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Clinical report

Continuous delivery of venous 5-fluorouracil and arterial 5-fluorodeoxyuridine for hepatic metastases from colorectal cancer: feasibility and tolerance in a randomized phase II trial comparing flat versus chronomodulated infusion

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High-dose chemotherapy combining regional hepatic artery infusion (HAI) of fluorodeoxyuridine (HAI FUDR) and systemic venous infusion of 5-fluorouracil (i.v. 5-FU) was delivered against liver metastases from colorectal cancer. The hypothesis that chronomodulation of delivery rate along the 24 h time scale would improve the tolerable doses of both drugs was tested. Combined HAI FUDR (80 mg/m^2/day) and i.v. 5-FU (1200 mg/m^2/day) were administered for five consecutive days every 3 weeks, either as a constant rate infusion (schedule A, 27 patients) or as chronotherapy (schedule B, 29 patients). This latter regimen consisted of a sinusoidal modulation of the delivery rate over the 24 h scale with a maximum at 16:00 for FUDR and 4:00 for 5-FU. Intrapatient dose escalation up to the individual maximum tolerated doses (MTD) was planned for both drugs in the absence of any previous grade 3 or 4 toxicity. All patients had metastatic colorectal cancer, with adjuvant or palliative chemotherapy given to six patients (22%) on schedule A and 12 patients on schedule B (41%). Severe stomatitis occurred in 71% of the patients and was dose limiting. No hepatic toxicity was encountered. Dose reductions of 5-FU and/or FUDR were required for 17 of 27 patients on schedule A (63%) as compared to 11 of 29 patients on schedule B (38%), following reaching the individual MTD ($p < 0.05$). Over the first six cycles, patients on schedule B received higher doses (mg/m^2/cycle; FUDR: 522 ± 85 versus 499 ± 50, p=0.004 and 5-FU: 5393 ± 962 versus 5136 ± 963, p=0.009) and higher dose intensities (mg/m^2/week; FUDR: 164 ± 46 versus 151 ± 52, p=0.018 and 5-FU: 1652 ± 478 versus 1553 ± 535, $p < 0.041$) of both drugs than patients on schedule A. As a result the number of courses with doses of 5-FU above 1200 mg/m^2/day and/or FUDR above 110 mg/m^2/day was larger in group B than in group A (5-FU, A: 67 of 268, 25% versus B: 133 of 321, 41% and FUDR, A: 86 of 268, 32% versus B: 155 of 321, 48%; $p < 0.001$). Objective responses were observed in 13 patients on schedule A (48%) and 11 patients on schedule B (38%). The results support the need for further exploration of chronotherapy of colorectal cancer liver metastases with combined arterial and venous fluoropyrimidine chemotherapy. [© 1999 Lippincott Williams & Wilkins.]

Key words: Ambulatory medicine, chronotherapy, circadian rhythms, colorectal cancer, hepatic artery infusion, liver metastases.

Introduction

Hepatic artery infusion (HAI) has been developed for increasing the selective chemotherapy exposure of neoplastic cells in liver.[1,2] This strategy was mostly applied to the treatment of liver metastases from colorectal cancer, using fluoropyrimidines.[2–20] Protracted fluorodeoxyuridine (FUDR) given by HAI produced objective response rates of 45% or greater in phase II trials and repeatedly achieved higher response rates than systemic fluoropyrimidine delivery in randomized phase III trials.[3–9] Yet the demonstration of a survival advantage in favor of HAI FUDR was only recently provided by the meta-analysis cooperative group.[10] Nevertheless, direct hepatic toxicity, biliary sclerosis or gastro-duodenal irritation or ulceration often compromise the therapeutic index of HAI of FUDR.[11–14] Cholecystectomy at the time of arterial catheter placement, shorter duration of treatment courses or dexamethasone have been proposed in order to reduce these toxic

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effects.[15-19] Furthermore, extrahepatic metastatic spread has consistently represented a major limit of regional hepatic treatments, thus leading to combining both hepatic artery and systemic venous treatments, which often resulted in additive toxicities.[2,11-13,20]

Experimental data have indicated that the toxicities of FUDR and 5-fluorouracil (5-FU) varied by 50% or more according to the time of administration along the 24 h time scale.[21-24] These changes were related to the circadian rhythms in enzymatic activities involved in the cellular metabolism of fluoropyrimidines. This was notably the case for anabolic enzymes such as thymidine kinase, uridine phosphorylase, orotate phosphoribosyltransferase and uridine kinase, and for dehydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme of the 5-FU catabolic pathway.[21,25-27] Highest tolerability of 5-FU corresponded to highest DPD activity and lowest TK activity in rats or mice.[22,25,27,28] DPD activities also followed a circadian pattern in circulating mononuclear cells of cancer patients;[29] maximum DPD activity occurred in the first half of the rest span both in mice or rats and in cancer patients,[22,25-29]

Tolerability of continuous 14 day infusion of FUDR, given via the i.v. or the intra-arterial route, was compared according to whether the delivery rate was constant or chronomodulated. In this latter schedule, two-thirds of the daily FUDR dose were given between 15:00 and 21:00 h.[30] Patients on the chronomodulated schedule received 30–45% higher dose intensity but experienced reduced overall toxicities as compared to those receiving flat infusion.[30] In a broad phase II randomized trial, comparing 14 days intra-hepatic constant rate versus circadian pattern FUDR continuous infusions, Wesen *et al.*[31] confirmed large schedule dependent differences in gastrointestinal tract toxicities.

Phase I–II trials have also indicated that the recommended dose of 5-FU given as a 5 day chronomodulated infusion with peak delivery at 4:00 h was 1400 mg/m^2/day, i.e. 40% or greater than the dose usually recommended for flat infusion.[32] Multicenter randomized phase III trials further confirmed that chronomodulated delivery of 5-FU, combined with folinic acid and oxaliplatin, resulted in a 5-fold decrease in the incidence of severe mucositis despite a 25% increase in 5-FU dose intensity, while achieving also a 22% increase in the objective response rate.[33,34] Moreover, in a randomized phase I study, Levi *et al.* have validated the choice of the time of administration of 5-FU and oxaliplatin: according to the time of peak delivery, the observed grades III–IV mucositis toxicity varied from 16 to 80%.[35] Finally, the trials of the European Chronotherapy Study Group have shown a clear-cut dose–response relationship for both 5-FU and oxaliplatin.[36]

The present phase II trial aimed at determining the feasibility, tolerability and maximum tolerated doses (MTD) of two modalities of a 5 day infusion combining HAI of FUDR with i.v. infusion of 5-FU. Circadian-time-modified delivery was compared to constant rate infusion. The timing of drug administration was established according to animal data and to previous phases I–III trials; thus, optimal tolerance was foreseen for 5-FU at 4:00 a.m. and for FUDR at 16:00 p.m.[21-24,30-36]

Patients and methods

The trial was designed in accordance with the recommendations of the Helsinki declaration on biomedical research involving human subjects and was performed after approval by the human investigation committee of each institution.

Patients

Patients younger than 76 years with a Karnofsky index greater than 60 (ECOG $\leqslant 2$) suffering from measurable unresectable hepatic metastases from a histologically proven colorectal cancer were eligible for the study. Adjuvant chemotherapy and a single 5-FU-based chemotherapy for metastatic disease were allowed. Limited extrahepatic disease (no more than two extrahepatic nodules at medical imaging) was not an exclusion criterion. No previous hepatic-directed therapy was permitted. Patients with active angina pectoris, congestive heart failure, myocardial infarction within the last 6 months or impaired left ventricular ejection fraction were excluded. Finally patients with active central nervous system (CNS) involvement, psychological problems impairing detailed follow-up, granulocyte or platelet counts less than 1500 or 100 000/μl, respectively, and serum creatinine or bilirubin levels above 2 mg/dl were also not eligible. All patients had cholecystectomy and gastroduodenal artery ligation at the time of surgical placement of the catheter into the hepatic artery.

Detailed staging was performed with computerized tomography (CT) scans of the thorax, abdomen and pelvis, usually complemented with abdominopelvic echography. CNS CT scans and bone scans were performed whenever indicated. Informed consent of patients was required before inclusion in the trial.

Treatment

After implantation of arterial hepatic and venous side-ports (Port-a-Cath; Pharmacia, Uppsala, Sweden), patients were scheduled to received a combined continuous administration of venous 5-FU 1200 mg/m^2/day and arterial FUDR 80 mg/m^2/day for 5 days, followed by a 16 day treatment-free interval. 5-FU and FUDR doses were determined according to previous phases I-II studies, from our group[32] and from that at MD Anderson, respectively.[17] Treatment criteria were: WHO clinical toxicity grade = 0, granulocyte count $\geqslant 1500/\mu l$, platelet count $\geqslant 100\,000/\mu l$ and alkaline phosphatase and bilirubins $\leqslant 125\%$ normal levels. If toxicity nadir was <2, intrapatient dose escalation was foreseen to 1400 mg/m^2/day for 5-FU and to 100 mg/m^2/day, then 120 mg/m^2/day for FUDR. In fact, a first cohort of 13 patients received the FUDR initial dose at 80 mg/m^2/day, a second cohort of 25 patients was treated at 100 mg/m^2/day and a third one of 18 cases received 120 mg/m^2/day. In case of acute grade 2 toxicity, doses of 5-FU and FUDR remained unchanged. Grade 3 or greater toxicity called for dose reduction by 200 mg/m^2/day for 5-FU in the case of mucositis or diarrhea, by 20 mg/m^2/day for FUDR in the case of hepatobiliary toxicity; in case of hematological toxicity, doses of both drugs were reduced as mentioned. In each individual patient, adaptations of doses to the maximum tolerated dose was projected.

Two schedules of 5 day continuous drug delivery were compared; 5-FU and FUDR were administered either at a constant rate (schedule A) or at a chronomodulated one (schedule B) (Figure 1). For this latter schedule, the delivery rate of both drugs varied in a sinusoidal pattern over 24 h, with a peak at 4:00 h for 5-FU and at 16:00 h for FUDR. The chemical stability of 5-FU and FUDR solution over time spans of 5 days or more has been proven.[37,38] Either complex delivery schedule of these drugs was administered to outpatients with an external portable multichannel programmable-in-time ambulatory pump (IntelliJect; Aguettant, Lyon, France). This pump is equipped with four channels, each utilizing a 30 ml disposable syringe. Three of the channels (one each for separate solution of 5-FU) were connected to the central venous line via a manifold. The fourth channel was connected to the second separate arterial line and delivered the FUDR solution. The plunger of each syringe was driven independently by a step motor. The rotation rate of the step motor varies in time according to the program that has been written in a programmable read-only memory chip located in the pump; this chip was programmed by an IBM PC using Intellimed software (Aguettant). Two 9 V batteries permit 15 days of operation of the pump using either a flat or a chronomodulated program, which was far beyond what was needed for one course.

Surgery

All patients underwent laparotomy for abdominal disease staging. Cholecystectomy was performed and an arterial access port was implanted, the catheter being positioned in the common hepatic artery after catheterization and ligation of the gastro-duodenal artery. In case of synchronous metastases, the primary tumor was removed on this occasion.

Patients were offered second-look laparotomy after a minimum of six courses if an objective or a minor response allowed for potential resection of metastases with curative intent.

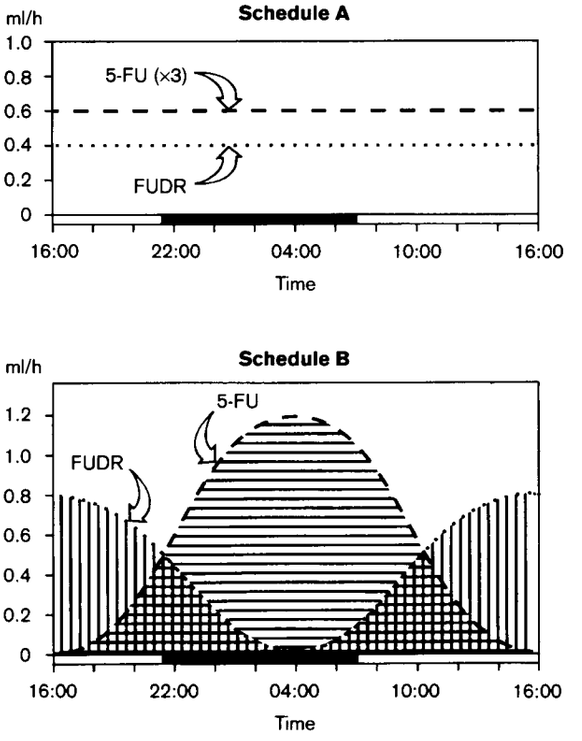

Figure 1. Schedules of i.v. (5-FU in three syringes) and intra-arterial (FUDR in the fourth syringe) infusions. Drug delivery was constant (schedule A) or chronomodulated (schedule B) over a 24 h period. Abcissa, local time in hours; ordinate, delivery rate. This cycle was repeated automatically for five consecutive days.

Endpoints

The primary endpoint of the trial was the evaluation of MTD and of comparative toxicity among both groups until at least the sixth course of treatment. The toxicity of each course was recorded in detail before the next one and graded according to WHO-modified criteria.[32,33,39]

Tumor responses were also recorded every third treatment course and defined according to WHO criteria.[36] However, it has to be stressed that tumor responses were not an endpoint in this trial.

Dose and dose intensities

Chemotherapy dose per course was evaluated for each drug as mg/m^2 effectively given. Dose intensities were expressed in mg/m^2/week over the first six courses of treatment according to Hryniuk and Goodyear.[40]

Study design and statistics

Registered patients were stratified according to institution (Villejuif or Liège) and to the presence or absence of limited extra-hepatic spread. Analyses were performed on all assessed courses and/or patients. χ^2 and Student's *t*-tests were used as appropriate.

Results

Patient characteristics

Twenty-seven patients were randomized to receive flat infusion (group A) and 29 were allocated to chronomodulated delivery (group B). Patients' characteristics were similar in both groups, except for prior therapy (Table 1). The number of previously treated patients was six on schedule A (22%, all with chemotherapy) and 15 on schedule B [52%, including 12 with chemotherapy (41%)]. All seven patients with previous palliative chemotherapy (schedule A, two patients, schedule B, 5 patients) had progressive disease upon registration in the trial. Accrual ranged from December 1987 to December 1993. The median numbers of courses given were similar. Patients flow is described in Figure 2.

Treatment withdrawals

No toxic death occurred. Seven patients on schedule A (26%) and two patients on schedule B (7%) were withdrawn from the trial over the initial four treatment months, i.e. before course 6 could be given (Table 2). One of them on schedule A exhibited 5-FU-related angina pectoris during the first treatment course. Basically, the treatment was stopped for excessive toxicity (two cases of schedule A, one on schedule B), problems with the arterial side-port (seven cases in arm A versus 8 cases in arm B) or tumoral evolution (Table 2).

Table 1. Patient characteristics

	Schedule A (27)	Schedule B (29)
Sex (M/F)	17/10	18/11
Age		
median	58	64
range	34–75	44–75
mean ± SD	56.1 ± 10.8	60.8 ± 7.9
Primary		
colon	18	23
rectum	9	6
Duke's		
B	2	1
C	7	7
D	17	21
unknown	1	0
Previous treatment		
surgery	27	29
adjuvant CT	4	5
palliative CT[a]	2	5
radiotherapy	0	3
adjuvant CT+RT	0	2
Hepatic metastases		
isolated	22	23
synchronous	17	21
metachronous	10	8
Volume (%)		
<25	6	9
25–50	19	19
<50	2	1
Performance status		
0	11	12
1	14	16
2	2	1
Center: Villejuif	12	13
Center: Liege	15	16
Number of courses		
total	268	321
median	10	11
range	1–21	2–21
mean ± SD	9.9 ± 5.2	11.1 ± 5.1

[a]All patients were progressing at the time of inclusion.

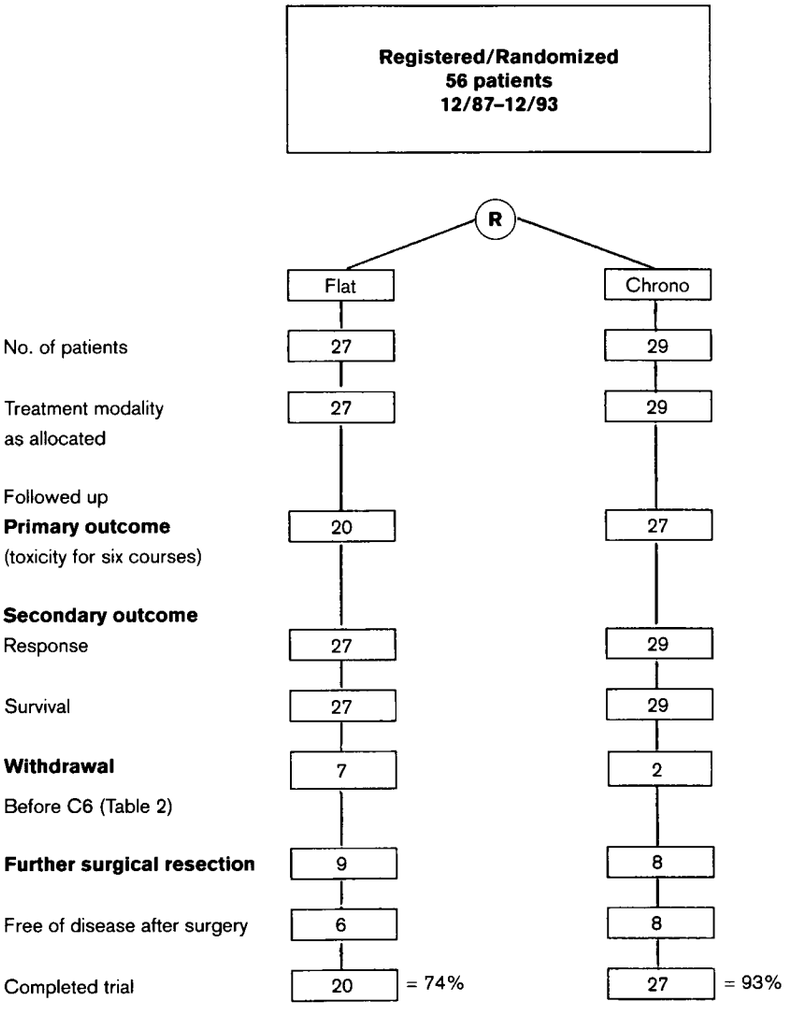

Figure 2. Trial profile.

MTD and dose intensities

Mucositis constituted the main dose-limiting toxicity. Grade 3–4 mucosal toxicity usually occurred between the first and the third treatment course. This was the case for 70% of the patients from group A and for 72% of patients from group B. As a result of dose adaptations, this grade 3–4 toxicity occurred in only 14 and 15% of courses in schedule A and schedule B, respectively (Table 3). This indicates that patients were treated near individual MTD. MTD were in fact similar in both groups for 5-FU (schedule A, 5924 ± 615 mg/m^2; schedule B, 6025 ± 576 mg/m^2), but were higher in group B than in group A for FUDR (schedule A, 509 ± 64; schedule B, 544 ± 68; $p = 0.027$). Further

Table 2. Treatment withdrawals

	Schedule A (27)	Schedule B (29)
Before course 6	7	2
arterial Port-a-Cath	3	2
progression	2	0
grade IV toxicity	1	0
cerebral stroke	1	0
After course 6	20	27
progression	12	15
arterial Port-a-Cath	4	6
tumour response	3	7
toxicity	1	0
refusal	0	1

dose reductions were required for 5-FU and/or FUDR in 17 patients on schedule A (63%) as compared to 11 patients on schedule B (38%) ($p < 0.05$).

Mean doses and dose-intensities over the first six courses were significantly larger for both 5-FU and FUDR in patients on schedule B than in those on schedule A (Table 4). Finally, more courses with 5-FU doses $\geqslant 6000$ mg/m^2 (A, 67 of 268, 25% versus B, 133 of 321, 41%) or FUDR doses $\geqslant 550$ mg/m^2 (A, 86 of 268, 32% versus B, 155 of 321, 48%) could be delivered on schedule B than on schedule A ($p < 0.001$). As a result, no major difference in toxicity was apparent between both treatment groups for mucositis, skin or digestive toxicity. Nevertheless, more patients experienced alopecia or mild granulocytopenia on schedule A than on schedule B (Table 3).

Responses

An objective response was achieved in 13 patients on schedule A [48%, no complete response (CR)] and in 11 patients on schedule B (38%, including one CR). Surgical resection of metastases was attempted in 17 patients (schedule A, nine patients; schedule B, eight patients). Following surgery, six patients on schedule A (22%) and eight patients on schedule B (27%) were rendered disease-free.

Table 3. Toxicity WHO grades (% courses/% patients)

Variables (WHO grades)	Schedule A[a]	Schedule B[a]	p
Mucitis (3+4)	13.8/70.4	15.4/72.4	NS
Skin (2+3)	11.2/44.4	18.8/52.7	–
Nausea–vomiting (2+3)	4.1/25.9	6.3/24.1	–
Diarrhea (3+4)	1.5/0.0	1.2/6.7	NS
Alopecia (3)	14.6/3.7	8.5/6.9	0.003/–
Hemoglobin (1+2)	3.4/14.8	4.7/17.2	–
Granulocytes (2+3)	3.6/14.8	0.3/3.4	0.002/0.1
Platelets	0/0	0/0	–

[a]Schedule A: 268 courses; 27 patients. Schedule B: 321 courses; 29 patients.
Note: No hepatitis nor sclerosis cholangitis related to therapy.

Discussion

The feasibility of combining high doses of i.v. 5-FU and intra-arterial FUDR was confirmed in this study. All patients received either drug infusion modality in fully ambulatory conditions, using an external multichannel pump. The only technical problem was related to the obstruction or dislodgment of the arterial catheter and/or thrombosis of the hepatic artery, which occurred in 15 patients (27%), thus confirming earlier reports mentioning that such complication could affect up to 50% of the patients.[6,11,12,14]

About 70% of the patients on each treatment schedule experienced severe mucosal toxicity (grade 3–4) as a result of the intrapatient dose escalation scheme. The MTD of 5-FU were similar in both groups, yet the MTD of HAI FUDR was significantly higher in the group receiving chronotherapy. Since no hepatobiliary toxicity was encountered, we estimate that extrahepatic passage of FUDR also contributed to systemic toxicity including mucositis and that such contribution was more pronounced in the flat infusion arm. Nevertheless, once individual MTD was reached, subsequent dose reductions of 5-FU and/or FUDR had to be performed in twice as many patients on schedule A as compared to schedule B. Thus, compliance over the first six courses was nearly 3-fold better with chronotherapy as compared to constant-rate infusion.

The lack of any FUDR-related sclerosing cholangitis or hepatitis supports the delivery of this drug as a 5 day rather than as a 14 day infusion, as already advocated.[14,17,18] The FUDR doses (400–600 mg/m^2/course) which were delivered were largely higher than those administered in the 14 day infusion schedule (400–600 versus 170 mg/m^2/course). In addition, a reduction in the hepatobiliary toxicity of HAI FUDR has been suggested with chronomodulated delivery of FUDR in the 14 day infusion schedule.[22,30] More recently, a single arterial bolus injection of FUDR doses ranging from 270 to 1350 mg/m^2/day was administered at 15:00, based upon chronobiological concepts.[19]

Table 4. Doses and dose intensities (C1–C6)

	5-FU			FUDR		
	Schedule A	Schedule B	p	Schedule A	Schedule B	p
Doses (mg/m^2/cycle)	5136±963	5393±962	0.009	501±88	534±79	<0.001
Dose intensities (mg/m^2/week)	1553±535	1652±478	0.041	151±52	164±46	0.008

The delivery rate of 5-FU was sinusoidally modulated along the 24 h time scale, with a maximum at 4:00 at night, for five consecutive days. Results from the present trial indicated that the starting 5-FU dose of 6 g/m^2/course was close to the MTD when combined with hepatic arterial FUDR. This dose was lower than that previously recommended for single-agent 5-FU chronotherapy (7 g/m^2/course).[32]

Treating all patients near the MTD resulted in objective response rates of 38–48%. This activity was similar to that reported earlier for HAI FUDR, keeping in mind that 32% of the present patient population had received prior fluoropyrimidine chemotherapy.[10,12–14] The achievement of an objective or a minor response allowed the surgical resection of previously inoperable liver metastases.[20,41,42] This second surgery has recently been proved to further favorably influence survival outcome.[20,41,42]

Conclusion

In this trial, we have confirmed the feasibility of a combined continuous administration of 5-FU by the venous route with FUDR by the arterial route for treating hepatic metastases from colorectal cancer. Both drugs could be delivered at high dosages. Chronomodulation allowed a significant increment in dose and dose intensities of both drugs without increased clinical toxicities, and resulted in better treatment compliance.

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