10.1053.paor.2000.0173 available online at http://www.idealibrary.com on IDEAL

ARTICLE

Retrospective Evaluation of 5-fluorouracil-interferon-α Treatment of Advanced Colorectal Cancer Patients

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The authors describe the retrospective analysis of treatment by 5-fluorouracil and interferon-α of 34 patients with advanced colorectal cancer. An average of 4.6 treatment cycles (3–12) was applied. Complete remission was not observed; partial remission was observed in 8 patients; in 13 patients no change occurred and progression was detected in 14 cases. Remission rate was 22.8%, mean response time was 5.2 (3–12) months, mean progress-free survival 5.6 (0–22) months. Mean survival from the start of treatment was 11.9 (1–42) months and from the establishment of the diagnosis 26.1 (3–60) months. Severe life-threatening side-effects did not occur; other side-effects such as fever, nausea, diarrhea, leucopenia, and anemia responded to drugs. Treatment by 5-FU and interferon, in accordance with other authors' findings, improved survival and well-being of patients but no breakthrough has been achieved. (Pathology Oncology Research Vol 6, No 3, 175–178, 2000)

Keywords: advanced colorectal cancer, interferon, 5-FU, survival

Introduction

30–50% of patients undergoing surgery because of colorectal cancer will present with recurrence of the local tumor or a distant metastasis within 1–5 years.[2] Untreated advanced colorectal cancer leads to the death of the patient within 5–7 months after the diagnosis. In light of these data it is important to emphasize the need for developing methods for early diagnosis, to increase the number of timely surgical interventions and to develop new treatment protocols for advanced cases. Irradiation or chemotherapy for advanced colorectal cancer, although do not cure the patient, can slow down the progression of the disease and can temporarily improve the well-being of the patient. Other treatment options such as radiotherapy, chemoembolisation or local intra-arterial chemotherapy can also be applied in selected patient groups,[2] whereas partial surgical resection of the liver – the most effective method for patients with liver metastasis – can be attempted in only 15–20% of such patients.[1,2] An alternative choice of chemotherapy is biomodulation when cytostatic agents such as 5-fluorouracil (5-FU) are combined with an immune modulating agent such as leucovorin or interferon-α (IF) in order to increase the effect of the cytostatic drug. 5-FU and interferon are known to act in a synergistic manner.[9] On the other hand, their side effects are less numerous than those with other combinations. 5-FU alone resulted in a remission rate of 10–25% with minimal side effects.[3,14,17] Interferon had been expected to improve this result but clinical investigations published so far showed a wide variability of remission rates of 5–63%.[4,5,7,10,12,18]

We started the treatment and follow-up of advanced colorectal cancer patients with 5-FU and IF in 1993. In this paper we evaluate data of 35 patients treated between 1993 and 1996 in order to provide further evidence for the effectiveness of the treatment and to describe side-effects.

Patients and methods

All patients were diagnosed in the 3rd Department of Internal Medicine of the University of Debrecen with advanced colorectal cancer. The diagnosis of adenocarcinoma was confirmed by histological examination of biopsy specimens obtained by laparoscopy. 5-FU and interferon were applied as primary therapy in cases of inoperable

Received: Jan 11, 1999, *revised:* Sept 10, 1999, *accepted:* Dec 5, 1999

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 1219-4956/00/030175+04 $ 12.00/0

extensive local tumors with or without metastases and were also applied when an inoperable metastasis was already present at the time of or developed following the removal of the primary colorectal tumor. All the patients received a minimum of 3 cycles. A four-week cycle consisted of the intravenous infusion of 750 mg/m^2 5-FU on the 1-5., 17., 24. days was applied. On the 1–5. days the 5-FU was administered continously throughout the 5 days by infusion pump. On the 17., 24. days it was infused for 4 hours. In addition, 3 million units of human recombinant interferon-2a was administered subcutaneously 3 times daily on the 1., 3. and 5. days and 9 million units of IF was administered once on the 8., 10., 12., 15., 17., 19., 22., 24. and 26. days. The application of IF three times daily during the first week let us to recognize side effects such as fever and leukopenia early.

Following 3 cycles the treatment was continued if the cancer showed regression or if there was no measurable regression in the size of tumor and/or metastasis but the patient tolerated the treatment well. When side-effects were observed treatment was stopped for one month, and then continued again. Treatment was discontinued if there was obvious progression.

Subjective complaints, clinical status, laboratory tests and parameters of the tumor and/or metastases were determined before the beginning of treatment and repeated every months. Site and size of the tumor and metastases was determined by colonoscopy, ultrasound, computed tomography and magnetic resonance imaging in order to monitor the efficacy of treatment. Mean duration of treatment was 4.6 months (3–12 months). Evaluation of the efficacy of treatment was based on WHO criteria: complete remission (CR): disappearance of the tumor; partial remission (PR): the size of tumor decreases by at least 50%; stable disease (SD): no change; progressive disease (PD): one or more tumors increase by 25% or new tumor appears. Side-effects were evaluated according to WHO criteria: I. mild, do not need treatment, II. moderate, treatment if needed, III. severe, requires medical treatment, IV. life-threatening.

Results

Mean age of the patients was 62.3 years (range: 37–76 years) with a female/male ratio of 1:2.5. Clinical status at admittance according to Karnofsky was 80% (60–100%).

Before treatment

Table 1. shows the location of tumors. In 74.3% of all cases the tumor was located in the rectum or sigmoid colon. *Table 2.* shows extracolonic involvement before treatment as determined by radiological methods described above. Metastases in the liver were most frequently detected (48.6%); and in 34.1% of the patients metastases were in an extra-abdominal localization. *Table 2.* shows the exact site and distribution of metastases. The number of patients in the table exceeds the total number of patients due to the fact that in some patients multiple metastases were detected. In the majority of patients with liver metastases multiple foci in the liver were detected; the most frequent combination of metastases ocurred in the liver and lung. Locoregional recurrence of the tumor was observed in 17.1% of the patients.

Table 1. **Location of tumors**

Site of tumor	*Number of patients*
Rectum	17
Colon, Total	18
Descendent	4
Transverse	2
Ascendent	2
Splenic flexure	1
Sigma	9

Following treatment

All patients received a minimum of 3 cycles of treatment. Complete remission was not observed. In 8 patients partial remission occurred (in 6 of them the liver metastases, in 2 of them the lymphoid metastases, regressed by more than 50%). In 13 patients no response were detected in the tumor mass, but 8 of these patients showed subjective improvement (increased well-being, weight increase, less subjective complaints). In 14 patients, obvious progression of the disease (growth of the metastases or appearance of new metastases) was observed.

Several (29) patients reported side-effects belonging to class I and II that responded to drugs. Flu-like symptoms

Table 2. **Metastases before therapy**

Site of metastasis	*Number of patients*
Liver, total	17
Single focus	3
2–5 foci	4
>5 foci	10
Lung	10
Lymph gland	6
Abdominal wall	3
Bone	2
Adrenal gland	2
Central nervous system	2
Spleen	1
Local reoccurrence	6

(tiredness, fatigue, muscle pain, fever) constituted the most frequently occurring side-effect, could be treated or prevented by paracetamol. Subfebrility or fever combined with mild myalgia were observed in many patients (most severely in those who had high tumor mass) in the first week of treatment but they were completely resolved within two weeks and later did not reoccur. Due to its myelotoxicity the dose of 5-FU had to be temporarily decreased in 7 patients, in another 13 patients treatment had to be postponed by one or two weeks to allow for the recovery of bone marrow. Seven patients received red blood cell transfusion, but severe thrombocytopenia did not occur. Vomitus and nausea could be prevented by serotonin antagonist drugs. A detailed list of side-effects is shown in *Table 3.* Severe diarrhoea following the intravenous administration of 5-FU was observed in 6 patients that resolved spontaneously in all cases. Stomatitis was treated by nystatine and chlorhexidine. All patients were recommended to use Nutridrink® or Ensure-plus® drink feeds that improved their appetite and general well-being.

For monitoring the patients, laboratory data, including levels of CEA and CA19-9, were measured monthly. The mean of the CEA serum levels was 63±39 µg/l before and 54±42 µg/l 2 monts after finishing treatment. The mean serum level of CA19-9 was 117±71 kU/l before and 95±80 kU/l 2 months after finishing treatment. Measurement of the level of these markers had positive predictive value regarding the progression of the disease, but it were not applicable to establish the actual stage of the disease. (data not shown)

Table 3. **Incidence of the side effects**

Cycles	*I.*	*II.*	*III.*
Leucopenia	6	13	2
Anemia	10	10	2
Thrombocytopenia	6	6	0
Diarrhea	6	7	6
Nausea, vomitus	12	3	1
Stomatitis	6	4	0
Infection	1	2	0
Neurotoxicity	1	2	1
Hair loss	12	6	3
Fever	15	2	2
Flu-like symptoms	13	2	0

Discussion

Due to difficulties regarding the early diagnosis of colorectal cancers and the relatively high number of advanced cases[17] there is a need to improve available therapeutic protocols for patients suffering from advanced colorectal cancer. Following the discovery of the antiinflammatory, immunregulatory and antiproliferative effects of interferon and its subtypes[9] it was reasonable to test its anticancer effect. The antiproliferative action of interferon has been shown to act by a mechanism partially common to that of 5-FU[8,15] resulting in an additive effect. In vitro experiments demonstrated that 5-FU and IF (alpha or beta) inhibit the proliferation of malignant cells in a synergistic manner. IF has been found to lead to a ten-fold increase in the level of fluoro-deoxyuridilate (the active metabolite of 5-FU) hereby contributing to the inhibition of the target enzyme of 5-FU, thymidilate synthase.[9]

IF has been unequivocally proven to be effective in hairy cell leukemia, chronic myeloid leukemia, myeloma multiplex, melanoma malignum and certain renal tumors.[16,19] The combination treatment of 5-FU and IF in advanced colorectal cancers has been investigated by several authors.[5,7,9,10,11,12,18] with variable results. Remission rates varied between 5 and 63%.[5,7,10,12,18]

According to our 3 years results in 35 patients with advanced colorectal cancer, no complete remission was found with the 5-FU–interferon therapeutic protocol detailed above. Eight patients showed partial remission, the mean remission rate was 22.8%, and mean duration of treatment was 4.6 months. In 13 patients progression was temporarily halted; mean duration of progress-free period (no increase in tumor mass) was 5.9 months, and mean response time was calculated to be 5.6 months. In 14 patients progression was observed during the treatment. Following a duration of variable length progression of the disease occurred in all patients; mean survival from the start of treatment was 11.9 (1-41) months, mean survival from the diagnosis was 26.1 (3-60) months.

Considering our results and those published by others it can be stated that the combination treatment of 5-FU and IF in advanced colorectal cancers did not radically change either the outcome of the disease or the length of survival[11,13] compared to that of the standard combination of 5-FU and Leucovorin. Nevertheless, a partial remission rate of approximately 20%, half a year of progression-free survival and a similar length of mean response time must be emphasized along with well recognizable improvements in the well-being of a significant proportion of the patients signalled by increased appetite, increase in body weight, decreased frequency of abdominal and other complaints etc., as results of the treatment.

Our results demonstrate that the 5-FU+IF treatment should not be discarded from the therapeutic “arsenal” for colorectal malignancies but indications for its use should be more strictly defined. Interferon and cytostatic agents are probably more effective in the early phase of disease, in those cases in which tumor mass is relatively low. The applicability of this combination in the postoperative treatment of micrometastases should be proven by clinical trials and the follow up of recurring tumors.

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