Clinical Therapeutics/Volume ∎, Number ∎, 2017

Moving Beyond Conventional Clinical Trial End Points in Treatment-Refractory Metastatic Colorectal Cancer: A Composite Quality-of-Life and Symptom Control End Point

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ABSTRACT

Purpose: This review highlights the evidence supporting symptom control and quality-of-life (QOL) measures as predictors of survival in treatment-refractory metastatic colorectal cancer (mCRC) and describes a composite symptom control and QOL end point recently reported in a Phase III trial that may serve as a more reasonable end point of efficacy in this population.

Methods: A literature search was conducted using MEDLINE to identify clinical studies (including case series and observational, retrospective, and prospective studies) that reported the predictive value of QOL measures for survival in mCRC. The search was limited by the following key words: *quality of life*, *survival*, and *colorectal cancer*. We then performed a second search limited to studies of randomized and Phase III design in mCRC to identify studies that used QOL assessments as their primary end points. A manual search was also performed to include additional studies of potential relevance.

Findings: There is increasing evidence to support that symptom control and QOL measures are predictors of survival in treatment-refractory mCRC and can serve as an alternative but equally as important end point to survival in this population. A recent large, randomized Phase III trial using a composite primary end point of lean body mass, pain, anorexia, and fatigue reported the feasibility in evaluating benefit in mCRC beyond conventional clinical trial end points.

Implications: Future studies in treatment-refractory mCRC may be better served by evaluating improvement in symptom control and QOL, which may otherwise serve as the best predictor of survival in last-line treatment settings. (*Clin Ther*. 2017;∎:∎∎∎–∎∎∎)

Key words: Metastatic colorectal cancer, endpoint, quality of life, symptom control, survival.

INTRODUCTION

Approximately 50% of patients with colorectal cancer (CRC) will develop metastases, and nearly 25% of patients with CRC present with metastatic disease at initial diagnosis.[1] Combination cytotoxic chemotherapy, including 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX); 5-FU, LV, and irinotecan (FOLFIRI); capecitabine and oxaliplatin (XELOX); and 5-FU, LV, oxaliplatin, and irinotecan (FOLFOXIRI), remains a backbone of treatment in metastatic colorectal cancer (mCRC).[2–6] The addition of monoclonal antibodies that target the epidermal growth factor receptor (ie, cetuximab or panitumumab in *RAS* and *BRAF* wild-type tumors) and the vascular endothelial growth factor A (ie, bevacizumab) to combination chemotherapy in mCRC has further improved outcomes in the first-line and second-line setting.[7–10] The combination of cytotoxic chemotherapy and targeted agents in mCRC has improved median overall survival (OS)

Accepted for publication September 29, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.09.015
0149-2918/$ - see front matter

to approximately 30 months, which is more than double that in decades past.[11]

Despite these developments, it appears that a plateau in OS has been reached in the treatment of mCRC. Metastatic or advanced CRC remains an incurable disease and prognosis remains dismal, particularly in treatment-refractory disease. The US Food and Drug Administration (FDA)–approved treatment options in patients with mCRC who have progressed on all standard therapies can afford improvements in median OS by 1.4 to 1.8 months compared with placebo, although often with clinically significant toxic effects in 38% to 93% of those treated.[12,13] In last-line settings and in cases of treatment-refractory disease, the toxic effects and impairment in quality of life (QOL) from systemic therapies may outweigh the small survival benefits offered in mCRC. In 2012, the European Medicines Agency (EMA) provided guidelines in support of the development of anticancer therapies that reduce the severity of debilitating symptoms in patients with cancer using clinical measures determined to have predictive value for survival.[14] Furthermore, the EMA proposed that symptom control, if related to antitumor effects of the therapeutic agent, represents a valid measure of therapeutic activity that may serve as a primary end point in late-line clinical studies. In this review, we highlight evidence that supports measures of symptom control and QOL as predictors of survival in treatment-refractory mCRC. Furthermore, we describe a composite symptom control and QOL end point introduced in a Phase III trial that revealed the feasibility in evaluating benefit in mCRC beyond conventional clinical trial end points.

METHODS

A literature search was performed using MEDLINE to first identify clinical studies describing the association between QOL and survival in metastatic and advanced CRC. This search was limited by using the following key words: *quality of life*, *survival*, and *colorectal cancer*. Observational, retrospective, and prospective studies were all included as evidence to support the predictive value of QOL measures for survival in mCRC. Full publications published in English-language biomedical journals up to May 2017 were included. From this initial search, we further limited studies to those of randomized and Phase III design in metastatic and advanced CRC to identify studies that used QOL assessments as their primary end points. A final manual search was also conducted to include additional studies of potential relevance.

RESULTS

QOL as Predictor of Survival in Advanced CRC

In an early systematic review of 39 Phase II and III trials of 13,874 patients with advanced solid tumors, multivariate analyses revealed that at least 1 health-care related QOL (HRQOL) measure was significantly associated with survival in 36 of 39 studies with varying effect sizes.[15] A meta-analysis of 30 randomized controlled trials (RCTs) of 7417 patients with 11 different primary cancers who had completed a baseline European Organization for Research and Treatment of Cancer–Quality of Life Core 30 (EORTC-QLQ-C30) assessment found that parameters of physical functioning (hazard ratio [HR] = 0.94; 95% CI, 0.92–0.96; $P < 0.0001$), appetite loss (HR = 1.05; 95% CI, 1.03–1.06; $P < 0.0001$), and pain (HR = 1.04; 95% CI, 1.02–1.06; $P < 0.0001$) carried significant prognostic value.[16] In an updated multivariate analysis from the same cohort of 7417 patients enrolled in 30 RCTs, HRQOL measures of physical functioning, nausea and vomiting, pain, and appetite loss were predictive of survival in 1492 patients predominantly with mCRC who had completed baseline EORTC-QLQ-C30 assessments.[17]

Dedicated studies on the predictive value of baseline QOL for survival in advanced CRC have similarly been conducted (Table I). An initial cooperative group study investigated the prognostic value of patient-completed QOL questionnaires in 1115 patients with advanced CRC and lung cancer enrolled in 1 of 6 RCTs.[18] In addition to 3 variables related to performance status (PS), patient-judged appetite represented a strong prognostic variable in this cohort ($P < 0.002$). One retrospective analysis illustrated the association between QOL indices and survival in 50 patients with mCRC and colorectal liver metastases by finding that baseline median physical scores ≤10 as assessed by the Rotterdam Symptom Checklist were significantly associated with a more prolonged OS compared with those with scores ≥10 (log-rank test, $P = 0.05$).[19] Furthermore, the physical symptom score was proposed as a potential surrogate end point