Treatment of Liver Metastases from Colorectal Cancer with Hepatic Artery Occlusion, Intraportal 5-Fluorouracil Infusion, and Oral Allopurinol

A Randomized Clinical Trial

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Background. **Regional therapy for colorectal liver metastases aimed at prolonging survival has not been tested fully in a randomized trial with untreated control subjects. This study explored the efficacy of temporary hepatic artery occlusion followed by intraportal infusion of 5-fluorouracil (5-FU) and oral allopurinol as biochemical modulators in prolonging the survival of patients with nonresectable liver metastases and no extrahepatic cancer.**

Methods. **Eighty-four patients were considered for randomization, of whom 24 were excluded at laparotomy because of extrahepatic cancer (n = 17) or resectable lesions (n = 5). In two patients, no cancer was identified in the liver. Thirty-two patients were allocated to receive treatment, and 28 were allocated to receive no regional or systemic treatment. Six patients were excluded after randomization because of major protocol violations.**

Results. **The median survival time for patients was 17 months (range, 0–66), and for control subjects, the median was 8 months (range, 0–31). Log rank analysis demonstrated a significant survival benefit for treatment versus no treatment ($P = 0.0039$). (In two patients, early death was due to toxicity from the wrong dose of 5-FU and the wrong route of administration, respectively; the mean and median survival were reduced by 1 month).**

Conclusion. **This study identified a treatment modality that prolongs survival in patients with nonresectable liver metastases and no extrahepatic metastases from colorectal cancer, suggesting that control subjects receiving no therapy may not be necessary in future randomized trials. *Cancer* 1994; 74:2749–56.**

Key words: colorectal cancer, liver metastases, hepatic artery occlusion, 5-fluorouracil, allopurinol, portal infusion.

The outcome of patients with nonresectable liver metastases from colorectal cancer is poor. The median survival time for patients who have no treatment is estimated to be 6–9 months, but some subgroups have longer survival times. Survival is related to the amount of tumor in the liver and the amount of extrahepatic tumor growth.[1–3]

Because it has not been proven in a randomized trial that any regional chemotherapy prolongs survival, all clinical trials evaluating such therapy of liver metastases must have an untreated control arm. To our knowledge, only two studies have randomly tested treatment versus observation of nonresectable liver metastases from colorectal primaries.[4,5] In the study by Rougier et al.,[5] 50% of the patients in the control group received 5-fluorouracil (5-FU) by intravenous infusion. However, several randomized studies have evaluated intraarterial floxuridine versus IV floxuridine of 5-FU.[6–8]

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Hepatic artery occlusion induces a significant necrosis of liver tumors, but no substantial survival benefit has been registered.[9]

The small differential in sensitivity between normal cells and neoplastic cells is a limiting factor in cytostatic therapy. By regional infusion of a drug and concomitant biochemical modulation of its side effects outside the liver, this problem can be partially ameliorated systemically, but not in terms of local toxicity.[10] Allopurinol modulates 5-FU toxicity, allowing approximately a twofold increase in dose[11] and increasing T1/2 by 67%.[12]

The clinical experience with portal vein 5-FU infusion is less than that with hepatic artery infusion. The response rate has not been properly explored. The size of the tumors influences the prevalence of a portal or arterial blood supply. The complication rate seems to be lower for portal vein than for arterial infusion. There are no conclusive data that favor either route of drug administration.[13]

Because most liver metastases from colorectal cancer are asymptomatic for most of their duration, the only rationale for treating these patients with no symptoms is to achieve prolonged survival.

The current study was undertaken to determine, in a randomized trial, if regional infusion of 5-FU intraportally in combination with oral allopurinol after temporary hepatic artery occlusion prolongs survival of patients with nonresectable liver metastases from colorectal cancer compared with survival of patients who receive no regional or systemic treatment for their liver metastases.

Patients and Methods

Patient Selection

The study was started in September 1984 and was concluded in September 1992. Inclusion criteria were: age younger than 76 years; histologically confirmed liver metastases from colorectal cancer that could not be surgically removed; no signs of extrahepatic cancer, i.e., negative chest X-ray, negative abdominal exploration, and negative biopsies from enlarged lymph nodes in the abdominal cavity. Eighty-four patients were considered for the study, of which 24 were excluded at laparotomy but before randomization because 5 could undergo liver resection, 17 had extrahepatic disease, and 2 had no identifiable cancer. Computed tomography scans were misleading in each instance (Table 1). Fifty-seven of the randomized patients were treated at one institution (Sahlgrenska) and 3 at another (Helsingborg) (Table 2).

The study protocol was approved by the Ethical Committee of the Medical Faculty of the University of Göteborg. Informed consent was obtained from all patients in agreement with the ethical rules of the university.

Table 1. Reasons for Exclusion at Laparotomy of Potential Subjects

Age (yr) (range)	62 (49–72)
Sex	
Male	10
Female	14
Location of primary tumor	
Colon	15
Rectum	9
Stage of primary tumor	
Dukes A	1
Dukes B	5
Dukes C	18
Grade of primary tumor	
High	0
Middle	15
Low	9
Liver metastases	
Synchronous metastases	7
Metachronous metastases	17
Exclusion reason	
Liver resection	5
Extrahepatic cancer	
Positive lymph nodes in hepatoduodenal ligament	10
Peritoneal carcinomatosis	2
Other extrahepatic cancer	5
No liver metastases identified	2

Randomization

Thirty-two patients were randomly allocated to the assigned therapy, and 28 served as control subjects. After randomization, four patients in the treatment group and two in the control group were excluded because of major protocol violations. The first randomized patient received 5-FU in an amount 50% greater than the estimated required dose, and one patient received a major portion of the 5-FU intravenously. Both patients died of drug toxicity within 30 days. Three patients were considered to have no extrahepatic cancer at exploration, but definitive histopathologic examination of lymph nodes from the hepatoduodenal ligament identified metastatic disease. One patient had cholangiocellular carcinoma instead of liver metastases. Of these 60 patients, 6 had undergone colon or rectum resection plus standardized exploration 2–61 days (2, 13, 22, 27, 33, and 61 days), before randomization but were randomized on these prerequisites to the control group, and did not undergo a new operation. All remaining patients with synchronous liver metastases underwent standardized laparotomy.

Table 2. Baseline Characteristics According to Treatment Group

	Treatment (n = 28)	Control (n = 26)	Major protocol violation (n = 6)
Hospital			
Sahlgrenska	28	24	5
Helsingborg	—	2	1
Age mean (range) (yr)	57 (37–75)	62 (41–74)	60 (48–66)
Sex			
Male	16	10	3
Female	12	16	3
Location of primary tumor			
Colon	17	20	5
Rectum	11	6	1
Stage of primary tumor			
Dukes A	1	1	0
Dukes B	10	8	3
Dukes C	17	16	3
Missing		1	
Grade of primary tumor			
High	3	2	
Middle	21	20	
Low	4	4	6
Liver metastases			
Synchronous	20	14	2
Metachronous	8	12	4
Volume of liver metastases			
Small (< 25%)	9	5	
Small intermediate (25–49%)	12	11	3
Large intermediate (50–74%)	5	7	3
Large (> 75%)	2	3	

The age and sex distributions did not differ significantly between the treatment and control groups. The prognostic criteria of the primary cancer according to synchronous versus metachronous, location in the colon or the rectum, staging according to Dukes criteria,[14] and tumor grade were not significantly different between the two groups (Table 2).

Treatment

All but seven patients underwent computed liver tomography preoperatively. Chest X-ray and standard liver function tests also were done. A selective liver angiogram to outline the vascular anatomy of the liver and to identify a patent portal vein also was performed.

At laparotomy the peritoneal cavity was explored for cancer elsewhere than in the liver. Biopsies were taken from the liver tumor and from lymph nodes in the hepatoduodenal ligament, and frozen sections were obtained.

The amount of cancer in the liver was roughly estimated by palpation and inspection according to a four-point scale: small amount, less than 25% of the liver parenchyma occupied by cancer; small intermediate, 25–49%; large intermediate, 50–74%; and large amount, more than 75% of the liver parenchyma occupied by cancer. Baseline characteristics of the material are presented in Table 2.

Plastic slings were placed around the proper hepatic artery and common hepatic artery and brought to the skin. Major hepatic tributary arteries from the superior mesenteric and left gastric artery were ligated. A Port-a-cath (Pharmacia, Uppsala, Sweden) catheter was placed via a mesenteric vein (mainly the middle colic vein) in the portal vein with the tip resting 1–2 cm proximal to its bifurcation. Five to 8 days after surgery, the slings around the hepatic arteries were tightened for 16 hours and released and removed. The efficacy of the occlusion was controlled by selective angiography and was retrospectively judged according to a three-point scale (complete occlusion, almost complete occlusion, and incomplete occlusion). Two to 4 days later, 5-FU was given intraportally (1000 mg/m^2 daily during a period of 4 hours in 1000 ml saline for 5 days). Starting 2

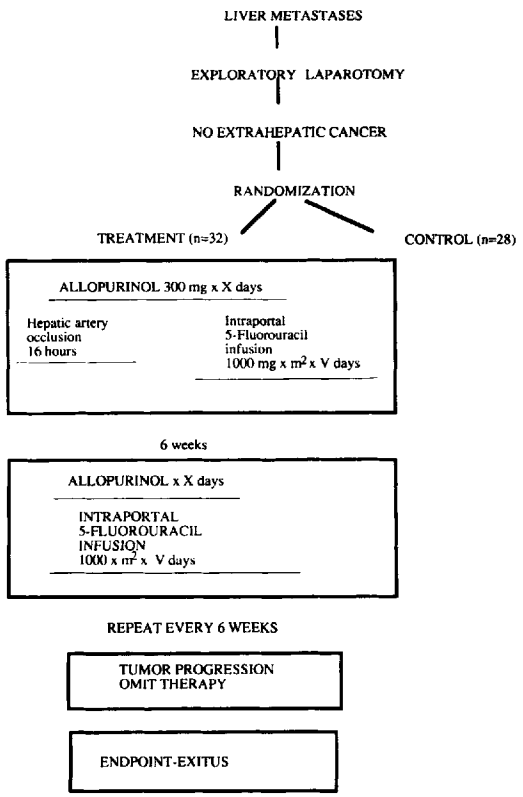

Figure 1. The design of the protocol.

days before hepatic artery occlusion and continuing for a total of 10 days, allopurinol 300 mg was given orally. The intraportal 5-FU and systemic allopurinol therapy was repeated every 6 weeks for 2 years, after which time the interval between treatments was prolonged. Most treatment cycles were given on an outpatient basis (Fig. 1).

Follow-up

In the follow-up of patients allocated to treatment, computed tomography scans of the liver and chest X-rays were done 3 months after initiation of therapy. The tumor effect was judged from these scans and classified according to World Health Organization criteria[15] as complete or partial remission, stable disease, or progressive disease. Computed tomography scans were done each 6 months or when symptoms occurred.

When tumor progression was identified, treatment was omitted. The median number of intraportal 5-FU treatment cycles was 8 (range, 0–25). In 21 patients, no additional therapy was given. In five patients, systemic cytostatic therapy was instituted, mainly a 5-FU-methotrexate-leucovorin schedule, and two patients received irradiation of the liver. In the control group, 23 patients did not undergo any tumor specific therapy, 1 patient was given oral 5-FU, and 2 patients received 5-FU, methotrexate, and leucovorin.

Table 3. Outcome of Treatment

	Treatment (n = 28)	Control (n = 26)	Major protocol violation (n = 6)
Mean survival (mo) ±SE	21 ± 2	21 ± 2	2 ± 1
Median survival (mo) (range)	17 (0–66)	8 (0–31)	2 (0–5)
Number surviving at			
> 5 yr	1	0	0
> 2 yr	7*	3	0
> 1 yr	17†	6	0

* $P = 0.179$ versus control (Fisher's exact test).
† $P = 0.005$ versus control (Fisher's exact test).

Statistics

The endpoint was death.

The material was evaluated 3 months after randomization of the last patient. In the treatment group, the median observation time was 33 months, and in the control group it was 43 months. (Two patients in the treatment group and one in the control group are alive with less than 12 months' observation time).

For the patients in the treatment group, tumor effect, side effects, and complications were analyzed. Subgroup analyses concerning stage and differentiation of primary tumors, synchronous versus metachronous metastases, and estimated liver tumor volume were performed.

It was estimated that a sample size of 30 patients in each treatment arm was necessary to achieve 80% statistical power at a P value of 0.05 to identify a 50% prolongation of survival. The two groups were compared by means of Fischer test for discrete variables. The length of survival was estimated by the Kaplan–Meier method. The treatment effects were tested with log rank statistics. All tests were performed according to intention to treat after randomization but excluding six patients with major protocol violations. The study was reviewed once after the accrual of 40 patients.

Results

The mean survival time after randomization in the treated group was 21 ± 2 months, and in the control group it was 12 ± 2 months. The median survival time in the treated group was 17 months (range, 0–66 months), and in the control group it was 8 months (range, 0–31 months). If survival is measured from the day of surgery in the control group, the median survival time is the same (8 months; range, 0–33 months) (Table 3). If the two patients with lethal toxicity within 30 days

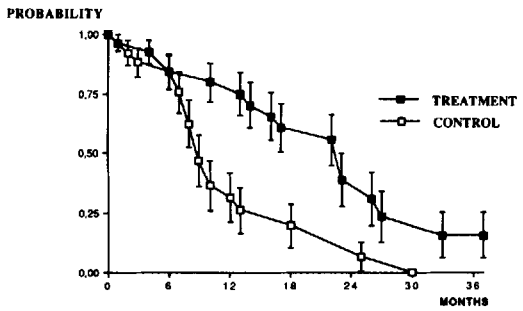

Figure 2. Survival curve estimate ± standard error for patients who underwent treatment (filled squares) and observation (open squares). Log rank test: $P = 0.0039$.

attributable to the wrong dose or wrong route of administration of 5-FU are included in the treated group, the mean and median survival time is 20 months and 16 months, respectively, and if all of patients with protocol violations are included as they were randomized, the median survival time in the treatment group is 16 months, and in the control group it is 8.5 months. If these patients are included in the analysis, the statistics and conclusions are not affected. If the patients who received additional treatment after failing are excluded (seven in the treatment group and three in the control group), the mean and median survival times are unchanged.

Log rank analysis showed a significant advantage for treatment ($P = 0.0039$) (Fig. 2). One patient in the treated group is alive 66 months after initiation of therapy. Seven treated patients and three patients in the control group have survived for 2 years or more ($P = 0.179$). There are 17 1-year survivors in the treated group and 6 in the control group ($P = 0.005$) (Table 3).

None of the patients who had major protocol violations survived 1 year.

In the group of patients who were excluded before randomization, the median survival time was 3 months (range, 0–53 months) for the 5 patients who underwent liver resection and 5 months (range, 1–21 months) for the 17 with extrahepatic cancer.

Hepatic artery occlusion was considered to be complete in 8 patients, almost complete in 12 patients, and incomplete in 6 patients. In two patients, the completeness of the occlusion was not investigated. An almost complete occlusion was considered one in which one or two minor collaterals were identified on the angiogram adjacent to, but not in, the liver, and an incomplete occlusion was considered when vessels were identified adjacent to or inside the liver. There was no correlation between the tumor effect at 3 months and the efficacy of the hepatic artery occlusion (Table 4).

The tumor effect was evaluated 3 months after hepatic artery occlusion and two cycles of 5-FU, and partial remission was found in 7 (25%) patients, stable disease in 11, and progressive disease in 9. One patient died before evaluation. The median survival time in the seven patients with partial remission was 22 months (range, 12–66 months); in the nine patients with progressive disease, it was 13 months (range, 4–21 months).

In the treated group, the median survival time was longer for patients with synchronous (23 months) than for those with metachronous metastases (13 months). In the control group, the survival time was longer for patients with less than 25% tumor volume in the liver than for those with more than 25% (Table 5) (Kaplan–Meier method).

No significant correlation between age and survival time was identified.

Complications of treatment were seen in eight patients; three had systemic toxicity, including bone marrow toxicity of Grade II in two patients and cardiac arrhythmia in one. Two patients in the control group and three patients in the protocol violation group had a significant postoperative complication (Table 6).

Discussion

In 30% of patients with colorectal cancer the liver is the only initial site of metastases.[16] The outcome for such patients with liver metastases from colorectal cancer when left untreated is always fatal, but survival time is related to the volume of cancer in the liver. Patients with extrahepatic cancer have an even worse prognosis.[1] In the current study, 17 patients were excluded before randomization because of the presence of extrahepatic cancer, and they had a short survival time (median, 5 months; range, 1–21 months).

Apart from liver resection, there is no established curative therapy for patients with liver metastases. Liver resection has given a 30% 5-year survival in several materials.[17] In this study, five patients were preoperatively considered to have bilobar or nonresectable liver metastases, but at exploration, liver resection could be performed with a strenuous effort. These patients survived for a median of 3 months, but one of them survived for 53 months. During the same period, liver resections for colorectal metastases were performed in a total of 63 patients in our institution. Radical liver resection was performed in 36 of these patients, and the median survival time was 28 months (range, 0–108 months). When the metastases were probably or definitely not radically resected (27 patients) the median survival time was 17 months (range, 0–72 months).

For patients with nonresectable liver metastases, systemically administered 5-FU with or without biochemical modulators is the standard palliative therapy, but regional intraarterial 5-FU is advocated by many

Table 4. Efficacy of Occlusion

	N	Median survival (mo) (range)	Tumor effect			Not evaluable
			PD	*SD*	*PR*	
Complete	8	19 (6–32)	4	4	—	—
Almost complete	12	16 (4–31)	3	4	5	—
Incomplete	6	16 (4–66)	2	2	2	—
Not evaluated	2	(0, 16)	—	1	—	1
Total	28	17 (0–66)	9	11	7	1

The efficacy of hepatic artery occlusion, judged by liver angiography related to the tumor effect 3 months after occlusion and two cycles of 5-fluorouracil plus allopurinol.

PD: progressive disease; SD: stable disease; PR: partial response.

authors.[18] Intraarterial 5-FU administration can induce tumor regression in 40–70% of patients, whereas systemic administration can achieve this in 20%. In most studies, no significant impact on survival has been established.[7,18,19] In the study by Rougier et al.,[5] there was a statistically significant difference in favor of the regionally infused group, with a survival rate at 2 years of 23% versus 13%. In a study by Chang et al.[20] comparing intraarterial and intravenous 5-fluorodeoxyuridine, there was a significantly improved response rate for regional therapy (62%) compared with intravenous treatment (17%); however, this did not translate to an improved survival rate. It was claimed that allopurinol could increase the therapeutic index of 5-FU by biochemical modulation,[21,22] but Phase II studies have not identified any synergy.[22] In the current study, allopurinol could act as a free radical scavenger in connection with the liver artery occlusion and as a biochemical modulator of 5-FU. Based on recently published results, the importance of allopurinol in this protocol must be questioned.[23,24]

The rationale for combining temporary hepatic ar-

Table 5. Survival for Patients in Treated and Control Groups According to Prognostic Criteria

	Treatment group		Control group	
	N	*Median (mo) (range)*	*N*	*Median (mo) (range)*
Sex				
Male	16	16 (0–34)	10	10 (2–25)
Female	12	23 (3–66)	16	9 (1–31)
Location of primary tumor				
Colon	17	23 (2–66)	20	8 (1–25)
Rectum	11	17 (0–25)	6	12 (7–31)
Stage of primary tumor				
Dukes A	1	(0)	1	(2)
Dukes B	10	24 (2–32)	8	10 (3–25)
Dukes C	17	16 (2–66)	16	9 (1–31)
Grade of primary tumor				
High	3	(2, 26, 66)	2	(5, 15)
Middle	21	23 (0–34)	20	9 (1–25)
Low	4	13 (4–16)	4	5 (1–31)
Liver metastases				
Synchronous	20	23 (2–66)	14	10 (1–31)
Metachronous	8	13 (0–24)	12	9 (5–25)
Tumor volume				
Small (< 25%)	9	23 (9–66)	5	18 (5–31)
Small intermediate (25–49%)	12	16 (2–34)	11	8 (5–25)
Large intermediate (50–74%)	5	9 (2–26)	7	3 (1–7)
Large (> 75%)	2	(0, 4)	3	(1, 8, 10)

Table 6. Complications

Treatment group	
Related to surgery	
Postoperative aspiration, atelectasis pneumonia	1
Permanent hepatic artery occlusion	1
Portal thrombosis	1
Acute liver failure	1
Related to regional infusion	
Sclerosing cholangitis	1
Bone marrow toxicity grade 2	2
Cardiac arrhythmia, ventricular fibrillation	1
Control group	
Postoperative intestinal obstruction	1
Postoperative bile leakage after liver biopsy	1
Protocol violation	
Bone marrow toxicity (grade 4)	2
Postoperative intestinal obstruction	1

tery occlusion and portal 5-FU was that the occlusion induces a tumor destructive effect, and by subsequent intraportal infusion, surviving tumor cells will be exposed to high concentrations of 5-FU. If the temporary artery occlusion induces a permanently reduced tumor blood flow and thereby a reduced inflow to the tumor of purines and pyrimidines necessary for the DNA synthesis, a synergistic effect with 5-FU theoretically could be achieved. In previous studies, the 16 hours' occlusion has been shown to induce significant tumor necrosis with only minor impairment of liver function.[25] There also is no development of collaterals to the liver during such a short period. Hepatic artery occlusion has been tested in several uncontrolled trials, but no effect on survival has been registered.[25,26]

One recent study has tested hepatic artery occlusion with and without portal infusion of 5-FU (600 mg/m^2/days for 10–20 days every sixth week). The median survival time for both groups was 12 months. The objective response rate was approximately 20%, which was claimed to be attributable to strict criteria of tumor measurement. Because of that and the high mortality, the authors concluded that the portal route for drug administration should be abandoned.[27] In the current study, the response rate was 25%, which is equivalent to the findings of that study by Gerard et al.[27]

The interval between hepatic artery occlusion and the start of intraportal 5-FU was attributable to the need for an observation period to see how the patients tolerated the occlusion.

In our study, multimodal therapy with an initial vascular attack on the tumor followed by portal 5-FU infusion prolonged the median survival from 8 to 17 months and the mean survival time from 12 to 21 months. This almost doubling of the survival time was achieved with acceptable toxicity using a dose 5-FU of 1000 mg/m^2 body surface area daily for 5 days. Except for the initial cycle, most treatment was given on an outpatient basis.

Few prior attempts have been made to compare regional treatment and no chemotherapy of liver metastases from colorectal cancer in prospective randomized studies. This study showed that temporary hepatic occlusion followed by 5-FU cycles every 6 weeks intraportally and allopurinol orally significantly prolonged survival times. With this regimen, only 2 of the 28 (7%) patients who received the prescribed dose and route of 5-FU experienced bone marrow toxicity (Grade II). One patient also experienced cardiac arrhythmia. Another four patients had significant local complications, one of whom died of acute liver failure. Thus, 11% of patients experienced systemic toxicity and 14% experienced local toxicity. In comparison with reported Phase II trials on regional therapy, the toxicity and side effects are favorable.

The possibility of expanding this study to a larger number of patients has been limited by a recent report from the Nordic Gastrointestinal Tumor Adjuvant Therapy Group, which has found that there is a prolongation of survival in patients with no symptoms who had advanced colorectal cancer treated with 5-FU, methotrexate, and leucovorin.[28] The outcome for the control subjects was equivalent to what has been reported in previous analyses of the natural course for patients with liver metastases from colorectal cancer.[3] Thus, it is unethical to have an untreated control arm.

There were minor, but not statistically significant, differences in prognostic factors between the treatment and observation groups, but the differences are not of such magnitude that they could explain the longer survival. In the treated group, one patient survived more than 5 years; in the treatment group seven and in the control group three patients survived 2 years.

In analyzing factors in the treated patients in an endeavor to identify subgroups that might be most suitable for therapy, it was found that synchronous versus metachronous ($P = 0.05$) and low versus middle differentiation ($P < 0.05$) had an influence. Because there was an imbalance concerning synchronous versus metachronous in the treatment group and because patients with synchronous metastases do better, one might argue that this accounts for the results.

Because there was no significant effect of completeness of occlusion of the hepatic artery, either on the tumor effect 3 months after occlusion or on survival time, this part of the treatment protocol is drawn into question. It must be emphasized that the small number of patients in the subgroup analyses for prognostic factors weakens these observations.

In conclusion, this regimen offers a survival advan-

tage over observation, suggesting that the use of no-treatment control subjects is not appropriate in future trials, and explorative studies should have the same or a better outcome than that of the current results. Our knowledge concerning 5-FU metabolism and the need for an increased intracellular concentration of reduced folates for maximal 5-FU effect indicates the use of leucovorin in future trials.[29]

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