Answering Patients' Needs: Oral Alternatives to Intravenous Therapy

Markus Borner,[a] Werner Scheithauer,[b] Chris Twelves,[c] Jean Maroun,[d] Hansjochen Wilke[e]

[a]University of Bern, Bern, Switzerland; [b]Vienna University Medical School, Vienna, Austria; [c]Cancer Research Campaign Department of Medical Oncology, University of Glasgow, and Beatson Oncology Centre, Glasgow, UK; [d]Ottawa Regional Cancer Centre, Ottawa, Canada; [e]Department of Internal Medicine and Oncology/Hematology, Kliniken Essen-Mitte, Essen, Germany

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Abstract

Metastatic colorectal cancer has traditionally been treated with i.v. 5-fluorouracil (5-FU), with or without leucovorin (LV). 5-FU is administered as either an i.v. bolus or a protracted infusion. Although schedules using the latter method offer efficacy benefits (objective response rate, time to disease progression), protracted infusion schedules are often associated with medical complications, inconvenience, high costs, and poor quality of life. Issues such as quality of life and convenience have influenced treatment decisions, but the availability of oral fluoropyrimidines represents a new development in this domain.

Studies have confirmed that the majority of patients prefer oral to i.v. chemotherapy. Questionnaire-based studies have also demonstrated a preference for home-based rather than hospital-/clinic-based therapy. This preference was one of the driving forces behind the development of the oral fluoropyrimidines capecitabine (Xeloda®) and uracil plus tegafur (UFT). Oral agents offer patients a more convenient treatment option that can be administered at home, providing patients with a greater sense of control over their therapy, while avoiding the medical complications and psychological distress associated with venous access.

This article highlights some of the problems associated with i.v. therapy and reviews the available data on patient preference, including results of a recent, randomized, phase II study. It also provides a critical evaluation of the efficacy and safety profiles of the only two oral fluoropyrimidines approved for prescription, capecitabine and UFT/LV (UFT/LV not available in Germany and the U.S.), compared with those of two infused, 5-FU-based regimens. Finally, the results of an interactive debate exploring the opinions of approximately 400 oncologists on the issues of oral versus i.v. therapy are presented. ***The Oncologist*** *2001;6(suppl 4):12-16*

Introduction

Cancer therapy has traditionally been evaluated using clinical outcomes such as objective response, time to disease progression, control of physical symptoms, and overall survival. However, increasing emphasis is being placed on quality of life and broader issues, such as convenience or allowing the patient to maintain a normal lifestyle. Traditionally, metastatic colorectal cancer has been treated with i.v. 5-fluorouracil (5-FU), administered either as a bolus or as a continuous or protracted infusion, with or without leucovorin (LV). Intravenously administered chemotherapy is inconvenient for patients, adversely affecting quality of life, and can be associated with significant toxicities, psychological distress, financial difficulties, and prolonged hospital stays [1].

Home-based treatment may reduce some of this burden. Treatment at home may be associated with improved quality of life, decreased analgesic requirements, and less psychosocial morbidity than hospital-based therapy in patients with advanced cancer [1, 2]. The use of ambulatory pumps and indwelling catheters enables home-based i.v. chemotherapy, but these administration techniques remain

Correspondence: Markus Borner, M.D., Institute of Medical Oncology, Inselspital, Berne 3010, Switzerland. Telephone: 41-31-632-2111; Fax: 41-31-382-1237; e-mail: markus.borner@insel.ch *Received July 13, 2001; accepted for publication July 19, 2001.*

inconvenient for patients. Insertion of central venous lines can be painful and occasionally leads to pneumothorax or hemorrhage. In the long term, they are often associated with medical complications such as infection, bleeding, and venous thrombosis [3, 4]. Oral chemotherapeutic agents, such as capecitabine, potentially offer a number of advantages, including greater convenience, fewer hospital/doctor's office visits, less pain, and the avoidance of problems related to venous access.

Patient Preference for Oral Therapy

Another important reason for developing oral chemotherapeutic agents is that patients tend to prefer oral treatment, as it offers a sense of control over treatment and interferes less with their daily lives and family or social activities. During the past decade, questionnaire-based studies have been conducted to assess patient preference for oral versus i.v. therapy in patients with cancer. In a prospective study, interviewers used a structured questionnaire to determine the preferred route of administration in 103 patients with advanced cancer who were likely to undergo palliative treatment [5]. The strength of preference and potential factors that might influence their choice were also evaluated. Finally, patients were asked whether they would accept decreased efficacy to keep their chosen route of administration.

In total, 89% of patients preferred oral therapy. Major reasons for this preference were convenience (57%), problems with i.v. lines or needles (55%), and a better environment for administration of chemotherapy (33%). The study also revealed that patients were not prepared to sacrifice efficacy in preference for oral treatment: 70% of patients were not willing to accept a lower response rate and 74% were not willing to accept a shorter duration of response.

A second study in 53 patients with advanced breast or ovarian cancers examined whether the site (home versus hospital-based) and method of administering chemotherapy influenced quality of life in patients receiving palliative chemotherapy for advanced cancer [1]. Quality of life was assessed by measuring anxiety, depression, self-esteem, health locus of control, physical performance, and symptoms using the Hospital Anxiety and Depression scale, the Rosenberg self-esteem scale, and the Multidimensional Health Locus of Control Scale. Results showed that global quality of life, derived using 10 psychological and physical variables, was significantly ($p = 0.001$) reduced in patients receiving hospital-administered chemotherapy compared with those treated at home.

More recently, patient preference for oral or i.v. treatment has been studied directly in a randomized, crossover trial comparing an oral fluoropyrimidine regimen (uracil plus tegafur [UFT] plus LV) versus i.v. bolus 5-FU/LV (Mayo Clinic regimen) in patients with advanced colorectal cancer [6]. Patients were randomly assigned to one cycle of oral therapy followed by one cycle of i.v. therapy, or vice versa. A questionnaire was used to assess patient preference and reasons for their preference, before receiving any treatment and again after completing both cycles of chemotherapy (without knowledge of tumor response). Patients then chose the treatment they wanted to continue receiving (i.v. or oral).

Of 31 evaluable patients, 84% preferred to continue with oral therapy. The order in which patients were exposed to therapy did not influence patient preference. Before therapy, the characteristics most frequently considered to be important were that treatment should not induce vomiting (77%), diarrhea (55%), or painful mouth ulcers (52%), and that the medication could be administered at home (48%). The risk of infection (39%) was also considered important. For the 84% of patients who preferred oral therapy, the most important treatment features recorded after treatment administration were that no i.v. access was required and that the drug could be taken at home (Table 1).

Comparison of Oral Versus i.v. Therapy

Given the fact that maintenance of treatment efficacy is clearly very important to patients when considering the benefits of different routes of administration for chemotherapy, it is important to look critically at outcome measures in trials of new therapeutic approaches. The development of new schedules and regimens for the first-line treatment of metastatic colorectal cancer and also the introduction of new agents led to the initiation of randomized, phase III trials to evaluate these new treatment options. Many of the trials used the Mayo Clinic regimen (20 mg/m^2 LV followed by 425 mg/m^2 5-FU, both administered as an i.v. bolus on days 1-5 of a 28-day cycle) as the reference arm. The Mayo Clinic regimen is frequently used as a comparator because it is a well-recognized and commonly used schedule with proven efficacy. In addition, it was the comparator arm required by the U.S. Food and Drug Administration (FDA) in registration trials for new colorectal cancer therapies.

The widespread use of the Mayo Clinic regimen as a reference treatment enables a comparison of several of the

Table 1. Key reasons for preferring oral chemotherapy

	***n* of patients 26 (%)**
"I preferred that it was a pill."	19 (73)
"I preferred taking the medicine at home."	18 (69)
"I had fewer mouth sores."	12 (46)
"The medication interfered less with my daily activities."	12 (46)
"I had less diarrhea."	8 (31)

newer fluoropyrimidine regimens. Four large (> 400 patients), randomized, phase III trials were included in a critical evaluation, all of which used the Mayo Clinic regimen as the reference arm. These trials evaluated the efficacy and tolerability of:

- capecitabine 1,250 mg/m^2 twice daily, days 1-14 every 21 days [7];
- UFT 100 mg/m^2 in combination with LV 25-30 mg, both administered three times daily, days 1-28 every 35 days [8];
- 5-FU de Gramont regimen (2-hour infusion of LV 200 mg/m^2, 5-FU 400 mg/m^2 bolus, 5-FU 600 mg/m^2 22-hour infusion days 1-2 repeated every 14 days [9];
- 5-FU German AIO regimen (5-FU 2,600 mg/m^2, 24-hour weekly infusion, weeks 1-6 every 7 weeks, with or without LV 500 mg/m^2 as a 2-hour infusion [10].

The patient pretreatment characteristics in the four trials were generally similar. However, a far greater proportion of patients in the capecitabine study (77%) had more than one metastatic site at baseline compared with the other studies in which this was recorded (15%-39%). Furthermore, fewer patients in the capecitabine trial had normal performance status (32%) compared with patients in the other studies (44%-53%).

The intervals between tumor assessments also differed between the studies. The longer interval between assessments in the UFT and de Gramont trials may cause time to disease progression to be overestimated, potentially magnifying or reducing the differences between the treatment arms.

None of the fluoropyrimidine regimens were significantly different from the Mayo Clinic regimen in terms of overall survival. However, clear therapeutic benefits were identified when other important endpoints, such as response rate, time to disease progression (Table 2), tolerability, convenience, and medical resource utilization, were assessed. Oral capecitabine achieved a significantly superior response rate compared with the Mayo Clinic regimen (26% versus 17%; $p < 0.0002$), and time to progression was at least equivalent. The hazard ratio for disease progression (capecitabine: 5-FU/LV) was 1.0 (95% confidence interval [CI]: 0.885-1.123), showing that the risk of disease progression was equivalent in patients treated with capecitabine compared with those receiving the Mayo Clinic regimen. In contrast, UFT/LV resulted in significantly inferior time to disease progression compared with the Mayo Clinic regimen ($p = 0.01$) with a hazard ratio for disease progression (5-FU/LV:UFT/LV) of 0.823 (95% CI: 0.708-0.958) using the Mayo Clinic regimen as a reference point [8]. Using UFT/LV as a reference point, calculation of the inverse of this ratio shows that the risk of disease progression when treated with UFT/LV is increased by 22%, as shown by the hazard ratio of 1.22 (UFT/LV: 5-FU/LV). A trend towards a lower response rate (12% versus 15%) was also apparent.

Both the infused de Gramont and AIO regimens offered modest increases in time to disease progression ($p \leq 0.02$) compared with the Mayo Clinic regimen; patients receiving the de Gramont 5-FU regimen also achieved a significantly superior response rate (33% versus 14%, $p = 0.004$). However, it is important to note that a substantial proportion of patients in the de Gramont trial were excluded from the efficacy analysis (21% of the intended-to-treat population), as they did not have measurable disease. Therefore, the differences in time to progression and response rate are likely to have been less pronounced in an intention-to-treat analysis as was undertaken for the capecitabine and UFT/LV trials. The failure to demonstrate a significantly superior response with the AIO regimen may also have been because of the small number of patients with measurable disease.

All four novel regimens demonstrated safety benefits, including significantly lower incidences of neutropenic fever/sepsis compared with the Mayo Clinic regimen.

Table 2. Time to disease progression for four fluoropyrimidine regimens

	Median TTP months	Hazard ratio	Relation to Mayo Clinic regimen	*p* value
Capecitabine	4.6/4.7	1.00	Equivalent	0.95
UFT/LV	3.5/3.8	1.22	Inferior	0.01
de Gramont	6.3/5.0	?	Superior	0.001
EORTC AIO				
(+ LV)	6.4/4.1	?	Superior	0.02
(– LV)	4.4/4.1	?	Equivalent	0.7

TTP = time to progression; EORTC = European Organization for the Research and Treatment of Cancer

Capecitabine was associated with significantly ($p < 0.05$) lower incidences of stomatitis (all grades and grades 3/4), nausea/vomiting, diarrhea, and alopecia compared with the Mayo Clinic regimen. The most common adverse event with capecitabine was hand-foot syndrome. Capecitabine was associated with a significantly lower incidence of treatment-related hospitalizations than the Mayo Clinic regimen (12% versus 18%; $p < 0.005$), and only two patients required hospitalization for hand-foot syndrome. UFT/LV was associated with significantly lower incidences of stomatitis (all grades and grades 3/4), nausea/vomiting, and diarrhea than the Mayo Clinic regimen. However, there was a trend towards an increased incidence of grade 3/4 diarrhea (Fig. 1), which occurred in more than 20% of patients receiving UFT/LV. The incidence of hand-foot syndrome with UFT/LV was low. Hand-foot syndrome is a side effect typical of prolonged infusion fluoropyrimidine therapy. The higher incidence of hand-foot syndrome with capecitabine compared with UFT/LV suggests that capecitabine may more closely mimic infused 5-FU. As previously mentioned, with capecitabine this side effect is rarely severe, usually does not interfere with daily activities, and usually resolves with treatment interruption with or without dose reduction.

With the de Gramont regimen, there was a significantly lower incidence of grade 3/4 diarrhea and stomatitis compared with the Mayo Clinic regimen. However, taking all grades of adverse events into account, there were no significant differences in the incidences of diarrhea, stomatitis, and nausea/vomiting between the de Gramont regimen and the Mayo Clinic regimen. With the other infused regimen, the German AIO schedule, grade 3/4 diarrhea was frequent, occurring in approximately 20% of patients. Grade 3/4 neutropenia was again less common than with the Mayo Clinic regimen, as described above. Toxicity data for all grades of diarrhea, stomatitis, and nausea/vomiting were not reported.

Another important difference between both the four novel regimens and the Mayo Clinic regimen is the convenience of administration. Central venous access complications, including those associated with insertion of lines and Port-a-Cath® systems (SIMS Deltec, Inc.; St. Paul, MN), were not reported for the two trials of infused regimens. However, infused regimens are generally associated with an increased number of administration visits, complications arising from the use of indwelling catheters, and the inconvenience of portable pumps. It has been reported that up to 30% of i.v. lines require elective removal due to infections/sepsis, thrombosis, migration or blockage, depending on the system used, although the complication rate appears lower when using Port-a-Cath systems [11]. Serious, albeit

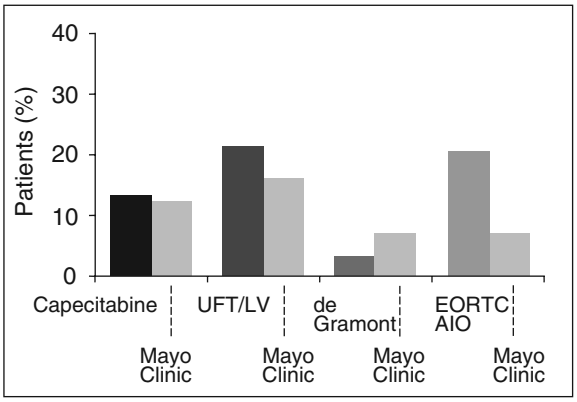

Figure 1. Incidence of grade 3/4 diarrhea: fluoropyrimidines versus the Mayo Clinic regimen.

uncommon, complications at the time of insertion include arrhythmia, arterial puncture, and pneumothorax. Pain and trauma are also frequently experienced by the patient. Among the five regimens assessed in the four trials described above, the infused regimens required the highest number of administration visits. During a 24-week treatment period, patients receiving either of the infused 5-FU regimens would typically require 36 visits. The Mayo Clinic regimen required an estimated 30 visits during a 24-week period, whereas patients receiving either capecitabine or UFT/LV treatment would typically make five to eight visits for administration of treatment.

The oral agents provide a more convenient administration schedule than the Mayo Clinic regimen or the infused regimens, and home-based therapy is possible, provided that patients are educated to recognize side effects and interrupt treatment when necessary. Both of the oral regimens also included a "drug holiday" during which chemotherapy is not administered. In the capecitabine regimen, 1 week in every 3 is drug free; 1 week in every 5 is drug free with UFT/LV treatment. However, with UFT/LV the patient has to swallow approximately twice as many pills as with capecitabine therapy. Furthermore, patients are required to fast for 6 hours per day, 1 hour before and after taking UFT/LV tablets three times a day, which may cause considerable disruption to the patient's daily routine. By contrast, capecitabine is taken twice daily and administered within 30 minutes of a meal and should have little or no impact on a patient's life style.

Patient Preference: Oral Versus i.v. Therapy

Taking into consideration the preference for oral therapy expressed by the majority of patients, the choice of oral versus i.v. therapy may seem straightforward. However, there are many other factors to be taken into consideration

when deciding what treatment is most appropriate for each patient.

When delegates attending the meeting were asked which single-agent fluoropyrimidine therapy they would prescribe as first-line treatment for metastatic colorectal cancer, the most frequent response was oral fluoropyrimidine therapy (42%). Infused 5-FU/LV or i.v. bolus 5-FU/LV was chosen by 37% and 15% of the audience, respectively. Delegates were then asked which single-agent fluoropyrimidine therapy their patients would prefer as first-line treatment of metastatic colorectal cancer. In total, 84% of the audience believed that their patients would prefer oral treatment, which is the same figure as in the direct patient preference study discussed above [6]. Only 8% of the audience thought that their patients would prefer infused 5-FU/LV, with 4% each choosing i.v. bolus 5-FU/LV and other treatments.

This apparent contradiction between the preference of the patient and his or her doctor raises the question of who should make the choice between oral and i.v. treatment. When this was put to the audience, 77% felt that the physician and the patient should decide together between oral and i.v. therapy, with only 16% stating that the decision should be made primarily by the physician. The principal reasons cited as potentially discouraging the physician from prescribing oral chemotherapy routinely were concerns about efficacy (34%) and over-/undercompliance (24%). Income issues and control of side effects were also of some concern (19% and 14%, respectively).

Conclusions

The choice of a fluoropyrimidine regimen in patients with advanced colorectal cancer is no longer straightforward. None of the newer regimens explored here provide a significant survival benefit, so other factors must be taken into account. Patients clearly prefer oral therapy, but only if efficacy is not compromised. Although both capecitabine and UFT/LV have advantages over the Mayo Clinic regimen in terms of toxicity, patients treated with UFT/LV have a 22% greater risk of disease progression than patients treated with 5-FU/LV. By contrast, capecitabine achieves superior tumor response rates, and at least equivalent time to progression and overall survival compared with standard 5-FU/LV therapy. In general, physicians and patients alike agree that treatment decisions should be made jointly. The combination of patient preference for oral treatment and efficacy offered by oral capecitabine makes this an attractive first-line treatment option for patients with colorectal cancer.

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