

ORIGINAL ARTICLE

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Intraperitoneal 5-fluoro-2'-deoxyuridine (FUDR) and (S)-leucovorin for disease predominantly confined to the peritoneal cavity: a pharmacokinetic and toxicity study

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Abstract Intraperitoneal (IP) administration of fluorinated pyrimidines has been evaluated for ovarian and gastrointestinal malignancies in phase I, II, and III trials. The tolerance and pharmacokinetic profile of IP 5-fluoro-2'-deoxyuridine (FUDR) alone and with (*R,S*)-leucovorin ((*R,S*)-LV) have each been evaluated in previous phase I studies. FUDR doses of 3 g per day with and without (*R,S*)-LV doses up to 640 mg per day given IP are well tolerated. The current phase I study was designed to determine the pharmacokinetic profiles and clinical tolerance of escalating doses of the pure biologically active *S*-isomer of leucovorin ((*S*)-LV) given IP with the same dosing schedule of FUDR. A group of 16 patients with disease confined to the abdominal cavity were treated in this study. Pharmacokinetic studies of blood and peritoneal fluid, toxicity profiles, and clinical response for the first three cycles are reported here. The toxicity profile did not significantly differ from the prior two studies. All non-hematologic toxicities, such as fatigue, nausea, vomiting, diarrhea, and abdominal discomfort were less than grade 4, and most were less than grade 3. Neutropenia and thrombocytopenia were uncommon and observed only in patients with compromised bone marrow reserve. The pharmacokinetic profiles were also congruent with the previous studies and indicate a three-log advantage for FUDR. The (*S*)-LV profiles in the peritoneal cavity paralleled those of FUDR. Antitumor ef-

fects or absence of progression until after cessation of therapy were documented in 11 patients. At a median follow-up of 18 months 44% of patients were alive. IP administration of 3-g of FUDR and up to 640 mg (*S*)-LV daily for three days was well tolerated. The tolerance and antitumor effects observed during IP FUDR and LV in these studies encourage further exploration of this regimen against ovarian and gastrointestinal malignancies. The actual role and optimal dose of LV as an enhancer of the antitumor actions of FUDR administered by this route remain unknown.

Key words FUDR · Floxuridine · Intraperitoneal (*S*)-Leucovorin

Introduction

Intraperitoneal (IP) administration of fluorinated pyrimidines has been previously evaluated for ovarian and gastrointestinal cancer in phase I, II, and III trials [1–11]. IP 5-fluoro-2'-deoxyuridine (FUDR) has been extensively studied at the USC Norris Cancer Center in phase I trials. The initial phase I study established that 3 g IP FUDR given daily for 3 days produces cytotoxic concentrations on peritoneal surfaces and an acceptable toxicity profile, and was a dose suitable for phase II studies [12]. Pharmacologic studies of FUDR had revealed linear pharmacokinetic profiles and a three-log advantage of the IP area under the curve (AUC) over the plasma AUC. A phase II Southwest Oncology Group (SWOG) study has confirmed the activity and clinical tolerance of IP FUDR at 3 g per day for 3 days in patients with epithelial ovarian cancer of small volume (< 1 cm) [13].

Various trials have indicated that leucovorin (LV) enhances the therapeutic activity of 5-fluorouracil (5-FU) in gastrointestinal cancers [14–16]. In vitro data suggest that LV potentiation of FUDR cytotoxicity may exceed that seen with 5-FU [17]. We conducted

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a phase I study utilizing 3 g IP FUDR with escalating doses of IP (*R,S*)-LV each day for 3 days [18]. The IP (*R,S*)-LV was well tolerated at doses up to 640 mg per day in combination with the IP FUDR with equivalent toxicities from the phase I study of IP FUDR alone. The pharmacokinetic data for FUDR were comparable to the preceding phase I study of IP FUDR without (*R,S*)-LV. Peritoneal clearance was shortened serially in one patient and was attributed to treatment- or disease- related changes in peritoneal membrane permeability.

This study was designed to examine the pharmacokinetic behavior and tolerance of three dose levels of IP administration of the pure biologically active *S*-isomer of leucovorin, (*S*)-LV, in combination with IP FUDR at the previously established dosage (3g/day \times 3 days) within the same patient. This design was adopted because our previous experience suggested no effect of LV on toxicity, and we wished to extend the pharmacokinetic and clinical observations [18].

Patients and methods

Patient population

This protocol, after approval by the local Institutional Review Board, was opened for patients consenting to be treated at the Kenneth Norris Jr Comprehensive Cancer Center and at the Los Angeles County/University of Southern California (USC) Medical Center from August 1991 to December 1992.

Patients were eligible for treatment with IP FUDR and (*S*)-LV if they had a histologically confirmed malignancy with residual, recurrent or metastatic disease within the peritoneal cavity and did not have other sites of symptomatic disease. A minimal residual volume of < 1 cm was preferred, but was not essential for eligibility. Patients with ovarian cancer had to have received prior systemic chemotherapy. No exclusion was made for prior IP therapy or for systemic fluoropyrimidine therapy. However, 3 weeks were required from the last chemotherapy (6 weeks for nitrosoureas) before starting treatment. A Karnofsky Performance Status (KPS) of at least 60%, normal liver and renal function (bilirubin < 2 mg/dl, creatinine r < 2 mg/dl, SGOT less than two times normal), and adequate bone marrow reserve (WBC > 3.5×10^6 /dl, platelets > 100×10^9 /dl) were also required to enter the study. Exceptions for preexisting marrow dysfunction were made for patients with ovarian cancer who had received prior carboplatin and alkylating agents with ensuing steady levels of mild neutropenia.

Treatment schedule and doses

All patients had a IP catheter implanted subcutaneously (e.g. Port-a-Cath) for access to the peritoneal cavity. Patients received IP contrast via the peritoneal catheters followed by a CT scan (as previously described [19]) in order to establish the existence of adequate distribution throughout the peritoneal cavity. The FUDR and (*S*)-LV were both given together via the IP route since no loss of activity was noted on mixing the two drugs for 72 h (K. Chan, unpublished). The dose of FUDR was fixed at 3000 mg per day for 3 days. The FUDR was diluted in 1.5–2l of normal saline and given on days 1–3 (volumes on days 2 and 3 were to be reduced to 1–1.5l if incomplete resorption of the prior day's administered volume or

patient discomfort occurred). The starting dose of (*S*)-LV was 160 mg per day administered on days 1–3 concomitantly with the FUDR. The dose of LV was to be escalated to 320 mg per day and then to 640 mg per day on cycles two and three, respectively, if allowed by toxicity parameters.

Dose modification

Treatment cycles were delayed until full recovery of all toxicities. The FUDR dose was decreased by 33% if any grade 3 or 4 toxicity occurred and (*S*)-LV doses were not escalated on subsequent cycles. If grade 2 toxicity resulted during subsequent cycles in these patients, the (*S*)-LV dose was to be reduced by 50% for the remainder of therapy.

Drug analysis

Blood and peritoneal samples for pharmacokinetic studies were acquired from each patient on days 1 and 4 of cycles 1, 2, and 3. Samples were obtained at time zero, and at 15, 60, 120, 240 and 360 min, and 24 h after the instillation of FUDR and (*S*)-LV.

Plasma FUDR and 5-FU were extracted by ethyl acetate, using the method of Au et al., and thymidine was used as the internal standard [20]. The extract was evaporated by nitrogen gas and the residue was frozen until high-pressure liquid chromatography (HPLC) analysis was performed. Following the removal of FUDR, 5-FU, and thymidine by extraction, (*S*)-LV was analyzed in the remaining plasma after the addition of more thymidine as the internal standard and protein precipitation. Thymidine (35 μ g), followed by 5 ml absolute ethanol for protein precipitation, was added to the remaining plasma and the mixture was centrifuged at 1500 *g* for 10 min. The supernatant was removed and evaporated by nitrogen gas and the residue was kept frozen until analysis. Peritoneal fluid levels of FUDR, 5-FU, and (*S*)-LV were quantitated directly by HPLC without extraction; thymidine was also used as the internal standard.

A BioRad 800 HPLC system coupled to a BioRad 1790 UV monitor (BioRad, Hercules, Calif) was used for the HPLC analysis. The wavelength for detection for FUDR and 5-FU was set at 270 nm, and at 290 nm for the internal standard, thymidine. A single wavelength of 302 nm was used for (*S*)-LV and thymidine. The HPLC analysis was performed using a C-18 10- μ m reversed-phase column (4.6 \times mm \times 250 mm i.d.; Alltech Deerfield, Ill.). A gradient method for a two-buffer system, consisting of buffer A (5 mM pH 6.7 ammonium acetate) and buffer B (70% buffer A plus 30% acetonitrile), was utilized. The solvent programme for plasma FUDR and 5-FU using buffer A was: 0–5 min 100% buffer A, 5–8 min 92%, 8–15 min 92%, 15–18 min 84%, 18–21 min 84%, 21–23 min 5%, 23–30 min 5%, 30–31 min 100%, and 31–38 min 100%. For plasma (*S*)-LV the solvent programme using buffer A was: 0–2 min 100% buffer A, 2–5 min 84%, 5–12 min 74%, 12–13 min 60%, 13–15 min 60%, 15–16 min 100%, and 16–22 min 100%. FUDR, 5-FU and (*S*)-LV in peritoneal fluid were analyzed in the same chromatographic run. The solvent programme used was: 0–4 min 100% buffer A, 4–7 min 82%, 7–11 min 76%, 11–13 min 76%, 13–14 min 65%, 14–16 min 65%, 16–17 min 100%, and 17–23 min 100% buffer A. The flow rate used was 1.0 ml/min. Under these conditions, the retention times for 5-FU, FUDR, and thymidine from the plasma extract were 7, 17.5, and 22.5 min, respectively. The retention time for plasma (*S*)-LV was 11.5 min. The retention times for peritoneal 5-FU, FUDR, (*S*)-LV, and thymidine were 7.5, 14.6, 11.5, and 16 min, respectively.

Plasma and peritoneal concentration–time data were analyzed by a compartmental approach using a standard non-linear least-squares computer program (MINSQ, Micromath, Salt Lake City, Utah). The systemic and peritoneal clearances, i.e. CL_T and CL_{PF} ,

respectively, were computed using the equations:

$$CL_T = \text{dose}/AUC_{PL} \quad \text{and} \quad CL_{PF} = \text{dose}/AUC_{PF}$$

where AUC_{PL} represents the area-under-the-concentration-time curve for plasma to time infinity and AUC_{PF} represents the area-under-the-concentration-time curve for peritoneal fluid to time infinity. The AUC values were calculated by the trapezoidal rule to the last observed concentration plus the extrapolated value which was estimated by the last concentration divided by the slope. The pharmacologic advantage R was represented by the ratio between the peritoneal clearance and the systematic clearance.

Results

Patient characteristics

As noted above, the goals of the study were to administer three courses of treatment for pharmacologic and toxicity evaluation. However, patients were allowed to continue treatment at the discretion of their physician for stable or responding disease if they did not encounter limiting toxicity. A total of 64 cycles were delivered, 42 at an (S)-LV dose of 160-mg, 8 at 320 mg, 11 at 640 mg, and 3 at 80 mg (de-escalated dose level). Eleven patients received three or more cycles of chemotherapy (range 3–14). Eight patients were dose escalated, and seven completed dose escalations through all three levels (160, 320, 640 mg). One patient was dropped from the study because of toxicity unacceptable to the patient which consisted of grade 2 vomiting. One patient's doses of FUDR/(S)-LV were de-escalated per protocol (to 2g/80 mg), and three patients remained at the 3 g/160 mg dose level due to grade 3 toxicities (for 2, 10 and 14 cycles), although all four of these patients remained in the study until disease progression occurred.

The median age of the patients was 59 years and the ages ranged from 41 to 76 years. The median initial Karnofsky Performance Status (KPS) was 90%. The primary sites of disease varied and included one unknown primary, two rectal, two small intestinal, four colon, and seven ovarian cancers. Of the 16 patients, 3 had ascites upon entry to the study, and 14 had been previously treated with chemotherapy. The patient characteristics are summarized in Table 1.

Toxicity

Toxicity was graded according to the Common Toxicity Criteria. All patients were evaluated for toxicity. Toxicity data are presented for the first three cycles only, when a full set of hematologic and toxicologic observations were available (Table 2). The side effects of therapy did not appear to be cumulative (data not shown). The most common toxicities were non-hematologic and all were grade 3 severity or less. Fatigue was experienced by 15 patients during the course of

Table 1 Patient characteristics

Patients entered	<i>n</i> = 16
Median age	59 years
Age range	41–76 years
Median initial KPS	90%
Range of initial KPS	60–90%
Female/male	12/4
Prior treatment	<i>n</i> = 14
Ascites	<i>n</i> = 3
Primary site	
Ovarian	<i>n</i> = 7
Colon	<i>n</i> = 4
Rectal	<i>n</i> = 2
Small intestine	<i>n</i> = 2
Unknown primary	<i>n</i> = 1

their treatment, and 12 of these 15 patients had fatigue of grade 2 severity or less. Most patients experienced mild nausea and vomiting. Three patients suffered grade 3 nausea and one patient had grade 3 vomiting. Either diarrhea or stomatitis occurred in 25% of the patients, but they were never more than moderate in character. One patient received (R,S)-LV in error on cycle 2 day 1 and had an episode of circumoral tingling and extremity paresthesias which cleared with antihistamine treatment. This reaction did not recur with subsequent (S)-LV treatments and was noted as an allergic response to the racemic LV. Mild abdominal discomfort associated with therapy was also common, but may have been related to distention and did not increase in severity with treatment. Two patients had grade 3 abdominal pain. Local extravasation occurred in one of these patients and the other patient experienced peritoneal bleeding on the second treatment day. Subsequently, this was followed by the formation of a sizable hematoma most likely within a pelvic tumor which had been partially resected 10 days earlier at the time of laparotomy and catheter insertion. Other catheter complications were not observed in this study.

Hematologic toxicity was uncommon in patients with normal pretreatment values. Anemia was not induced or worsened by IP FUDR and (S)-LV. Thrombocytopenia also did not occur. Four patients experienced grades 3/4 neutropenia. Three of the patients who suffered grade 4 neutropenia (all of whom had received carboplatin for ovarian cancer) had low granulocyte counts prior to beginning this IP therapy with baseline values of 1000, 1300, and 1800 cells/dl. The fourth patient had a normal baseline absolute granulocyte count (AGC) of 5000 cells/dl; he had a long history of ulcerative colitis and therapy had included azulfidine which may have played a role in his susceptibility to granulocytopenia [21, 22]. This patient was treated with a 33% reduction of FUDR in subsequent cycles without neutropenia. There were no episodes of neutropenic fever or sepsis. There were no of treatment-related deaths.

Table 2 The most severe grade of each type of toxicity encountered per patient during the first three cycles

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Fever	1	—	—	—
Fatigue	8	4	3	—
Abdominal pain	6	5	2	—
Nausea	6	5	3	—
Vomiting	4	5	1	—
Diarrhea	2	2	—	—
Stomatitis	2	2	—	—
Sensory	1	—	—	—
Neutropenia	—	—	1 ^a	3 ^b
Thrombocytopenia	—	—	—	—
Anemia	—	—	—	—
Allergic reaction	1 ^c	—	—	—

^aBaseline AGC 1500

^bBaseline AGCs 1000, 1300, 5000 (this last patient had ulcerative colitis on azulfidine)

^cPatient received (R,S)-LV IP in error

Pharmacokinetics

Pharmacokinetics were analyzed in 11 patients. Pharmacokinetic profiles were completed in only one patient for three escalating doses of (S)-LV. Profiles were obtained for two patients completing two escalating doses, and for three patients who received repeated doses of 160 mg of (S)-LV. A total of 18 sets of profiles were obtained of which 17 were evaluable.

Similar to prior results, peritoneal FUDR levels exhibited monophasic exponential profiles (in eight instances), but ten also had biexponential profiles [12]. The terminal half-lives were quite variable: the mean value was 3 h (range 1.9–5.0) (Table 3); this was slightly longer than the 2 h previously reported. This difference in terminal half-lives may be attributed to longer time points in the present study (24 h vs 4 h in the previous study). One patient exhibited an unusually long terminal half-life of 22.4 h and was not included in this calculation. The mean peritoneal clearance of FUDR was 14.9 ± 9.2 ml/min (SD), also lower than the mean value of 25 ml/min reported previously. The $t_{1/2}$ and peritoneal clearance of FUDR did not appear to be influenced by the (S)-LV dose: the peritoneal clearances were 13.7, 18.0, and 13.4 ml/min with (S)-LV doses of 160, 320, and 640 mg, respectively. The pharmacologic advantage, R, was quite variable and had a mean value of 997.3 ± 998.8 . This value remained rather large, though again, smaller than the previously reported value of 2700. Longer term monitoring of the drug levels used in this study is likely to provide a more accurate assessment of these pharmacokinetic parameters. This is unlikely to be due to the concomitant administration of (S)-LV.

The peritoneal (S)-LV profiles also showed mixed mono- (in ten) and biexponential decline (in seven). The mean terminal half-life was 5.2 h (range 2.6–13.1 h). The mean $t_{1/2}$ did not vary with increasing dose (Table 3) and no apparent dose-dependent kinetics were detected at these dose ranges. The mean peritoneal clearance values were 4.6, 7.7, 4.6 ml/min for 160, 320, 640 mg

total doses, respectively. The overall mean value was 5.4 ± 2.5 ml/min. Thus, the peritoneal clearance remained unchanged with dose changes and was significantly smaller than FUDR values. The pharmacologic advantage of (S)-LV was also significantly smaller than that of FUDR with a mean R value of 38.5 ± 26.2 . One profile had a very divergent R value of 216 and was not included in the calculation. Also, no apparent change in the pharmacologic advantage was detected with changes in dose. The 5-methyl metabolite was not detected in the peritoneal fluid or plasma.

Therapeutic outcome

In patients with ovarian cancer, CA125 decreased in three, and ascites decreased in another during the study treatment. Prolonged survival was experienced by five of these patients with ovarian cancer, all of whom received subsequent paclitaxel (Table 4). One of these patients was changed to paclitaxel after achieving stable pleural disease and a decrease in CA-125. She had a subsequent laparotomy for volvulus. No IP disease was noted at laparotomy, whereas her pleural disease was still present during paclitaxel therapy. Patient number 5 with resected residual disease at laparotomy had no abnormalities while in the study and maintained no evidence of disease for 15 months before manifesting an increase in CA-125. Only one patient progressed during the study treatment: she sustained an IP bleed during her first treatment after excision of a pelvic tumor and succumbed due to disease progression 2 months later.

In patients with gastrointestinal or other cancers, serum CEA and ascites decreased in one patient each during therapy. Two other patients receiving multiple cycles were stable for 9 and 11 months. Four patients experienced progression in extraperitoneal sites after receiving one, one, three, and three cycles of FUDR/(S)-LV. Particularly rapid progression was noted in patients with jejunal and duodenal primaries. One patient

Table 3 Relevant pharmacokinetic parameters of FUDR and (S)-LV in peritoneal fluid. The FUDR dose was 3000 mg IP with the various indicated doses of (S)-LV. The values are means with range or standard deviations

	FUDR				(S)-LV			
	All	160 mg(S)-LV	320 mg(S)-LV	640 mg(S)-LV	All	160 mg	320 mg	640 mg
$t_{1/2}$ (h)	3.0 ^a	3.3 ^b	2.4	2.4	5.2 ^a	5.3 ^c	4.2	5.5
Range	1.9–5.0	2.5–5.0	2.0–2.7	1.9–3.3	2.6–13.1	2.6–13.1	3.9–4.4	2.6–4.7
AUC ($\mu\text{g/ml}\cdot\text{h}$)	4451	4723	2454	5204	–	711	712 ^c	3581
SD	2405	2091	551	3603	–	318	286	3314
CL _{PF} (ml/min)	14.9	13.7	18.0	13.4 ^d	5.4 ^a	4.6	7.7	4.6
SD	9.2	10	5.5	8.3	2.5	2.7	1.7	2.5
R-value	997.3 ^e	–	–	–	38.5 ^f	44.5 ^b	19.0	33.4
SD	998.8	–	–	–	26.2	25.9	18.4	29.8
Maximum no. of profiles	18	11	3	4	18	11	3	4

^a17 evaluable profiles^b10 evaluable profiles^c2 evaluable profiles^d3 evaluable profiles^e16 evaluable profiles^f15 evaluable profiles**Table 4** Evidence of antitumor effects during IP FUDR/(S)-LV treatment

Patient	Age/sex	Primary site	Prior chemotherapy	No. of cycles	Best response
1 BK	54/F	Ovarian	Y	2	Stable disease, started paclitaxel
2 EB	43/F	Ovarian	Y	4	CA125 decreased, started paclitaxel
3 LD	59/F	Ovarian	Y	3	CA 125 decreased, started paclitaxel
4 RN	65/F	Ovarian	Y	3	Stable disease, started paclitaxel
5 MF	62/F	Ovarian	Y	4	CA125 decreased started paclitaxel
6 MW	68/F	Ovarian	Y	3	No evidence of disease 15 months
7 CB	41/M	Colon	N	10	Stable disease 11 months
8 SP	59/F	Colon	Y	6	Stable disease + CEA decrease 8 months
9 LY	53/F	Recto-sigmoid	Y	14	Stable disease 9 months
10 HY	67/F	Appendix	Y	6	Stable disease + ascites decreased 4 months

with an unknown primary experienced progression in the peritoneum.

Of the 16 patients, 7 were alive at follow-up of 2–32 months (median 18 months). Three patients were alive with abnormal markers only at 19, 25 and 29 months of follow-up, respectively. Nine patients died at a median of 11 months (range 2–32 months).

Discussion

Clinical results

The results of this study extend the observations made during our prior studies of FUDR alone and in

combination with (*R,S*)-LV. The toxicity profile of IP FUDR at a dose of 3000 mg daily for 3 days has been well delineated previously and indicates only the occurrence of myelosuppressive and gastrointestinal toxicities typical of fluoropyrimidines. These toxicities were severe in 10–20% of patients, but have been uncomplicated. An abnormal bone marrow reserve was clearly implicated in the grade 3 or 4 neutropenia encountered in three of the four patients so afflicted in the current study. The contributions of (*S*)-LV, or the (*R,S*)-LV in the prior study, to toxicity are not discernible [18].

Pharmacologic profiles

The pharmacologic findings were also consistent with prior observations. IP/plasma FUDR ratios exhibited marked interpatient variability, but always approached three logs. On the other hand, similar values for (*S*)-LV were lower, but still showed interpatient variability. Inpatient changes in pharmacokinetics also were observed in some patients. The (*S*)-LV pharmacokinetic profiles in the peritoneal cavity paralleled those of FUDR. These serial changes in clearance undoubtedly indicate a change in the peritoneal permeability rather than a drug interaction. Sugarbaker et al. have similarly suggested such a change in pharmacology between days 1 and 5 in studies with IP FU given in a 5-day daily IP schedule [23].

In conclusion, pharmacokinetic profiles indicate achievement of high IP concentrations of FUDR and also appreciable levels of FU that may contribute to the antitumor effects against peritoneal tumors. An augmentation of antitumor effects by LV modulation is conjectural. IP FUDR at millimolar concentrations probably does not require such modulation for optimal cytotoxicity. Nevertheless, some potentiation could occur at other sites where drug concentrations may be lower [17].

The (*S*)-LV pharmacologic parameters may be compared to the (*R,S*)-LV parameters at the 160-mg dose level; too few patients were entered at the 320 mg or 640 mg levels for a similar comparison. The AUC ratios of peritoneal fluid to plasma (pharmacologic advantage) in 11 patients was much greater for (*S*)-LV (44.5) than for (*R,S*)-LV in the preceding study (10.6). The peritoneal clearance for (*R,S*)-LV in the preceding study was faster than that of (*S*)-LV in the current study, even though the $T_{1/2}$ values were not so different.

The slower mean peritoneal clearance of (*S*)-LV may be explained by later time points obtained in the current study. The pharmacologic advantage of (*S*)-LV may be explained, in part, by the metabolism of (*S*)-LV. The (*S*)-LV alone and the (*S*)-LV component of the racemic mixture is cleared faster from the plasma resulting in lower circulating LV levels when (*S*)-LV is

administered. Also, the additional time points yielding a slower peritoneal clearance for (*S*)-LV magnify the ratio. Finally, plasma levels are proportionately higher than the peritoneal LV levels for (*R,S*)-LV relative to (*S*)-LV. This combination of factors results in a net higher pharmacologic advantage following (*S*)-LV administration compared to (*R,S*)-LV.

Antitumor effects

Antitumor effects in this patient population must be confined to changes in markers or control of ascites. Lack of progression in some circumstances also lends some encouragement for exploration of FUDR alone or with LV as part of the treatment strategy for malignancies that commonly spread within the peritoneal cavity.

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