position of the lesion on the cervix,7 and the presence of possible cofactors such as herpetic viruses in carcinogenesis.


Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer

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Abstract

Objectives—to compare the length of survival and quality of life in patients given combination chemotherapy in addition to supportive care and in patients given only supportive care.

Design—Randomised study.

Setting—Gastrointestinal oncology departments.

Patients—40 previously untreated patients with histologically confirmed, measurable colorectal cancer that was locally recurrent or metastatic.

Interventions—Patients were allocated randomly to receive chemotherapy or only supportive care in a ratio of 2:1 according to performance status, metastatic disease of the liver, and weight loss in the six months before entering the study. Chemotherapy consisted of four weeks of intravenous leucovorin (200 mg/m2/day) followed by 5-fluorouracil (550 mg/m2/day) and cisplatin (20 mg/m2/day), each drug being given on the first four days of the cycle.

Main outcome measures—Length of survival and quality of life score with an optimised functional living index—cancer scale.

Results—Overall survival was significantly longer for patients given chemotherapy (11-0 months) than for those receiving supportive care alone (5-0 months; p=0-006). Despite common association of chemotherapy with mild to moderate gastrointestinal symptoms, there was no significant difference between the two groups in global or subgroup quality of life scores. In patients with abnormal scores before treatment, quality of life seemed better in the chemotherapy arm.

Conclusions—in this sample of patients with disseminated colorectal cancer the chemotherapy regimen was an effective form of palliative treatment.

Introduction

Chemotherapeutic management of advanced colorectal cancer has been a challenge to medical oncologists for the past three decades. Although tumours in 15-20% of patients have responded to fluorinated pyrimidines, in particular 5-fluorouracil, there has been no evidence of improved survival.1 Empirically derived combinations of chemotherapeutic drugs have given disappointing results.2 Recent attempts to enhance the therapeutic activity of 5-fluorouracil have focused on biochemical modulation: several randomised studies have shown that its effect is greater when used in combination with leucovorin.3 The optimal dose, schedule, and route of administration, however, have not been established. Complete response is rare, and the improvement in median survival seems small. Furthermore, most 5-fluorouracil and leucovorin dose schedules have a high incidence of severe gastrointestinal side effects4 and may thus interfere with the patients’ quality of life, one of the most important aspects to be considered in palliative treatment.

Because of uncertainty about the true palliative benefit of combined regimens we conducted a randomised study of the effects of chemotherapy and supportive care on survival and quality of life of patients with colorectal cancer. The chemotherapeutic regimen chosen was a combination of 5-fluorouracil and leucovorin with cisplatin. Cisplatin was included
because of experimental evidence that it further poten-
tiates inhibition of thymidylate synthase, its enc-
rouring therapeutic results in pretreated breast and 
advanced head and neck cancer, and the recent 
demonstration of a good therapeutic index in metastatic 
colorectal cancer.

Patients and methods

Patients who had inoperable, measurable, histologi-
cally confirmed metastatic or locally recurrent adeno-
carcinoma of the colon or rectum were eligible for 
entry into the study. Additional requirements for inclusion
in the study were age under 75 years, life expectancy 
over two months, Eastern Cooperative Oncology 
Group performance status ≤ 3, no previous chemo-
otherapy, and adequate haematological (leucocyte 
count >4×10⁹/l, platelet >150×10⁹/l), hepatic (no jaun-
dice and serum aminotransferase concentra-
tions <100 IU/l), and renal (serum creatinine 
<132 μmol/l, creatinine clearance >1 ml/s) 
functions.

After fully informed consent was obtained eligible 
patients were registered by phone at the central 
statistical office at the University of Vienna. They were 
allocated randomly to receive supportive care plus 
chemotherapy (arm A) or supportive care only (arm B) in 
the ratio of 2:1 (which was based on the assumption 
of a higher refusal rate in arm B). The assignment was 
determined by randomisation in blocks of six (as 
defined by a computer generated random number list) 
according to performance status (score 0-1 ≤ 2-3), 
metastatic disease of the liver (assessed by ultra-
sonography or computed tomography, or both), and 
weight loss in the six months before entering the study.

Supportive care consisted of analgesics, nutritional 
support, blood transfusions to correct severe anaemia, 
and psychosocial support. Chemotherapy consisted of 
leucovorin 200 mg/m²/day by intravenous push 
followed 30 minutes later by bolus 5-fluorouracil 
550 mg/m²/day and cisplatin 20 mg/m²/day, given as a 
two hour infusion with adequate hydration. An anti-
emetic regimen comprising dexamethasone, meto-
clorpramide, and lorazepam was routinely used. All 
chemotherapeutic drugs were given on four consecutive 
days at four week intervals for a total of six months or 
until there was evidence of tumour progression.

Quality of life was assessed at entry to the study and 
every two months with the functional living index for 
cancer (FLIC). This is a contemporary, well validated, 
22 item self report scale developed for repeated use by 
patients with cancer. It provides a single quality of life 
score based on indices of perceived physical wellbeing, 
psychological state, and sociability. To counteract 
difficulties in collection and methodological evaluation 
of the data we used several refinements of the method, 
including designation of a central data coordinator and 
use of a simple 10 point (rather than a continuous) 

score. Furthermore, serial results in individual patients 
at successive time points have been evaluated accord-
ing to the criteria proposed by Presant et al for 
assessing palliative response by quality of life (box). Analyses of changes in quality of life were performed 
separately for patients whose scores were all normal 
before treatment and for patients who had at least one 
score (global score or subgrouping) that was abnormal 
—that is, more than two standard deviations above 
results in normal people. Twenty healthy volunteers 
completed the questionnaire. They had a mean score of 
41 (SD 16), and this was used to define a normal value. 
The duration of palliative response was measured from 
the time that the response was first observed until a 
significantly lower score was obtained on two successive 
measurements. A significant change in score was 
defined by the 95% confidence interval of the int-
strument on test-retest analysis assessed during the 
eyearly part of this trial.

Results

Between April 1988 and September 1989, 40 patients 
were accrued to the study. Two patients in each 
treatment arm refused to accept the treatment assigned 
or participate in the research study, or both. Thus, 36 
patients were eligible for analysis of response and 
toxicity. Of these, 24 were randomised to receive 
chemotherapy with 5-fluorouracil, leucovorin, and 
cisplatin (arm A) and 12 to receive no chemotherapy 
(arm B). During the study two patients randomised to 
no chemotherapy were treated with 5-fluorouracil 
alone when symptomatic tumour progression occurred. 
This decision was made by the patients’ doctors; neither 
patient responded, but both have been included in 
this analysis.

The pretreatment characteristics of patients in the 
two groups were similar (table I), although the median 
time from original diagnosis of colorectal cancer to 
entry was slightly longer for patients with chemo-
therapy (8.5 (range 0 to 61) months) than for those who 
received supportive treatment alone (5-5 (0 to 22) months).

Table II summarises the results of chemotherapy or 
supportive care in the two groups. Of the 24 patients 
randomised to chemotherapy, eight partially 
responded. The median number of treatment cycles 
administered was 4.5 (range 1 to 8), and the median 
duration of response was 35 (16 to 56) weeks. Nine 
patients (38%) had stable disease and seven (29%) 
progressive disease. Three (25%) of the 12 patients 
randomised to no chemotherapy were classified as
having stable disease and nine (75%) as having progressive disease. Median time to progression was 6-0 (2.1 to 14) months for treated patients and 2-3 (1.5 to 8.0) months for controls; this difference was significant (p=0.0008).

Thirty three of the 36 patients in the study had died at the end of the study period, 21 (87%) in the chemotherapy group and all 12 in the supportive care group. The minimum follow up of the three survivors was 28 months. Figure 1 gives the actuarial survival curves for all subjects by randomisation status (including the four patients who refused the assigned treatment). The curves for the two groups were significantly different (p=0.006). Median survival times were 11.0 (4.0 to 37.0) months for patients randomised to chemotherapy and 5.1 (1.5 to 23.0) months for those receiving supportive care. The sample size was too small to rule out any differences in survival between patients of different prognostic groups.

Toxicity was common in the chemotherapy group, though symptoms were generally mild to moderate. No patient stopped chemotherapy because of side effects, and only two had to have the dose reduced (by 25%) because of grade 3 haematological and gastrointestinal side effects (table III). In the supportive care group, mild nausea, diarrhoea, and infection were indicated by two, three, and one patient, respectively; no other systemic toxicities were recorded.

Eighteen (75%) patients who received chemotherapy and eight (67%) symptomatically treated patients completed at least two questionnaires on quality of life, including one at baseline, and were thus considered evaluable. The remaining patients were unwilling to complete the form (two), had problems with reading because of poor vision or language (two), or died early (six). An average of five evaluations was available for all patients (range 3 to 10). The mean total scores in the chemotherapy group (87-5 (SD 44)) and in the supportive care group (80-2 (40)) were similar at baseline, as were mean factor scores.

Table IV gives the quality of life in the two treatment groups. Overall, there was no difference between the two patient groups, though in patients with abnormal scores before treatment the quality of life seemed better in the chemotherapy group. In the chemotherapy group a transient slight deterioration in quality of life was noticed during treatment with cytotoxic drugs (fig 2). Thereafter, quality of life improved compared with baseline and with patients in the supportive care group. In the supportive care group supportive drugs resulted in an initial improvement of the quality of life. The improvement was short lived, however, because of disease progression. No significant difference was found between the scores in the two groups.
Discussion

Many doctors and their patients reject conventional anticancer chemotherapy for disseminated colorectal cancer in favour of unproved alternatives because of uncertainty about therapeutic gain and concern about toxic effects. Whether and how much chemotherapy prolongs survival in advanced colorectal cancer, despite its use for several decades, is not known. 5-Fluorouracil, which was the standard treatment until one or two years ago, was not considered to prolong median survival, although a controlled trial against no chemotherapy has never been done. Several trials comparing 5-fluorouracil alone with combinations based on biochemical modulation have indicated better objective tumour response with the combination treatment. An improvement in survival with combinations of 5-fluorouracil and leucovorin, however, has been observed in only two of seven randomised studies, and the improvement was only moderate.

We found that combination chemotherapy with 5-fluorouracil, leucovorin, and cisplatin in patients with metastatic colorectal cancer increased time to progression and length of survival compared with those in patients given only supportive care. Because of the small numbers of patients studied, our findings are only preliminary. Nevertheless, the median increase in survival in patients receiving chemotherapy was six months, during which time, overall quality of life was at least as good as in patients receiving supportive care. In patients with symptomatic disease the quality of life, in fact, seemed better in the chemotherapy arm despite its common association with mild to moderate gastrointestinal side effects.

The advantage of chemotherapy in previously asymptomatic patients might be questioned in view of the side effects and the initial, though only minor and transient, decrease in patients’ subjective wellbeing. However, our study was conducted before oxandronetron became available, which in our experience would probably have prevented the initial decrease in quality of life in patients receiving cisplatin. Furthermore, the overall gain in time to progression and length of survival was seen in patients both with and without tumour related symptoms. The potential advantage of early treatment in asymptomatic patients with advanced colorectal cancer seems to have been confirmed by a trial from the Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Further advances in the knowledge of prognostic factors should help to identify subgroups of (asymptomatic) patients with a more prolonged clinical course, in whom a wait and see policy seems adequate.

Whether the addition of cisplatin to 5-fluorouracil and leucovorin had any influence on the apparent beneficial effect of palliative chemotherapy in this study remains uncertain. Comparison of objective tumour response rate and median survival time in our chemotherapy group and in phase II and III studies with conventional 5-fluorouracil and leucovorin regimens suggest that this is not the case. Severe toxicity was less common in our study, however, and the three drug combination seems to have a better therapeutic index.

In conclusion, our data indicate that chemotherapy with 5-fluorouracil, leucovorin, and cisplatin improves quality of life in symptomatic patients with metastatic colorectal cancer and prolongs survival. Although the small numbers studied reduces the strength of our results, they support previous, indirect evidence of a beneficial effect of chemotherapy in this disease. In addition, the distribution of characteristics known to affect survival in colorectal cancer was similar in the two study groups.


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