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Advanced colorectal carcinoma: redefining the role of oral ftorafur

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The therapeutic performance, effect on quality of life and cost effectiveness of an orally administered medication in a home care setting were examined prospectively in a group of 61 patients presenting with advanced colorectal carcinoma. A regimen of daily ftorafur capsules (370 mg/m^2) and leucovorin tablets (20 mg/m^2) was offered to 35 symptomatic patients with poor performance status; the standard in-hospital i.v. protocol of 5-fluouracil and leucovorin was given to the remaining 26 patients. Follow-up and survival analysis indicated that there was no compromise in survival associated with home care and oral chemotherapy. There were statistically significant advantages in terms of reduced toxicity and improved Karnofsky performance status in this group. Home care was approximately 70% less expensive. A home treatment program based on oral ftorafur may be the most desirable option for all patients with advanced colorectal carcinoma.

Key words: Advanced colorectal carcinoma, anti-tumor, cost effective, oral ftorafur.

Introduction

Colorectal adenocarcinomas are both common and refractory to treatment, with an average reported response rate of about 15–20% (range 8–80%)[1–4] to the preferred chemotherapy. In recent years, the therapy of choice has been the combination of the antimetabolite, 5-fluorouracil (5-FU),[2,5] together with the biochemical modulator, folinic acid (leucovorin).[6,7]

Although both 5-FU and leucovorin exist in oral forms, this regimen must be i.v. administered due to the unpredictable gastrointestinal absorption of 5-FU. Because bolus administration of 5-FU is associated with dose-limiting bone marrow suppression as well as gastrointestinal toxicity (nausea, vomiting, diarrhea, stomatitis), it has long been recognized that the technique of constant infusion is best utilized.[4] This form of administration diminishes hematologic symptoms, with stomatitis remaining as the dose-limiting factor.[4,8] However, continuous infusion necessitates a hospital or clinic setting, with associated financial costs and stress to often already debilitated patients.

Ftorafur, an *in vivo* pro-drug of 5-FU[8,9] and, structurally, a tetrahydro-2-furanyl derivative of it, is also a known antineoplastic agent in colorectal carcinoma.[1,10–14] Although it, too, is effective via the i.v. route, yielding an 11–25% overall response rate,[11,12,15] there is an associated significant and dose-related neurological toxicity in 15–70% of patients, due to its ability to easily cross the blood–brain barrier.[10,16] However, in contrast to 5-FU, ftorafur is predictably well absorbed orally, and, when it is given in combination with oral leucovorin, there is a reported 20% overall response in gastrointestinal cancers with an associated toxicity less than that which follows upon the standard combination of i.v. 5-FU and leucovorin.[16]

These two features, i.e. oral effectiveness of ftorafur with leucovorin and reduced associated toxicity compared with i.v. treatment, would seem to make a home-administered, ftorafur-based therapeutic regimen feasible.

In view of the difficulties and costs of administering aggressive i.v. treatment to elderly patients with advanced colorectal adenocarcinoma, especially those with concomitant medical problems, we prospectively studied the efficacy and expense of such a treatment program in comparison to standard in-hospital treatment with 5-FU, both being given with leucovorin.

Patients and methods

Selection and treatment

This study, carried out at the Tel Aviv Sourasky Medical Center, was activated in February 1991 and closed in November 1992 after accruing 61 predominantly elderly patients, all of whom had undergone resection of histologically confirmed adenocarcinoma of the large bowel and rectum. They had been found to have extension of the

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disease (staging at Dukes B2-D) but had not yet received chemotherapy. General patient characteristics appear in Table 1: there were slightly more males than females (1.5:1.0) and a broad age range (33–82 years).

Consecutively presenting patients were non-randomly divided into two groups on the basis of Karnofsky performance status (KPS), as assigned by the treating physician and symptomaticity.

Group A consisted of 35 patients who were symptomatic, had low KPS scores (average 53.7%) and more advanced disease; 22 (63%) of the group had a Dukes D (invasive with metastases) staging. In the interests of maximizing patient care, we eschewed randomization and suggested that this group agree to the experimental home regimen of self-administered daily oral leucovorin (20 mg/m^2) at 22:00 followed 1 h later by oral ftorafur (370 mg/m^2). The treatment was continued indefinitely unless there was progression of disease or severe side effects. Group B included 26 patients with an average KPS of 80.8% and less advanced disease; only eight (31%) were at the Dukes D stage and even these patients complained of fewer symptoms. This generally more fit group received the standard day clinic protocol of 5 days of i.v. leucovorin (20 mg/m^2) with i.v. 5-FU (370 mg/m^2) 1 h later; the chemotherapy was given every 28 days until and unless tumor progression was noted. Patients living far from the hospital were hospitalized for the 5 days of treatment.

Evaluation

Baseline assessment of all patients included physical examination, full blood count, serum chemistries and marker (carcinoembryonic antigen) measurement. Evaluable disease was established by computerized axial tomography, abdominal ultrasound and chest radiography.

Patients were re-evaluated for signs of response, using standard WHO criteria.[17] They underwent routine blood tests at 6 week intervals and radiological assessment every 3 months. Patients receiving home treatment were evaluated by a visiting oncology nurse who took a biweekly complete blood count; once every 6 weeks during treatment, they were required to appear for assessment by the oncologist.

Reasons for discontinuation of treatment and withdrawal from study participation included unequivocal disease progression, drug toxicity, treatment success and patient preference.

Survival was estimated using the Kaplan–Meier life table method with significance of survival differences and changes in KPS analyzed by Breslow and Matel–Cox tests.

Cost comparison

Cost comparison of 1 month of treatment for in-patient and out-patient schedules was calculated

Table 1. Characteristics of patients in group A (home care) and group B (hospital care)

Descriptor	Group A	Group B
Protocol	ftorafur and leucovorin, orally, at home	5-FU and leucovorin, i.v., in clinic
No. of enrolled patients	35	26
Age in years: mean (range)	69.2 (54–82)	67.3 (33–80)
Gender ratio (M:F)	22:13	15:11
Dukes staging:		
B2	6	6
C	8	12
D	22	8
KPS		
100%	—	6
90%	—	6
80%	—	3
70%	9	6
60%	6	5
50%	11	—
40%	7	—
30%	1	—
mean	52.9	80.8

using figures from both the Tel Aviv Sourasky Medical Center and the pharmaceutical supplier (Abic, Israel). Certain figures, such as the cost of the home nurse's time, are estimates only, while others, such as cost to the patient for conveyance and value of hours lost from work by accompanying friends and family, were not available to us at the time but must figure importantly in future, detailed analyses.

Results

All 61 enrolled patients were evaluable for response; results appear in Tables 2 and 3. The group A patients (35 recipients of oral ftorafur and leucovorin) had a better, albeit not statistically significant, objective response rate than did the group B patients, who had received i.v. 5-FU with leucovorin (30% for A versus 20.8% for B). All group A responses (six patients) were partial (PR). In Group B, one patient achieved complete response and three patients had PR.

Subjective assessment of response (improved KPS) was seen in 57.1% (20 patients) of the home-treated group A and 50.0% (13 patients) out of 26 in group B (Table 2). In neither group was there a correlation between stage and response (either objective or subjective).

Table 3 demonstrates the differences in KPS after 3 and 6 months of treatment in both arms. The differences were statistically significant ($p = 0.01$ after 3 months and $p < 0.001$ after 6 months) favoring the ftorafur and leucovorin combination.

The mean duration of treatment in the ftorafur and leucovorin group was 6.40 months (range 2–18 months), and for the 5-FU and leucovorin group was 7.20 months (range 2–18 months), Table 2. Reasons for cessation of therapy are also summarized in Table

Table 2. Type and duration of response and reasons for stopping chemotherapy

	Group A	Group B
Protocol	ftorafur and leucovorin, orally, at home	5-FU and leucovorin, i.v., in clinic
No. of patients	35	26
Objective response		
complete	—	1
partial	6	4
no change and disease progression	29	21
Clinical response		
(KPS improved)	20	13
Duration of treatment in months: mean (range)	6.40 (2–18)	7.20 (2–18)
Survival (months)		
median	8	9
mean	10.61	14.87
Reasons for stopping treatment		
disease progression		
objective	15	10
subjective	7	6
side effects	2	4
complete response	—	1
patient refusal	2	1

Table 3. Mean changes in KPS (ΔKPS) during treatment

	Group A	Group B	*p* value
Protocol	ftorafur and leucovorin, orally, at home	5-FU and leucovorin, i.v., in clinic	—
No. of patients	35	26	—
ΔKPS at 3 months	+14.53	−6.87	0.01
ΔKPS at 6 months	+20.0	−14.41	<0.001

2 and were, in each group, most often the discovery of objective signs of disease progression (43% of A and 39% of B). Lessening of KPS was also an important reason for discontinuing treatment in each group (20% in A and 23% in B), with severe side effects considerably less influential a factor (6% in A and 4% in B). Three patients discontinued therapy for personal, unstated reasons and, in one happy group B case, there was a complete response with total remission of symptoms.

The mean survival time of group A was 10.61 months with a median time of 8 months and for group B the mean survival was 14.87 months with a median of 9 months. Survival analysis using Breslow and Matel–Cox test statistics did not show significant differences between the two treatment groups. Figure 1 illustrates the Kaplan–Meier estimates of the survival curves in patients treated with the two regimens, each of them further divided into responders and non-responders. The prolongation in survival of the patients who responded to either of the protocols was statistically significant after 3 and 6 months ($p = 0.008$). The apparently insignificant overall survival difference is interesting in light of the fact that the group with slightly shorter survival was considerably more symptomatic and had lower KPS at the initiation of the experimental treatment (Table 1).

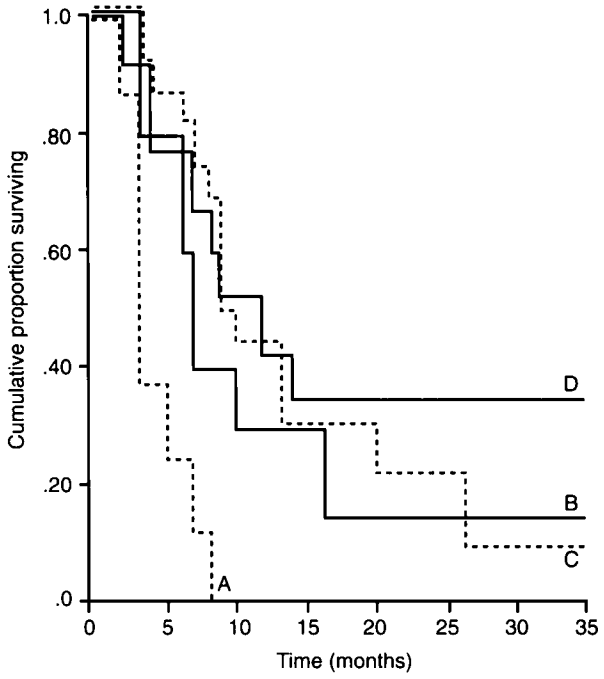

Figure 1. Survival curves for group A and group B patients. (A) Ftoral + leucovorin (non-responders). (B) 5-FU + leucovorin (non-responders). (C) Ftoral + leucovorin (responders). (D) 5-FU + leucovorin (responders).

Toxicity

The occurrence of toxic effects according to WHO criteria is shown in Table 4. During 24 months of treatment, 16 patients (45.7%) from group A and seven patients (26.9%) from group B had no side effects. Nine patients (34.6%) on i.v. 5-FU and leucovorin suffered grade 3 and 4 side effects as compared to three patients (8.6%) on oral ftorafur and leucovorin treatment. In the cases of grade 4 toxicity, the treatment was discontinued and where there was grade 3 toxicity, a 50% dose reduction was instituted. The most frequent side effects were grade 1–3 diarrhea and abdominal pain. Grade 1–2 neurological toxicity (mainly dizziness and insomnia) was observed in three (8.6%) of the ftorafur patients and a lethargic manifestation in three (11.5%) of the 5-FU patients. In one patient who had received daily oral ftorafur and leucovorin for more than 12 months, a bone marrow examination revealed a mild to moderate decrease in cellularity. No renal and cardiac toxicities were seen in either group.

Table 4. Toxicity associated with treatments

	Group A	Group B
Protocol	ftorafur and leucovorin, orally, at home	5-FU and leucovorin, i.v., in clinic
No. of patients	35	26
Diarrhea	6 (17.1%)	8 (30.8%)
Abdominal pain	4 (11.4%)	5 (19.2%)
Vomiting	2 (5.7%)	4 (15.4%)
Nausea	2 (5.7%)	1 (3.8%)
Lethargy	—	3 (11.5%)
Dizziness, insomnia	3 (8.6%)	—
Skin eruption	2 (5.7%)	—
Hematological toxicity	1 (2.9%)	—
None	16 (45.7%)	7 (26.9%)

Costs of treatment

We use a recent conversion rate of US$1.00 = 3.00 shekels in order to give dollar equivalencies of all costs. The data are consolidated in Table 5. The 5-FU was supplied to the hospital at a cost of approximately $3.00 per vial of 1000 mg. Oral ftorafur in 200 mg capsules was made available for about $56.00 for an average monthly dose. Although both drugs are inexpensive, ftorafur tablets are about three times as expensive per milligram as is 5-FU in ampoules. Leucovorin was priced at approximately $21.00 for a 500 mg ampoule while each 15 mg tablet cost $1.00. The price per milligram was twice as high for tablets as for the injectable form.

The cost of a day of clinic care in the medical center's oncology clinic is $435.00 and an assumption was made that a month of home visits made by the oncology nurse (at least twice per month) totaled in cost the equivalent of a day of clinic care.

Using the above figures and assumptions, the ratio of costs of home to hospital care were 1:3.6, or a difference of 70%, favoring home care.

Discussion

Home-based therapy, unlike home-based pain palliation programs, has not become part of the standard medical care paradigm for cancer patients although outpatient treatment in ambulatory daycare clinics represents a step, increasingly taken, in that direction. If there are indeed psychological and financial advantages to homecare and if these are established, the treatment of advanced colorectal cancer may be an appropriate setting in which a change in the mode of care provision may be routinely instituted. The implications for both quality of life and cost of care of an oral chemotherapeutic protocol which may be self-administered at home formed the basis of this study. Our prime interest was in the outcome, both medical and psychological, of home treatment for advanced colorectal carcinoma, and, secondarily, in cost-effectiveness.

Table 5. Cost comparison for 1 month of treatment of hospital and home-treated patients[a]

	Home care protocol: ftorafur and leucovorin every day × 30 days	Clinical care protocol: 5-FU and leucovorin × 5 days per month
Ftorafur capsules	$56.00	—
5-FU i.v. ampoules	—	$15.00
Leucovorin tablets	$116.00	—
Leucovorin i.v. ampoules	—	$21.00
Clinic services	—	$2166.00
Home nurse service	$433.00	—
Total cost	$606.00	$2203.00
Cost ratio	1	3.6

[a]1 US$ = 3 shekels.

The chemotherapeutic drugs which are most effective in advanced colorectal cancer are available in both oral and i.v. forms, but because the most widely used of these, 5-FU, is unpredictably absorbed from the gastrointestinal system, the i.v. regimen has become standard. However, ftorafur, an anti-metabolite closely related to 5-FU and with comparable antineoplastic activity, differs importantly from 5-FU in that it is effective when used orally.

Our 61 patients were prospectively but non-randomly invited to one of two treatment groups; oral home-based treatment was urged on the more symptomatic group of 35 patients while the remaining 21 were able and willing to receive standard hospital-based i.v. chemotherapy.

We assessed the medical efficacy of oral treatment by means of the ultimately important parameter of survival time. There was no statistically significant difference in survival times associated with either regimen; median survival among the home care group (8 months) was somewhat less than that of the hospital-treated group (9 months) while average survival times (home, 10.61 months; hospital 14.87 months) differed more widely. The insignificance of the differences is in itself of interest as the home-treated group was generally at a later stage of disease and with lower KPS and, therefore, might have been expected to manifest a significantly shortened survival time. In this context, our outcomes suggest some survival advantage conferred either by the oral treatment or the home setting.

The assessment of general health and quality of life for patients receiving home-administered oral therapy was based upon both their KPS assessments and their objective responses during the course of therapy. There was a highly significant advantage in terms of KPS improvement in the home-treated ftorafur group at 3 and at 6 months of follow-up ($p = 0.01$ and $p < 0.001$, respectively). An insignificant difference in objective response to treatment by both groups slightly favored the at-home group.

Both regimens were associated with characteristic side effects although the levels were tolerable. Gastrointestinal toxicity (diarrhea, abdominal pain and vomiting) occurred more often in association with i.v. administered 5-FU and leucovorin with a slightly higher frequency of grade 3 and 4 side effects than with ftorafur. CNS disturbances occurred in 9% of the ftorafur- and leucovorin-treated patients in this study and mild lethargy in three (11.5%) of the 5-FU-treated group. Neither oral ftorafur nor i.v. 5-FU showed significant hematologic toxicity when given as scheduled in this group.

A cost analysis of the two regimens suggests that the oral therapy is 70% less expensive to the medical system than in-hospital therapy; the difference is mainly attributable to a reduced demand on staff and facility time. Estimates of savings to patients and their families were not attempted.

Among this group of 61 advanced colorectal carcinoma patients, the ftorafur and leucovorin oral chemotherapy regimen given at home did not compromise survival but did appear to reduce the physical and psychological stresses of even out-patient treatment; such stresses include conveyance to an out-patient facility, lost time from work of accompanying family members or friends and attendance in the high-stress milieu of an oncology clinic.

Conclusions

This study suggests that home-based care for patients with advanced colorectal carcinoma using orally administered ftorafur and leucovorin is at least as effective as and much less costly than the current standard i.v. therapy (5-FU and leucovorin) in providing significant anti-tumor effect, palliation, ease of administration and relatively few side effects. Confirmation of these findings by other workers would suggest that oral ftorafur may well be the treatment of choice for all patients with advanced colorectal carcinoma.

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