference is based on the univariate data analysis without adjusting for treatment factor. Even so, these early findings provide support that maintenance therapy could improve disease outcomes and justify a randomized clinical trial. Sixth, lack of randomization to a no-treatment arm challenges proscribing a definite conclusion. Nonetheless, the data were compared to estimates of survival generated by SEER which is frequently used by clinicians for prognostic purposes.

Conclusion

Capecitabine is approved for the treatment of patients with mCRC. This indication plausibly suggests that the drug could be more efficacious when applied in the early-stage, low-tumor burden disease setting. Heretofore, proof-of-concept maintenance therapy has never been tested in patients with surgically resected, high-risk CRC. The initial findings of this retrospective analysis suggest that some patients, especially those with stage 2C (and likely 2B), 3B, 3C, or completely resected stage 4 disease, will gain additional benefit by extending the duration of systemic therapy. While the use of capecitabine beyond six months (of standard adjuvant therapy, usually the FOLFOX regimen) is practicable the optimal dose, schedule and duration of maintenance therapy remain undetermined.

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Statement of Ethics

Retrospective collection of clinical outcomes data for analysis received full approval of the Institutional Review Board of West Virginia University (IRB Protocol Notice: Protocol 2009110099 Approved). Relevant patient-specific data were accessed from electronic medical records (*Epic* Hyperspace^R). Since this was not a formal clinical trial, written informed consent forms were not mandated. Still, all subjects in this report gave fully informed consent for treatment as indicated in the Patients and Methods section.

Conflict of Interest Statement

The authors do not have any relationship, financial or otherwise (i.e., support in the form of employment, consultancies, honoraria, stock ownership and options, expert testimony, grants or patents received or pending, or royalties), with the manufacturer of the agent described that influenced the writing of this manuscript.

Author Contributions

M.L.A. contributed to study concept, data acquisition, and manuscript review and editing. S.W. contributed to data analyses and manuscript review. G.H. contributed to data analyses and manuscript review. G.M.H. contributed to study concept, data acquisition and interpretation, and presided over writing and editing the manuscript. The authors approved the final draft of the manuscript and are accountable for all aspects of the work including its accuracy and integrity and all parts of their involvement in this proffered article.

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