Assessing the Impact of Chemotherapy on Tumor-Related Symptoms in Advanced Colorectal Cancer

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In all patients with advanced colorectal cancer, disease eventually progresses following fluorouracil (5-FU) therapy, with a worsening of disease-related symptoms and quality of life (QOL). Irinotecan (CPT-11 [Camptosar])

Introduction

Colorectal cancer is the second most common cause of cancer-related death in industrialized populations. Despite intensive investigation, the prognosis of patients with metastatic disease has not improved over the past 30 years. Estimated 5-year survival is 5%,[1] and systemic therapy affords only a modest survival advantage over supportive care alone.[2] Systemic therapy is therefore given with palliative intent. Disease-related symptoms and quality of life (QOL) are the most relevant end points of palliation and are of major concern to patients with advanced disease.[3,4]

For the first time in many years, a number of new agents are now available for the treatment of advanced colorectal cancer. Assessment of drug efficacy is usually based on the standard criteria of radiologic response, time to progression, and overall survival. These end points do not always correspond to palliation. The assessment of these new agents, therefore, should include a measure of the impact of therapy on disease-related symptoms and quality of life. In this article, we will discuss the basis of this approach and its use in the design of a phase II trial to assess the palliative benefit of irinotecan (CPT-11 [Camptosar]) in patients with colorectal cancer refractory to fluorouracil (5-FU).

Systemic Therapy for Colorectal Cancer

Fluorouracil-Based Therapy

The antimetabolite 5-FU is the most widely used cytotoxic agent in advanced colorectal cancer. It acts through the binding of its metabolite, 5-fluorodeoxyuridylate monophosphate (FdUMP), to thymidylate synthase, which results in the depletion of substrates for DNA synthesis. Response rates of between 15% and 20% have been reported for 5-FU as initial monotherapy.[5]

Over the last decade, biochemical modulators, including leucovorin, have been used to enhance the therapeutic efficacy of 5-FU. A published meta-analysis of nine trials randomizing 1,381 patients to 5-FU and leucovorin vs 5-FU alone confirmed overall response rates of 23% and 11%, respectively. There was no survival advantage reported for either regimen.[6] Improved tumor response rates have also been achieved by varying the administration regimen of 5-FU, especially by using a continuous infusion.[7,8]

In all patients with advanced colorectal cancer, disease eventually progresses on 5-FU therapy, with worsening of disease-related symptoms and QOL. The role of systemic therapy in this patient population is poorly defined, given the poor activity of currently available standard cytotoxic agents.[9] Of the newer agents currently under evaluation, the camptothecin derivatives have generated considerable clinical attention, especially in this population with refractory/resistant disease.

Camptothecin and Its Analogs
The camptothecins act by inhibiting topoisomerase I, an enzyme that forms a covalently linked cleavable complex with DNA, resulting in a single-strand break.[10] Then, the enzyme-DNA complex allows for swiveling of the single strand, followed by replication and subsequent repair. The camptothecin derivatives stabilize this complex, maintaining the single-strand break.[11] With prolonged exposure to the camptothecins, the replication fork collides with the drug-stabilized cleavable complex, inducing a lethal double-strand DNA break.[12]

Irinotecan is a semisynthetic analog of camptothecin that has better water solubility, an improved toxicity profile, and greater activity.[13] In vivo, irinotecan is converted by hepatic carboxylesterase to its active metabolite, 7-ethyl 10-hydroxy-camptothecin (SN-38), [14,15] which has demonstrated a greater than 250-fold antitumor activity than the prodrug in vitro.[16] Phase I studies of irinotecan have been carried out in Japan, the United States, and France using various administration schedules. Activity has been observed in non-small-cell lung, breast, colon, and cervical cancers, with minor activity in other malignancies.[16]

The toxicities reported include delayed-onset diarrhea, neutropenia, nausea, vomiting, an acute cholinergic syndrome, fatigue, and alopecia; these have been discussed in detail in a recent review.[17] The principal toxicity in the pivotal US phase II trials in colorectal cancer was delayed diarrhea, which has the potential to diminish QOL. It has a median onset of 11 days from the commencement of therapy, with 31% of patients suffering National Cancer Institute (NCI) grade 3 or 4 toxicity.[18]

The severity of delayed diarrhea has been reduced by the use of intensive, high-dose antidiarrheal medications.[19] In the aforementioned phase II trials, the incidence of severe diarrhea was reduced from 17.5% to 9.8% of courses when this regimen was begun at the onset of diarrhea.[18]

**Irinotecan in Previously Treated Colorectal Cancer**

**Phase II Trials**

Phase II trials of irinotecan in patients with previously treated colorectal cancer have been completed in Japan, France, and multiple centers within the United States. A Japanese phase II study evaluated irinotecan at a dose of 100 mg/m² weekly or 150 mg/m² every 2 weeks in 67 colorectal cancer patients, including 51 who had previously received chemotherapy (oral fluoropyrimidines, intravenous 5-FU, or 5-FU and leucovorin). Irinotecan produced an overall partial response rate of 27%, with a median duration of response of 50 days (range, 9 to 120 days). The response rate in patients previously treated with chemotherapy or radiotherapy was 25%.[20]

Pooled data have been analyzed from US multicenter single-agent trials involving 304 patients with cancers that were refractory or resistant to 5-FU (ie, those who progressed during or relapsed following initial chemotherapy). Irinotecan was administered in a 6-week regimen (weekly treatment for 4 weeks, followed by 2 weeks of rest) at a starting dose of 100, 125, or 150 mg/m². Of the 304 patients, 193 commenced treatment at a dose of 125 mg/m². On an intent-to-treat analysis, response rates based on starting dose were as follows: 22% for the 150-mg/m² dose, 15% for 125 mg/m², and 8% for 100 mg/m². Overall, 49% of patients had stable disease for at least 2 months. The median duration of response was 6.0 months.[18]

The European experience with a 3-week regimen in previously treated patients has also been reported. Of 130 pretreated patients enrolled in the trial, 62 patients had progressed while receiving prior 5-FU-based chemotherapy and were defined as 5-FU-resistant. Similar to the US trials, the European investigators observed a response rate to irinotecan of 17.7% in pretreated patients, including a response rate of 16.1% in the 5-FU-resistant subset. The median time to response was 9.3 weeks, and median survival duration was 10 months.[21]

**Phase III Trial of Irinotecan as Second-Line Therapy**

As reported by Cunningham et al,[22] an inter-European phase III randomized trial comparing irinotecan to best supportive care and to best second-line 5-FU-based therapy in patients with
5-FU-refractory disease has been completed. This trial is described in detail in another article in this supplement; this article will focus on the trial's results with respect to QOL and disease-related symptoms.

Both studies prospectively assessed, as secondary end points, the effect of irinotecan on patients' QOL and disease-related symptoms using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 version 2.0 instrument. In the comparison of irinotecan to best second-line therapy, the irinotecan arm demonstrated an improvement in pain-free survival of 10.3 vs 8.5 months (P = .06), with a reduction in analgesic requirements and an improvement in performance status.

In the comparison of second-line irinotecan vs best supportive care, there was a significant improvement in the global QOL score in favor of irinotecan. In addition, the irinotecan-treated patients demonstrated a significant improvement in pain intensity, as measured by the EORTC QLQ-C30 instrument (P = .002), which was associated with a decrease in analgesic requirements.

**Effect of Systemic Therapy on DRS and QOL**

Quality of life is a person's subjective sense of well-being derived from his or her current experience of life as a whole. An assessment of health-related QOL, including disease-related symptoms (DRS), aims to explore the effects of disease and its treatment on the multidimensional aspects of a patient's life. Chemotherapy is used generally with palliative intent in the treatment of most metastatic cancers in adults, given its modest influence on overall survival. The goal of palliative therapy is quality of survival, but the most widely used end points in oncology have been tumor shrinkage or response, which do not necessarily correspond to palliative benefit.

For chemotherapy to result in palliation, its main influence is likely to be an improvement in QOL due to a reduction in disease-related symptoms. Evaluation of QOL and disease-related symptoms should be included in studies of palliation; these are the most relevant end points and are of major concern to oncology patients.

Quality of life is a subjective evaluation, in the sense of its importance to the individual. Therefore, it can be truly measured only by the patient, as assessment by health professionals is not only inappropriate but also inaccurate. Studies have demonstrated considerable disagreement between the parallel assessment of QOL by doctors and cancer patients. Clinicians in general may regard the subjective evaluation of QOL as "soft" or nonreproducible data, but its measurement is as reproducible as evaluation of tumor response.

Quality of life, as well as providing an important end point in clinical trials, also may have a prognostic role, in terms of response to treatment and survival. Trials in breast cancer, melanoma, lung cancer, and prostate cancer have demonstrated that both a patient-based QOL scale and performance status were strong predictors of survival in a multivariate analysis.

A recent multicenter trial evaluated the prognostic association of QOL scores among patients with advanced malignancies in routine clinical practice. In all, 735 patients with advanced malignancy in 10 countries completed the EORTC QLC30. The single-item QOL scores for overall physical condition, overall QOL, and the global and social functioning scales were independently prognostic, after adjustments were made for performance status, age, and metastatic site.

**Studies Assessing Palliative Benefit in Colorectal Cancer**

Common symptoms in patients with advanced colorectal carcinoma include declining performance status, fatigue, pain, nausea and vomiting, and anorexia. Several trials, including the randomized phase III trials of irinotecan have demonstrated the potential palliative benefit of systemic therapy in these patients. The trials in colorectal cancer, described below, did consider quality of life and disease-related symptoms.
A recent Nordic Gastrointestinal Tumour Adjuvant Therapy Group study compared early chemotherapy, consisting of sequential methotrexate, 5-FU, and leucovorin rescue for 6 months, in asymptomatic patients with metastatic colorectal carcinoma to expectant therapy at the onset of disease-related symptoms. Early treatment was associated with superior survival duration (14 vs 9 months), as well as prolonged duration without symptoms and time to progression of approximately 6 months relative to patients treated expectantly.[34] A parallel assessment of quality of life in a subset of patients confirmed that QOL was not reduced in asymptomatic patients receiving chemotherapy.[35]

Another Norwegian multicenter randomized trial evaluated the effect of 5-FU combined with methotrexate or folinic acid on patient- and physician-rated quality of life and standard response criteria in 70 symptomatic patients with advanced colorectal carcinoma. The study reported an objective response rate of 21% and an overall improvement in QOL of 36%. There was a correlation between the objective response rate, subjective response, and improvement in QOL.[36]

Another study randomized patients with advanced colorectal cancer to 5-FU-based combination chemotherapy and best supportive care to best supportive care alone. The main outcome measures were length of survival and a QOL score, as measured by an optimized Functional Living Index-Cancer (FLIC) scale. Overall survival was significantly longer in patients given chemotherapy than in those given best supportive care alone (11 vs 5 months; P = .006). Global or subset QOL scores did not differ significantly between the treatment arms. In patients with abnormal QOL scores at baseline, QOL appeared to improve in the chemotherapy arm.[2]

**Studies Assessing Palliative Benefit in Other Malignancies**

Recently, two randomized clinical trials of other malignancies have been published that used changes in disease-related symptoms as the primary end point. The trials were performed in prostate and pancreatic cancers; both have in common patients debilitated by significant disease-related symptoms, together with the considerable difficulty in assessing a standard radiologic response to systemic therapy. The FDA accepted the results of these two studies as the primary evidence for subsequent licensing of the relevant drugs.

**Prostate Cancer**

In a National Cancer Institute of Canada phase III randomized trial, 161 patients with hormone-refractory prostate cancer were randomized to receive chemotherapy with mitoxantrone (Novantrone) and prednisone or prednisone alone.[32] Mitoxantrone was selected as a well-tolerated cytotoxic in this population of generally debilitated symptomatic elderly patients.

The primary end point of the trial was palliative, defined as a 2-point decrease in pain (assessed on a 6-point pain scale) without an increase in analgesic medication, maintained for at least 6 weeks. The secondary end point was a 50% reduction in analgesics without an increase in pain. Information about other aspects of QOL was assessed by the Prostate Cancer-Specific Quality-of-Life Instrument (PROSQOLI), a series of nine linear analog scale assessment (LASA) items together with pain intensity and analgesic consumption scales, and by the EORTC QLQ-C30 with a disease-specific module.[32]

Based on the primary end point alone, a palliative response was observed in 29% of patients in the chemotherapy arm vs 12% in the control arm (P < .01). The total palliative response rates for the combined primary and secondary end points were 38% vs 21%. The chemotherapy arm produced a significantly longer duration of palliation (P < .001). The majority of patients who achieved a palliative response had improvements in most domains of QOL, including a significant improvement in overall well-being, as well as a prostate-specific antigen (PSA) response.[32]

**Pancreatic Cancer**

The second report described a North American multicenter randomized trial comparing the new
agent gemcitabine (Gemzar) to 5-FU in patients with symptomatic untreated advanced pancreatic cancer.[37] Patients with advanced pancreatic cancer are usually quite debilitated by disease-related symptoms, which include pain, malignant cachexia, and jaundice. There is also considerable difficulty assessing the primary site of disease for radiologic response due to its retroperitoneal location and to surrounding inflammatory reaction.[38]

The primary end point of this trial was defined prospectively as a clinical benefit response (Figure 1).[39] The components of clinical benefit were pain (assessed by pain intensity on the Memorial Pain Assessment Card), analgesic consumption, and functional impairment (Karnofsky performance scale, or KPS,[40] assessed by two independent observers). A positive clinical benefit was prospectively specified as: (1) at least a 50% improvement in pain intensity; (2) at least a 50% decrease in analgesic consumption; and (3) at least a 20-point improvement in KPS. The improvement needed to be maintained for at least 4 weeks without deterioration in the other two parameters.

Clinical palliative benefit was observed in 24% of patients treated with gemcitabine, as compared with 5% of those treated with 5-FU. Patients in the gemcitabine arm also had a significant improvement in median survival (5.6 vs 4.4 months; P = .0025).[37]

**Phase II Trial of Irinotecan in Refractory Advanced Colorectal Cancer**

Irinotecan has demonstrated activity in patients with 5-FU-refractory colorectal cancer. The palliative benefit of this agent was not well documented in the original studies. Consequently, an open-label single-arm phase II study was designed to determine the palliative benefit of irinotecan in this group of patients. The primary end points were patient oriented, with a specific focus on disease-related symptoms and QOL.

The aims of this study are:

- To assess the effect of irinotecan on the disease-related symptoms and QOL in patients with advanced colorectal cancer refractory or resistant to 5-FU, using prospectively defined palliative end points to assess response.

- To determine the response rate, time to tumor progression, toxicity profile, and overall survival of patients treated on this trial.

**Eligibility Criteria**

To be eligible for the trial, patients were required to have histologically confirmed, locally advanced or metastatic adenocarcinoma of the colon or rectum. The cancer had to be incurable with surgery or radiotherapy and measurable or evaluable. Furthermore, disease had to be refractory or resistant to 5-FU, defined as either progression or relapse during or within 6 months of completing 5-FU-based therapy in the adjuvant or advanced setting.

Patients were required to have *disease-related symptoms at baseline*, defined prospectively as one or more of the following:

- KPS of 60% to 80%[40];

- Pain on average attributable to disease of severity greater than 1 cm along a 10-cm pain LASA [41]; and

- Baseline narcotic analgesic consumption of 10 mg/d of morphine sulfate (or its equivalent),
averaged over the preceding 7 days.

Pain secondary to disease had to be stable and controlled optimally with narcotic and nonnarcotic analgesia. If, in the opinion of the investigator, the patient had pain secondary to disease that was unstable or poorly controlled, a pain stabilization period of no more than 1 week was required prior to study entry, during which time analgesia was optimized. When pain could not be stabilized in this period, the patient was not entered. This allowed for any assessment of pain during the trial to truly reflect the effect of therapy (ie, improvement) or disease progression (ie, increase in severity).

Eligible patients had to be able to complete QOL questionnaires (EORTC QLQ-C30 version 2 instrument[23]) and maintain a record of disease-related symptoms (using LASA[41]; Table 1) and a daily analgesic usage diary. A research nurse provided instruction.

Informed written consent was obtained according to the institutional and university requirements.

In the pivotal US phase II trials of irinotecan in refractory colorectal cancer, 92% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, equivalent to a KPS of >90 points.[18] This is a selected population of refractory/resistant patients, in whom it would be difficult to identify a palliative response and impact of therapy if used as entry criteria in this trial. The majority of patients who show no response to initial 5-FU do become symptomatic and have a declining performance status.

**Treatment Administration**

Irinotecan was administered intravenously in 500 mL of 5% dextrose solution over 90 minutes and was given weekly (on days 1, 8, 15, 22) for 4 weeks followed by a 2-week rest. Treatment was repeated every 6 weeks. The starting dose was 125 mg/m² intravenously. Patients were to receive a planned maximum of six cycles and were withdrawn from study if there was clinical or radiologic progression, unacceptable toxicity, or patient request.

**Dose Modifications**

Dose modifications made during the treatment cycles were based on the worst NCI grade toxicity since the last dose of irinotecan. Dose modifications for the first dose of a treatment cycle were based on the worst toxicities observed during the previous cycle. The dose reduction schema was similar to that outlined by Rothenberg et al.[42] Patients who could not tolerate 50 mg/m² or who required a greater than 2-week delay of treatment due to toxicity were taken off the study. Patients who experienced no toxicity following the first course of therapy at the starting dose level of 125 mg/m²/wk could have a dose escalation to 150 mg/m²/wk. Patients who had an omission of the week 2, 3, or 4 dose could, at the discretion of the investigator, receive a 1-week rather than 2-week break after the completion of three doses in a 5-week treatment course.

**Supportive Care**

All patients received prophylactic antiemetic therapy consisting of ondansetron and dexamethasone. Patients who experienced the early cholinergic syndrome (diaphoresis, lacrimation, abdominal cramping, or early diarrhea occurring during or within 12 hours following irinotecan administration) received 0.25 to 1 mg of intravenous atropine (unless clinically contraindicated). Late diarrhea was treated as described in the literature.[19,42]

**Patient Evaluation**

Parameters of palliative response were assessed frequently during each cycle of therapy. This
provided a detailed assessment of the effects of therapy (benefit and toxicity) on the patient during a treatment course.

The patient and a doctor or nurse assessed KPS. The LASA of symptoms related to disease, including pain (Table 1), together with EORTC QLQ-C30, were completed by the patient every 2 weeks, prior to being seen by medical staff. The research nurse monitored compliance. Approximately 15 minutes of patient time were required to complete these assessments. The LASA and EORTC QLQ-C30 instruments have been validated and have been demonstrated to be reliable and responsive to changes in aspects of health-related QOL.[43-45]

Patients recorded their daily analgesic intake in a provided diary. Opiate intake, measured as milligrams of morphine (or equivalent) per day was averaged over the preceding 7 days.

**Tumor Evaluation**

The same method of radiologic assessment of disease was employed as was used in the initial assessment. Radiologic assessment of marker lesions was done every 6 weeks for the first 12 weeks, and then every 12 weeks (or earlier if there was clinical suspicion of progression). The World Health Organization (WHO) response criteria were used.[46]

In all patients who exhibited a response (complete or partial response), this had to be confirmed radiologically 6 weeks after the first documentation of response. Once response was confirmed, tumor measurements were repeated every 12 weeks until tumor progression. Patients with ≥ 25% but ≤ 50% reduction in tumor size at 12 weeks also underwent assessments at 18 weeks in order to precisely estimate the onset of response (if no true response was detected, assessment returned to the every-12-week schedule). To determine the time to progression, the investigator was encouraged to obtain radiologic assessments earlier than 12 weeks if there was a strong clinical suspicion of disease progression in order to confirm or refute this impression.

**Palliative Response Assessment**

The primary end points of this study were the impact of irinotecan on disease-related symptoms and QOL. Palliative response benefit was defined as one or more of the following (Figure 2):

- ≥ 50% decrease in pain score (on a linear analog scale) from baseline in the setting of stable or decreased analgesic usage; or

- ≥ 50% decrease in narcotic analgesic usage from baseline in the setting of stable or decreased pain intensity; or

- ≥ 10 point increase in KPS from baseline without deterioration of the other two categories.

Each of these determinants of response had to be maintained for at least 4 weeks. The first end point excludes the circumstance of improved pain control with an increase in analgesic intake. Similarly, the second end point excludes a decrease or withdrawal of narcotic analgesia due to lack of efficacy.

**Statistical Issues**

The planned accrual is 50 patients overall, with an expected palliative response rate of 30% (95% confidence interval, 17% to 43%). Palliative response rate will be calculated as the number of patients satisfying the above palliative response criteria divided by the total number of evaluable patients. Patients who die before the palliative response is measured will be classified as nonresponders.
All patients entered in the study will be analyzed for the secondary end points. Disease-free survival and overall survival will be analyzed using the Product-Limit method. The Cox model will also be used to assess the relationship between survival outcomes and baseline prognostic factors. The QOL data will be used to evaluate patients who achieved a palliative response.

Results

From April 1997 to February 28, 1998, 60 patients have been entered, and the study is closed to accrual. As the data are still being collected and the results are preliminary, they will not be presented here.

Conclusions

The design of this phase II study provides an example of methodology for the use of patient-oriented end points to evaluate new systemic agents. These patient-oriented end points are not "soft" measures, as they can be reliably and reproducibly measured. Moreover, these are issues of importance to any cancer patient. Baseline measures of relevant disease-related symptoms or QOL should be integrated into the eligibility criteria of trials when the expected gain in overall survival is modest.

This phase II study will better define the palliative benefit of irinotecan in 5-FU-refractory colorectal cancer. The results, when combined with the data from the European phase III studies, should provide valuable information for both patients and clinicians faced with the difficult clinical problem of 5-FU-refractory disease.

References:


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