

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/231862812>

# Levoleucovorin as Replacement for Leucovorin in Cancer Treatment

Article in *Annals of Pharmacotherapy* · October 2012

DOI: 10.1345/aph.1Q677 · Source: PubMed

---

CITATIONS

5

READS

1,783

2 authors, including:



**Victor Chuang**

Monash University (Malaysia), Bandar Sunway, Malaysia

75 PUBLICATIONS 2,063 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



Photoaffinity labeling of human serum albumin [View project](#)



Albumin binding [View project](#)

## Levoleucovorin as Replacement for Leucovorin in Cancer Treatment

Victor Tuan Giam Chuang and Manabu Suno

Levoleucovorin is the pharmacologically active levoisomer of racemic leucovorin, or folinic acid, a synthetic folate analogue. Levoleucovorin (Fuxilev; Spectrum Pharmaceutical) is available as a ready-to-use solution in 175-mg and 250-mg vials and as a freeze-dried powder in 50-mg vials.<sup>1</sup>

Levoleucovorin was approved by the Food and Drug Administration (FDA) for use as a rescue agent after high-dose methotrexate therapy in treating osteosarcoma to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of the inadvertent overdosage of folic acid antagonists, and in combination with fluorouracil for the palliative treatment of patients with advanced metastatic colorectal cancer.

To date, few reports on the pharmacology, adverse effects, and drug interactions of the biological active levoleucovorin have been published. This could be because levoleucovorin has been shown to be the biologically active isomer; hence, information gathered for leucovorin so far reflects, to a great extent, the properties of levoleucovorin. This notion can be supported by the fact that the d-isomer has been reported to be essentially devoid of pharmacologic activity. Furthermore, although d-levoleucovorin ex-

**OBJECTIVE:** To comprehensively review the literature regarding the efficacy, safety, and costs associated with the use of levoleucovorin in cancer treatment and to assess whether levoleucovorin would be a reasonable alternative to the use of racemic leucovorin.

**DATA SOURCES:** A MEDLINE search was conducted for English-language human studies published between January 1980 and April 2012 using the terms l-LV, levoleucovorin, d,l-LV, leucovorin, folinic acid, folinate, 5-formyltetrahydrofolate, folic acid, folates, methotrexate, 5-fluorouracil, and clinical trials.

**STUDY SELECTION AND DATA EXTRACTION:** Articles pertinent to clinical trials (Phase 1, 2, 3) related to evaluating the efficacy, interchangeability, and safety of levoleucovorin were collected and their contents reviewed.

**DATA SYNTHESIS:** From these pharmacokinetics and clinical studies, information on the use of levoleucovorin as a modulator of fluorouracil as well as when combined with other antitumor agents were scrutinized and extracted for comparison with leucovorin whenever possible. Two randomized Phase 3 clinical studies comparing the efficacy and adverse effect profiles of leucovorin and levoleucovorin demonstrated that levoleucovorin is as effective as leucovorin in terms of response, toxicity, and survival. Six randomized Phase 3 clinical studies demonstrated the safety and efficacy of levoleucovorin as a modulator of fluorouracil in combination with/without other antitumor agents in colorectal cancer patients. Levoleucovorin has been studied in other cancers. These clinical Phase 1/2/3 studies demonstrated efficacy and safety of levoleucovorin in combination chemotherapeutic regimens comprising fluorouracil and other antitumor agents.

**CONCLUSIONS:** The results of the clinical studies suggest that levoleucovorin is efficacious and can be used safely in combination with fluorouracil and other antitumor agents. Levoleucovorin can be used interchangeably with leucovorin for modulating fluorouracil. The current shortage of the supply of leucovorin centered in North America renders levoleucovorin a reasonable alternative in terms of efficacy and toxicity profile, but from the perspective of cost, leucovorin remains the drug of choice.

**KEY WORDS:** colorectal cancer, fluorouracil, levoleucovorin, leucovorin, methotrexate.

*Ann Pharmacother* 2012;46:1349-57.

Published Online, 2 Oct 2012, *theannals.com*, doi: 10.1345/aph.1Q677

Author information provided at end of text.

hibits different pharmacokinetic properties, it does not appear to affect the pharmacokinetics of levoleucovorin.

This article reviews the English-language literature regarding the use of levoleucovorin to determine whether levoleucovorin is interchangeable with leucovorin in cancer treatment.

## Pharmacology

Folic acid is an essential cofactor for certain enzymes that are involved in the synthesis of purine, thymidine, and methionine.<sup>2</sup> Folates are transported into cells in the form of monoglutamate derivatives and function as a cofactor in 1-carbon transfer reactions. Each 1-carbon form of folate is a required cofactor for 1 or more biosynthetic pathways. To accomplish this, folate must first be reduced by dihydrofolate reductase (DHFR) into the functional metabolic cofactors, dihydrofolate (DHF) and tetrahydrofolate (THF). THF polyglutamates participate in 1-carbon metabolism, where a carbon unit from serine, choline, or glycine is transferred to THF to form methylene-THF, which is either involved in the synthesis of thymidine, which is then incorporated into DNA, oxidized to formyl-THF for the synthesis of purines, or reduced to methyl-THF to form methionine. 5-Formyl-THF (folinic acid, citrovorum factor, leucovorin) is more stable than folate. It does not serve as a metabolic cofactor but may be a storage form of folate.

### HIGH-DOSE METHOTREXATE THERAPY

Methotrexate, an antifolate agent, inhibits DHFR and also directly inhibits folate-dependent enzymes that are involved in de novo purine and thymidylate synthesis.<sup>3</sup> In the synthesis of thymidylate, 5,10-methylene-THF is oxidized to DHF. DHF must then be reduced to THF by DHFR to regain its function as a cofactor. Methotrexate prevents the formation of THF through high-affinity binding to DHFR, producing an acute intracellular deficiency of certain folate coenzymes and a vast accumulation of the toxic inhibitory substrate, DHF polyglutamates, as the result of the inhibition of DHFR.<sup>4</sup> This termination of 1-carbon transfer reactions is crucial for the de novo synthesis of purine nucleotides and thymidylate, resulting in the subsequent interruption of the synthesis of DNA and RNA and other vital metabolic reactions.

The toxic effect of methotrexate can be alleviated by leucovorin. Leucovorin antagonises the activity of methotrexate by several mechanisms. It competes with methotrexate for entry into the cell and for folylpolyglutamate synthetase and DHFR enzymes, leading to a reduction in the concentrations of methotrexate polyglutamates and a diminished inhibition of DHFR. Leucovorin does not require reduction by DHFR to participate in reactions in which folates are used as a source of 1-carbon moieties.

Moreover, leucovorin is rapidly converted to other reduced folates, thereby restoring the pool of reduced folates. The dextro isomer of leucovorin has been reported to be incapable of reversing the toxicity of methotrexate or potentiating the effect of fluorouracil.<sup>5</sup> On the other hand, levoleucovorin has been shown to be as effective as leucovorin for use as a rescue agent after the administration of high doses of methotrexate in the treatment of osteosarcoma.<sup>5-7</sup> Therefore, levoleucovorin is useful as an antidote to the inhibition of DHFR caused by high doses of methotrexate.

### IN COMBINATION WITH FLUOROURACIL

Fluorouracil, a pyrimidine analogue, is metabolized to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which binds to and inhibits thymidylate synthase, an important enzyme in DNA repair and replication. The smaller fluorine group at position 5 of fluorouracil allows the molecule to mimic uracil biochemically, but the fluorine-carbon bond is much stronger than that of C-H and prevents the methylation of the 5 position of fluorouracil by thymidylate synthase. In the presence of the physiologic cofactor 5,10-methylene-THF, fluoropyrimidine locks the enzyme in an inhibited state.<sup>8</sup>

The cytotoxic contribution by levoleucovorin is derived from its ability to potentiate the action of fluorouracil.<sup>9,10</sup> Levoleucovorin is readily converted into 5,10-methylene-THF. This reduced folate acts to stabilize the binding of FdUMP, the active metabolite of fluorouracil, to thymidylate synthase. This stabilization further enhances the inhibition of this enzyme, which is important in DNA repair and replication. For this reason, clinical outcomes in terms of antitumor activity, safety, and the tolerability profiles of fluorouracil are believed to be derived more directly from the cytotoxic agents used rather than the direct action of levoleucovorin on tumors.

### Pharmacodynamics and Pharmacokinetics

Intravenous administration of a 25-mg bolus dose or a 15-minute infusion of 300 mg/day of leucovorin showed that levoleucovorin was rapidly cleared from the plasma by conversion to 5-methyl-THF and urinary excretion that can be described by a biexponential function. The urinary clearance of levoleucovorin or 5-methyl-THF differed only slightly from that for creatinine.<sup>11,12</sup> Furthermore, the constant intravenous infusion of large doses of leucovorin 500 mg/m<sup>2</sup> daily for 5.5 days considerably expands the intracellular pools of active folate.<sup>13,14</sup> The mechanisms for the distribution, metabolism, and excretion of leucovorin are not saturable over the dose range of 25-100 mg. However, the conversion of levoleucovorin to 5-methyl-THF was saturable following a 2-hour intravenous infusion of leucovorin 1000 mg, producing equivalent areas under the

curve for levoleucovorin and 5-methyl-THF.<sup>15,16</sup> In contrast, d-levoleucovorin, which is not metabolized and is slowly excreted into the urine, persisted in plasma at concentrations greatly exceeding those of levoleucovorin and 5-methyl-THF.<sup>7,15,17</sup> The low renal clearance of d-levoleucovorin can be attributed to the extensive stereoselective binding of d-levoleucovorin to plasma proteins, particularly human serum albumin.<sup>14,17</sup> This discrepancy in protein binding may influence the biochemical modulation of fluorouracil by THFs because hypoalbuminemia is common in patients with advanced colorectal cancer.<sup>18</sup>

Mader et al.<sup>19</sup> reported 2 significant differences in the kinetics of levoleucovorin when the single isomer was administered via a 2-hour intravenous infusion of levoleucovorin 200 mg/m<sup>2</sup> with a loading dose of levoleucovorin 100 mg/m<sup>2</sup>. The maximum concentration and area under the curve of the 5-methyl-THF were greater than those observed after an intravenous infusion of leucovorin 400 mg/m<sup>2</sup> with a leucovorin loading dose of 200 mg/m<sup>2</sup>. Zitoun reported similar observations and concluded that the use of levoleucovorin may prevent the interference of the inactive isomer, especially in patients receiving high doses of leucovorin.<sup>5</sup>

## Clinical Studies

### INTERCHANGEABILITY OF LEUCOVORIN WITH LEVOLEUCOVORIN AS A MODULATOR OF FLUOROURACIL

The North Central Cancer Treatment Group (Goldberg et al.) carried out a randomized Phase 3 trial involving patients with advanced colorectal cancer in which the efficacy of different forms of leucovorin was examined.<sup>20</sup> This study had 3 arms combining fluorouracil with levoleucovorin, oral leucovorin, or intravenous leucovorin: A (fluorouracil 370 mg/m<sup>2</sup> and levoleucovorin 100 mg/m<sup>2</sup>), B (fluorouracil 370 mg/m<sup>2</sup> and oral leucovorin 125 mg/m<sup>2</sup>), and C (control, fluorouracil 370 mg/m<sup>2</sup> and after an intravenous dose of leucovorin 200 mg/m<sup>2</sup>). Only data related to arms A and arm C were discussed in our article. The

most frequent adverse events are listed in Table 1. The adverse events, response, survival, and time to progression were comparable between the 2 arms. Therefore, the available data indicate that levoleucovorin is as effective as leucovorin in terms of response, toxicity, and survival.

Scheithauer et al. published a randomized Phase 3 trial in which the efficacy and adverse effect profile of fluorouracil used with either leucovorin or with levoleucovorin in patients with advanced colorectal cancer were compared.<sup>21</sup> The clinical trial involved treatment with a bolus injection of levoleucovorin or leucovorin at a dose of 100 mg/m<sup>2</sup> per day, followed by fluorouracil for 5 consecutive days. The dose of leucovorin was the same with both formulations. Thus, patients in the levoleucovorin arm received double the effective dose of leucovorin. The authors found that the 2 arms were not significantly different in terms of efficacy in the leucovorin versus levoleucovorin arms. In addition, no significant difference was found in the 2 arms in terms of patient adherence to chemotherapy and the relative dose intensity of levoleucovorin. However, the incidence of adverse effects was similar in both arms. As such, the 2 randomized studies indicate that levoleucovorin is as effective as leucovorin in terms of response, toxicity, and survival.

### SAFETY AND EFFICACY OF LEVOLEUCOVORIN

Levoleucovorin used in trials as a modulator of fluorouracil in combination chemotherapy with/without other antitumor agents are listed in Table 2.<sup>22-28</sup> In these studies, levoleucovorin was used interchangeably with leucovorin. However, no subset analysis was performed to assess whether there was any difference in efficacy and grade 3 or 4 toxicity profiles in patients who received levoleucovorin or leucovorin.

Phase 3 studies on the use of levoleucovorin as a modulator of fluorouracil in combination with irinotecan, raltitrexed, methotrexate, and oxaliplatin<sup>22-28</sup> demonstrated that the maximal benefit of irinotecan plus levoleucovorin-modulated fluorouracil can be obtained in patients with no weight loss, preserved performance status, and a limited

**Table 1.** Adverse Events Reported with Levoleucovorin and d,l-Leucovorin

Adverse Event	Levoleucovorin/Fluorouracil, n (%) (n = 318)		d,l-Leucovorin/Fluorouracil, n (%) (n = 307)	
	Grade 1-4	Grades 3, 4	Grade 1-4	Grades 3, 4
Stomatitis	229 (72)	37 (12)	221 (72)	44 (14)
Diarrhea	222 (70)	61 (19)	201 (65)	51 (17)
Nausea and vomiting	197 (62)	25 (8)	186 (61)	26 (8)
Abdominal pain	45 (14)	10 (3)	57 (19)	10 (3)
Anorexia/decreased appetite	76 (24)	13 (4)	77 (25)	5 (2)
Dermatitis	91 (29)	3 (1)	86 (28)	4 (1)
Alopecia	83 (26)	1 (0.3)	87 (28)	3 (1)

**Table 2.** Use of Levoleucovorin in Combination Chemotherapeutic Regimens for Colorectal Cancer

Reference	Cancer Type, (no. of Pts.)	Design	Regimen	Results
Andre (2003) <sup>22</sup>	Colon and high rectum adenocarcinoma, N = 905	Randomized Phase 3	Leucovorin/fluorouracil 2: Levoleucovorin 100 mg/m <sup>2</sup> (d,1-LV 200 mg/m <sup>2</sup> ) iv 2-hour infusion followed by fluorouracil iv bolus 400 mg/m <sup>2</sup> and 22-hour iv infusion of 600 mg/m <sup>2</sup> (repeated every 14 days) FUFOL: Levoleucovorin 100 mg/m <sup>2</sup> (leucovorin 200 mg/m <sup>2</sup> ) 15-minute infusion followed by fluorouracil 400 mg/m <sup>2</sup> infusion, repeated daily for 5 days (repeated every 28 days)	OS: not significant ( at 41 months of follow-up) Grade 3/4 toxicities: mucositis, neutropenia, and diarrhea seen less with leucovorin/ fluorouracil (p < 0.001)
Comella (2000, 2002) <sup>23,24</sup>	Advanced colorectal carcinoma (159)	Randomized Phase 2/3	Arm A day 1: irinotecan 100 mg/m <sup>2</sup> day 2: levoleucovorin 250 mg/m <sup>2</sup> and fluorouracil 850 mg/m <sup>2</sup> bolus Arm B day1: raltitrexed 3 mg/m <sup>2</sup> day 2: levoleucovorin 250 mg/m <sup>2</sup> and fluorouracil 1050 mg/m <sup>2</sup> bolus Arm C day 1: methotrexate 750 mg/m <sup>2</sup> day 2: levoleucovorin 250 mg/m <sup>2</sup> and fluorouracil 800 mg/m <sup>2</sup> bolus	ORR: Arm A: 34%, Arm B: 24%, Arm C: 24% Grade 3/4 toxicities: Arm A: neutropenia: 46%; diarrhea: 16% Arm B: neutropenia: 16%; diarrhea: 16%
Comella (2005) <sup>25</sup>	Advanced colorectal carcinoma (274)	Randomized Phase 3	(IRIFAFU) day 1: irinotecan 200 mg/m <sup>2</sup> day 2: levoleucovorin 250 mg/m <sup>2</sup> and fluorouracil 850 mg/m <sup>2</sup> bolus (OXAFAFU): day 1: oxaliplatin 100 mg/m <sup>2</sup> day 2: levoleucovorin 250 mg/m <sup>2</sup> and fluorouracil 1050 mg/m <sup>2</sup> bolus	ORR: (p = 0.029): IRIFAFU: 31%, OXAFAFU: 44% Grade 3/4 toxicities: IRIFAFU: neutropenia: 31%; diarrhea: 24% OXAFAFU: neutropenia: 29%; diarrhea: 12%
Douillard (2000) <sup>26</sup>	Metastatic colorectal cancer (387)	Randomized Phase 3	Irinotecan: Irinotecan/fluorouracil/calcium folinate No irinotecan: fluorouracil/calcium folinate	RR: Irinotecan: 49%, no irinotecan: 31% OS: Irinotecan: 17.4 months, no irinotecan: 14.1 months Grade 3/4 toxicities: significantly more frequent with irinotecan; effects were predictable, reversible, noncumulative, manageable
Tournigand (2004) <sup>27</sup>	Metastatic colorectal cancer (220)	Randomized Phase 3 (FOLFIRI followed by FOLFOX6 or the reverse sequence)	Arm A FOLFIRI (oxaliplatin replaced irinotecan at progression) Arm B FOLFOX6 (irinotecan replaced at progression)	RR: First-line: Arm A: 56%; Arm B: 54% Second-line: Arm A: 15%; Arm B: 4% Grades 3/4 toxicity: First-line: Arm A: neutropenia: 21.8%; diarrhea: 12.7%; mucositis: 9% Arm B: neutropenia: 40%; diarrhea: 10%; mucositis: 1% (p = 0.26) Second-line: Similar (mainly neutropenia and diarrhea) Neurological event significantly more frequent in the FOLFOX6
Labianca (2011) <sup>28</sup>	Advanced colorectal carcinoma (337)	Randomized Phase 3	Arm A FOLFIRI (administered every 2 weeks; 2 months on and 2 months off) Arm B FOLFIRI (administered continuously)	OS: Arm A: 18 months, Arm B: 17 months Grades 3/4 toxicity: Similar (mainly myelosuppression, fever and diarrhea)

d,1-LV = d,1-leucovorin; FOLFIRI = fluorouracil/leucovorin/irinotecan; FOLFOX = fluorouracil/ leucovorin/oxaliplatin; FUFOL = fluorouracil/leucovorin or levoleucovorin; IRIFAFU = irinotecan/levoleucovorin/fluorouracil; ORR = overall response rate; OS = overall survival; OXAFAFU = oxaliplatin/levoleucovorin/fluorouracil; RR = response rate.



extent of the disease. This regimen was tolerated well and was found to be efficacious in the elderly.<sup>24</sup>

The efficacy and safety of levoleucovorin in high-dose methotrexate with leucovorin rescue regimens were investigated in a group of 15 patients with osteosarcoma. Adverse effects were mild and myelosuppression was not severe. These results support the conclusion that levoleucovorin effectively rescues patients from the toxicity of high-doses of methotrexate.<sup>29</sup> Similar results and conclusions were reported on the use of levoleucovorin in rescue of high-dose methotrexate therapy in 14 children with acute lymphocytic leukemia.<sup>30</sup> For levoleucovorin or leucovorin rescue, the elimination half-life of methotrexate was similar, 13.9 hours. No significant differences in adverse events such as granulocytes, platelets, transaminase levels, serum creatinine levels, and oral mucositis, were found following levoleucovorin or leucovorin rescue.

From these clinical studies, the use of levoleucovorin as a biochemical modulator of fluorouracil or in high-dose methotrexate therapy rescue demonstrate that levoleucovorin is as efficacious as leucovorin and that no clear increase in the percentage of grade 3 or 4 toxicity profiles when patients were given levoleucovorin.

#### USE OF LEVOLEUCOVORIN IN OTHER TUMOR CHEMOTHERAPY

In addition to being used in the treatment of colorectal carcinomas, levoleucovorin has been evaluated for use in the treatment of other types of cancer, including head and neck, breast, pancreas, gastric, and neuroendocrine cancers in Phase 1, pharmacokinetic, and Phase 2 clinical trials. These studies are summarized in Table 3.<sup>31-34</sup> The doses of levoleucovorin used in these studies ranged from 100 mg/m<sup>2</sup> to 250 mg/m<sup>2</sup> and were administered in combination with cisplatin and fluorouracil/methotrexate, respec-

tively. The Phase 2 trials showed modest response rates in their tumor types.<sup>31,33,34</sup> The Phase 1 clinical trial reported acceptable tolerability of 250 mg/m<sup>2</sup> of levoleucovorin, with maximum doses of 1050 mg/m<sup>2</sup> with starting doses of 660 mg/m<sup>2</sup> as a bolus dose of fluorouracil and 3 mg/m<sup>2</sup> of raltitrexed.<sup>31</sup> Thus, with promising results from these early trials, to evaluate the role of levoleucovorin in the chemotherapy regimens for these cancers, randomized Phase 3 trials are necessary

#### Adverse Effects

Reactions to leucovorin appear to be rare. A few cases of leucovorin hypersensitivity reactions have been reported, including a rash during the first treatment course, hypotension and a rash during the second course, urticaria and difficulty in breathing, flushing, hives, body pain, headaches, elevated blood pressures, and general discomfort during the second course<sup>35</sup> (Table 1). Patients receiving levoleucovorin as a rescue agent after high-dose methotrexate therapy have experienced vomiting (38%), stomatitis (38%), and nausea (19%). Diarrhea, nausea, and stomatitis were the most common (>50%) adverse reactions in patients with advanced colorectal cancer receiving levoleucovorin in combination with fluorouracil.<sup>1</sup>

Because of the calcium content of the preparation, no more than 16 mL (160 mg) of levoleucovorin solution should be injected intravenously per minute. Rapid administration of calcium may produce arrhythmia, hypotension, myocardial infarction, and vasodilation. In addition, fluorouracil and levoleucovorin should be administered separately to avoid the formation of a precipitate.<sup>36</sup> Hence, levoleucovorin should not be administered with other therapeutic agents in the same intravenous admixture.

As shown in Table 1, there were no significant differences between levoleucovorin and leucovorin with respect to adverse events.<sup>20</sup>

**Table 3.** Use of Levoleucovorin in Treating Other Tumor Subtypes

Reference	Tumor type (no. of pts.)	Phase	Treatment	Results
Caponigro (1999) <sup>31</sup>	Advanced head and neck cancer (17)	PK, 1	Day 1: raltitrexed Day 2: levoleucovorin 250 mg/m <sup>2</sup> and escalating bolus of fluorouracil 600 mg/m <sup>2</sup>	ORR: 35%, well tolerated
Bajetta (1998) <sup>32</sup>	Advanced breast cancer (73, elderly)	2	Doxifluridine 600 mg/m <sup>2</sup> orally twice daily and levoleucovorin 25 mg every 12 hours for 4 consecutive days every 12 days	RR: 26%, well tolerated
Comella (1996) <sup>33</sup>	Stomach, colorectal, and biliary tract cancers (94)	2	Day 1: methotrexate 500 mg/m <sup>2</sup> 2-hour infusion followed by levoleucovorin 250 mg/m <sup>2</sup> 2-hour infusion Day 2: fluorouracil 600 mg/m <sup>2</sup> iv bolus, repeated every 2 weeks	RR: 30% in chemotherapy-naïve pts.
Artale (2005) <sup>34</sup>	Neuroendocrine (8)	2	Cisplatin 45 mg/m <sup>2</sup> , levoleucovorin 100 mg/m <sup>2</sup> over 2 hours and fluorouracil 400 mg/m <sup>2</sup> bolus followed by 600 mg/m <sup>2</sup> over 22 hours, repeated every 14 days	3 PRs

ORR = overall response rate; PK = pharmacokinetic; PR = partial response; RR = response rate.

## Drug Interactions

Leucovorin has been reported to decrease the efficacy of phenytoin, possibly by reducing the plasma concentration of phenytoin,<sup>37,38</sup> although leucovorin may be effective in treating neonatal seizures.<sup>39</sup> Other antiepileptic drugs that have been reported to be affected by leucovorin include phenobarbital and primidone, where the frequency of seizures increased in susceptible patients.<sup>1</sup> Leucovorin has been reported to potentially interact with trimethoprim-sulfamethoxazole, causing therapeutic failure of the latter in HIV patients with *Pneumocystis jiroveci* pneumonia.<sup>40</sup>

A markedly increased toxicity has been reported when capecitabine, a prodrug of fluorouracil developed for oral administration, was administered after fluorouracil/leucovorin treatment. This is believed to be caused by intracellular folate that is retained after fluorouracil/leucovorin therapy, although the exact mechanism for this is not clear. Leucovorin is known to lower the maximum tolerated dose of fluoropyrimidines, hence making patients more vulnerable to the subsequent fluoropyrimidine regimens with even low-level folate supplementation. Care should be taken when converting therapy from fluorouracil/leucovorin to capecitabine-based regimens.<sup>41</sup> It is not clear to what extent a weekly bolus dose of leucovorin increases folate pools in patients, but it is interesting that such tolerability of fluoropyrimidines shows regional differences. The highest rates of toxicity observed have been reported in the US, possibly resulting from ethnic variation in gene polymorphisms and differences in dietary folic acid intake because of the mandatory fortification of cereal grain products with folic acid to prevent neural tube birth defects, has been in force in the US since 1998.<sup>42</sup> At present, recommendations for a safe washout period or dose reduction for patients switching from fluorouracil/leucovorin to capecitabine are still inconclusive.

Alkalinization of urine and leucovorin administration are implicated in the clinical management of high-dose methotrexate-induced renal dysfunction. Glucarpidase (carboxypeptidase G2) has been reported to be highly effective in rapid and sustained reduction of high concentrations of methotrexate as a result of impaired renal function.<sup>43-45</sup> Glucarpidase is used when unexpected toxicity or renal failure occurs during high-dose methotrexate therapy.<sup>46</sup> The results of an in vitro study suggest that the protective effects of leucovorin can potentially be antagonized by glucarpidase if the drugs are used concurrently.<sup>47</sup> Since leucovorin is a substrate for glucarpidase, the FDA has recommended that leucovorin should not be administered within 2 hours before or after a dose of glucarpidase.<sup>46</sup> A later study reported the beneficial effects of using the combination of glucarpidase and leucovorin in high-dose methotrexate-induced renal dysfunction.<sup>43</sup> However, a similar effect could be achieved with a high dose of leucovorin alone.<sup>48</sup>

Leucovorin has the potential for use as a rescue agent in a few patients treated with raltitrexed, an antifolate thymidylate synthase inhibitor that is not available as a treatment choice in the US, who present a severe pattern of antiproliferative toxicities. Leucovorin competes with raltitrexed for transport and polyglutamation in both tumor and normal tissues, inhibiting further drug uptake and polyglutamation and resulting in the redistribution and/or reduction in the concentration of preformed raltitrexed polyglutamates. The use of leucovorin is not recommended routinely because the antitumor activity of raltitrexed may similarly be reversed.<sup>49</sup>

## Dosing and Cost of Levoleucovorin Versus Leucovorin

The d-isomer of leucovorin has no biological activity. Preclinical studies have shown that the d-isomer might compete with the l-isomer for transport into cells.<sup>21,50</sup> Furthermore, the d-isomer is an inhibitor for polyglutamate synthetase, which might cause deleterious effects on the modulation of fluorouracil.<sup>5,21</sup> These reasons provide a scientific rationale for using levoleucovorin, which is devoid of the “unnatural” d-isomer. Ultimately, the sole modification made when using levoleucovorin instead of the racemic form is to administer only half of the dose of the racemic formulation.<sup>7</sup> The dose for levoleucovorin is 50% of the usual dose of leucovorin. For example, 200 mg/m<sup>2</sup> of levoleucovorin, which is equivalent to 400 mg/m<sup>2</sup> of leucovorin, is administered in the FOLFOX6 or FOLFIRI regimen in colorectal cancer. In the widely used FOLFOX6 and FOLFIRI regimens, a patient receives about 400 mg of levoleucovorin, which is equivalent to 800 mg of leucovorin. In Japan, approximately \$800 for levoleucovorin and \$15 for leucovorin are needed for 1 treatment course of FOLFOX6 and FOLFIRI. This higher cost for treatment courses using levoleucovorin could be because the generic product for levoleucovorin is not available. While there are generic products of leucovorin in the market, none is available for levoleucovorin because the therapeutic composition patent for levoleucovorin will not expire until December 2019.<sup>51</sup>

## Discussion

Clinical outcomes with levoleucovorin modulation of fluorouracil are reasonably believed to be derived from the cytotoxic agents themselves, both in terms of antitumor efficacy and adverse event profiles. Goldberg et al. demonstrated that levoleucovorin and leucovorin are equivalent, and one direct clinical pharmacokinetic comparison of levoleucovorin and leucovorin showed no difference in pharmacokinetic parameters.<sup>20</sup>

In our literature review of these studies incorporating levoleucovorin, some European studies used levoleucovorin or leucovorin according to institutional practice, but several others used levoleucovorin exclusively. While

there were studies that included levoleucovorin or leucovorin with fluorouracil only, subsequent studies found favorable efficacy results with additional chemotherapeutic agents, mostly irinotecan and oxaliplatin, but also with the expected hematologic and nonhematologic toxicities. Most of the studies described included patients with colon or rectal cancer, but studies related to gastric, pancreatic, and neuroendocrine tumors have also been published (Table 3).<sup>31-34</sup> Some of the studies involved fluorouracil prodrug, including tegafur-uracil and capecitabine. Other studies also explored the results of double biochemical modulation regimens of fluorouracil, methotrexate, and levoleucovorin. Representing approaches that are advanced from the bolus infusions administered during the 1990s, several studies explored the use of chronomodulation and approaches involving the continuous infusion of modulated fluorouracil-containing chemotherapy regimens.

## Summary

This review shows that levoleucovorin has been used interchangeably with leucovorin for modulating fluorouracil in patients with malignancies. There appears to be no significant difference in efficacy or adverse effects between levoleucovorin and leucovorin, regardless of whether they are used in combination with other chemotherapeutic agents. However, care should be taken to prevent prescribing the wrong dose when levoleucovorin is substituted for leucovorin. Furthermore, no more than 16 mL (160 mg) of levoleucovorin solution should be injected intravenously per minute, because of the calcium content of the preparation. In our institution in Japan, the cost of a vial containing 50 mg of levoleucovorin is approximately \$200 (USD) compared with a vial containing 50 mg of leucovorin, which costs only \$14. The current shortage of leucovorin supply centered in North America renders levoleucovorin a reasonable alternative in terms of efficacy and toxicity profile, but without clear evidence of the correlation of adverse effects to the biological inactive d-isomer of leucovorin, and from the perspective of cost the drug of choice would still be leucovorin.

**Victor Tuan Giam Chuang** BPharm(Hons) MSc PhD, Senior Lecturer, School of Pharmacy, Faculty of Health Sciences, Curtin Health Innovation & Research Institute, Curtin University, Perth Western Australia, Australia

**Manabu Suno** PhD, Associate Professor, Department of Oncology Pharmaceutical Care & Sciences, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

**Correspondence:** Dr. Suno, sunoma@pheasant.okayama-u.ac.jp

**Reprints/Online Access:** www.theannals.com/cgi/reprint/aph.1Q677

**Conflict of interest:** Authors reported none

## References

1. Product information. Fusilev (levoleucovorin). Spectrum Pharmaceuticals, Inc, Henderson, NV, April 2011.

2. Stover PJ, Field MS. Trafficking of intracellular folates. *Adv Nutr* 2011;2:325-31. Epub 2012/02/15. doi: 10.3945/an.111.000596
3. Allegra CJ, Hoang K, Yeh GC, Drake JC, Baram J. Evidence for direct inhibition of de novo purine synthesis in human MCF-7 breast cells as a principal mode of metabolic inhibition by methotrexate. *J Biol Chem* 1987;262:13520-6.
4. Allegra CJ, Chabner BA, Drake JC, Lutz R, Rodbard D, Jolivet J. Enhanced inhibition of thymidylate synthase by methotrexate polyglutamates. *J Biol Chem* 1985;260:9720-6.
5. Zittoun J. Pharmacokinetics and in vitro studies of l-leucovorin. Comparison with the d and d,l-leucovorin. *Ann Oncol* 1993;4(suppl 2):1-5.
6. Jaffe N, Jorgensen K, Robertson R, George M, Letvak L, Barrett G. Substitution of l-leucovorin for d,l-leucovorin in the rescue from high-dose methotrexate treatment in patients with osteosarcoma. *Anticancer Drugs* 1993;4:559-64.
7. Goorin A, Strother D, Poplack D, Letvak LA, George M, Link M. Safety and efficacy of l-leucovorin rescue following high-dose methotrexate for osteosarcoma. *Med Pediatr Oncol* 1995;24:362-7.
8. Hyatt DC, Maley F, Montfort WR. Use of strain in a stereospecific catalytic mechanism: crystal structures of *Escherichia coli* thymidylate synthase bound to FdUMP and methylenetetrahydrofolate. *Biochemistry* 1997;36:4585-94. doi: 10.1021/bi962936j
9. Sugimoto Y, Ohe Y, Nishio K, Ohmori T, Fujiwara Y, Saijo N. In vitro enhancement of fluoropyrimidine-induced cytotoxicity by leucovorin in colorectal and gastric carcinoma cell lines but not in non-small-cell lung carcinoma cell lines. *Cancer Chemother Pharmacol* 1992;30:417-22. Epub 1992/01/01.
10. Tsujimoto H, Tsukioka S, Ono S, et al. Effect of leucovorin on the antitumor efficacy of the 5-FU prodrug, tegafur-uracil, in human colorectal cancer xenografts with various expression levels of thymidylate synthase. *Oncol Lett* 2010;1:973-80. Epub 2010/11/01. doi: 10.3892/ol.2010.172
11. Greiner PO, Zittoun J, Marquet J, Cheron JM. Pharmacokinetics of (-)-folinic acid after oral and intravenous administration of the racemate. *Br J Clin Pharmacol* 1989;28:289-95.
12. Schalhorn A, Kuhl M, Stupp-Poutot G, Nussler V. Pharmacokinetics of reduced folates after short-term infusion of d, l-folinic acid. *Cancer Chemother Pharmacol* 1990;25:440-4.
13. Straw JA, Newman EM, Doroshow JH. Pharmacokinetics of leucovorin (D,L-5-formyltetrahydrofolate) after intravenous injection and constant intravenous infusion. *Natl Cancer Inst Monogr* 1987;41-5.
14. Newman EM, Straw JA, Doroshow JH. Pharmacokinetics of diastereoisomers of (6R,S)-folinic acid (leucovorin) in humans during constant high-dose intravenous infusion. *Cancer Res* 1989;49:5755-60.
15. Schilsky RL, Ratain MJ. Clinical pharmacokinetics of high-dose leucovorin calcium after intravenous and oral administration. *J Natl Cancer Inst* 1990;82:1411-5.
16. Newman EM, Akman SA, Harrison JS, et al. Pharmacokinetics and toxicity of continuous infusion (6S)-folinic acid and bolus 5-fluorouracil in patients with advanced cancer. *Cancer Res* 1992;52:2408-12.
17. Straw JA, Szapary D, Wynn WT. Pharmacokinetics of the diastereoisomers of leucovorin after intravenous and oral administration to normal subjects. *Cancer Res* 1984;44:3114-9.
18. Mader RM, Steger GG, Rizovski B, Jakesz R, Rainer H. Different stereospecific protein binding of tetrahydrofolates to human serum albumin. *J Pharm Sci* 1994;83:1247-9.
19. Mader RM, Steger GG, Rizovski B, et al. Pharmacokinetics of rac-leucovorin vs [S]-leucovorin in patients with advanced gastrointestinal cancer. *Br J Clin Pharmacol* 1994;37:243-8.
20. Goldberg RM, Hatfield AK, Kahn M, et al. Prospectively randomized North Central Cancer Treatment Group trial of intensive-course fluorouracil combined with the l-isomer of intravenous leucovorin, oral leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. *J Clin Oncol* 1997;15:3320-9.
21. Scheithauer W, Kornek G, Marczell A, et al. Fluorouracil plus racemic leucovorin versus fluorouracil combined with the pure l-isomer of leucovorin for the treatment of advanced colorectal cancer: a randomized phase III study. *J Clin Oncol* 1997;15:908-14.



22. André T, Colin P, Louvet C, et al. Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. *J Clin Oncol* 2003;21:2896.
23. Comella P, Casaretti R, Crucitta E, et al. Oxaliplatin plus raltitrexed and leucovorin-modulated 5-Fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002;86:1871-5. doi: 10.1038/sj.bjc.6600414
24. Comella P, De Vita F, Mancarella S, et al. Biweekly irinotecan or raltitrexed plus 6S-leucovorin and bolus 5-fluorouracil in advanced colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase II-III randomized trial. *Ann Oncol* 2000;11:1323-33.
25. Comella P, Massidda B, Filippelli G, et al. Oxaliplatin plus high-dose folinic acid and 5-fluorouracil i.v. bolus (OXAFUFU) versus irinotecan plus high-dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial. *Ann Oncol* 2005;16:878-86. doi: 10.1093/annonc/mdi185
26. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;355:1041-7.
27. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229-37. doi: 10.1200/JCO.2004.05.113
28. Labianca R, Sobrero A, Isa L, et al. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol* 2011;22:1236-42. doi: 10.1093/annonc/mdq580
29. Kobayashi H, Morita T, Hirata Y, Kato T, Okada Y, Sato T. [Toxicosis of high-dose methotrexate (HD-MTX) for osteosarcoma, cured with treatment by leucovorin (LV) rescue and hemoperfusion—a case report]. *Gan To Kagaku Ryoho* 2000;27:475-8.
30. Etienne MC, Thyss A, Bertrand Y, et al. l-Folinic acid versus d,l-folinic acid in rescue of high-dose methotrexate therapy in children. *J Natl Cancer Inst* 1992;84:1190-5.
31. Caponigro F, Avallone A, McLeod H, et al. Phase I and pharmacokinetic study of Tomudex combined with 5-fluorouracil plus levofolinic acid in advanced head and neck cancer and colorectal cancer. *Clinical Cancer Research* 1999;5:3948-55.
32. Bajetta E, Biganzoli L, Carnaghi C, et al. Oral doxifluridine plus levoleucovorin in elderly patients with advanced breast cancer. *Cancer* 1998;83:1136-41.
33. Comella P, Palmieri G, Lorusso V, et al. Double biochemical modulation of 5-fluorouracil by methotrexate and levo-folinic acid in the treatment of advanced digestive tract malignancies. *Eur J Cancer* 1996;32A:1719-26.
34. Artale S, Giannetta L, Cerea G, et al. Treatment of metastatic neuroendocrine carcinomas based on WHO classification. *Anticancer Res* 2005;25:4463-9.
35. Damaske A, Ma N, Williams R. Leucovorin-induced hypersensitivity reaction. *J Oncol Pharm Pract* 2012;18:136-9. doi: 10.1177/1078155210396577
36. Milano G, Renee N. [Physicochemical compatibility of 5-fluorouracil (new French preparation) and folinic acid]. *Bull Cancer* 1995;82:189-95.
37. Veldhorst-Janssen NM, Boersma HH, de Krom MC, van Rijswijk RE. Oral tegafur/folinic acid chemotherapy decreases phenytoin efficacy. *Br J Cancer* 2004;90:745. doi: 10.1038/sj.bjc.6601607
38. Yamasaki D, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Possible mechanisms for the pharmacokinetic interaction between phenytoin and folinate in rats. *Ther Drug Monit* 2007;29:404-11. doi: 10.1097/FTD.0b013e318074dcf3
39. Torres OA, Miller VS, Buist NM, Hyland K. Folinic acid-responsive neonatal seizures. *J Child Neurol* 1999;14:529-32.
40. Razavi B, Lund B, Allen BL, Schlesinger L. Failure of trimethoprim/sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia with concurrent leucovorin use. *Infection* 2002;30:41-2.
41. Hennig IM, Naik JD, Brown S, et al. Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin. *J Clin Oncol* 2008;26:3411-7. doi: 10.1200/JCO.2007.15.9426
42. Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol* 2008;26:2118-23. doi: 10.1200/JCO.2007.15.2090
43. Widemann BC, Balis FM, Kim A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol* 2010;28:3979-86. doi: 10.1200/JCO.2009.25.4540
44. Tuffaha HW, Al Omar S. Glucarpidase rescue in a patient with high-dose methotrexate-induced nephrotoxicity. *J Oncol Pharm Pract* 2011;17:136-40. doi: 10.1177/1078155209348720
45. Patterson DM, Lee SM. Glucarpidase following high-dose methotrexate: update on development. *Expert Opin Biol Ther* 2010;10:105-11. doi: 10.1517/14712590903468677
46. Food and Drug Administration (FDA) of the United States. Approved drugs: Glucarpidase. 2012. <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm288016.htm> (accessed 2012 Sept 20).
47. Hempel G, Lingg R, Boos J. Interactions of carboxypeptidase G2 with 6S-leucovorin and 6R-leucovorin in vitro: implications for the application in case of methotrexate intoxications. *Cancer Chemother Pharmacol* 2005;55:347-53. doi: 10.1007/s00280-004-0910-2
48. Meyers PA, Flombaum C. High-dose methotrexate-induced renal dysfunction: is glucarpidase necessary for rescue? *J Clin Oncol* 2011;29:e180. doi: 10.1200/JCO.2010.32.8245
49. Farrugia DC, Aherne GW, Brunton L, Clarke SJ, Jackman AL. Leucovorin rescue from raltitrexed (Tomudex)-induced antiproliferative effects: in vitro cell line and in vivo mouse studies. *Clin Cancer Res* 2000;6:3646-56.
50. Priest DG, Schmitz JC, Bunni MA, Stuart RK. Pharmacokinetics of leucovorin metabolites in human plasma as a function of dose administered orally and intravenously. *J Natl Cancer Inst* 1991;83:1806-12.
51. Orange Book: approved drug products with therapeutic equivalence evaluations. [http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnewcfm?Appl\\_No=020140&Product\\_No=002&table1=OB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnewcfm?Appl_No=020140&Product_No=002&table1=OB_Rx) (accessed 2012 Sept 20).

## EXTRACTO

Levoleucovorina Puede Reemplazar Leucovorina en el Tratamiento del Cáncer

VTG Chuang y M Suno

*Ann Pharmacother* 2012;46:1349-57.

**OBJETIVO:** El objetivo de este artículo es revisar de forma exhaustiva la literatura existente sobre la eficacia, seguridad, y costes asociados con el uso de levoleucovorina (I-LV) en el tratamiento del cáncer y evaluar si I-LV podría ser una alternativa razonable al uso de leucovorina (LV) racémico.

**FUENTES DE INFORMACIÓN:** Se llevó a cabo una búsqueda en la base de datos de MEDLINE de estudios escritos en inglés realizados en humanos publicados entre enero de 1980 y abril de 2012 mediante los siguientes términos de búsqueda en inglés: I-LV, levoleucovorina (levoleucovorin), d,l-LV, leucovorina (leucovorin), ácido folínico (folinic acid), folinato (folinate), 5-formiltetrahidrofolato (5-formyltetrahydrofolate), ácido fólico (folic acid), folatos (folates), metotrexato (methotrexate) (MTX), 5-Fluorouracilo (5-Fluorouracil) (5-FU), y ensayos clínicos (clinical trials).

**SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS:** Se recopilaron artículos pertinentes a ensayos clínicos (fase I, II, III) relacionados con la evaluación de la eficacia, intercambiabilidad y seguridad de I-LV y se revisaron sus contenidos.

**SÍNTESIS:** De estos estudios farmacocinéticos y clínicos, se examinó la información sobre el uso de I-LV como modulador de 5-FU así como su combinación con otros agentes antitumorales y se extrajo para su comparación con LV siempre que fuera posible. Dos estudios clínicos aleatorizados de fase 3 que comparaban los perfiles de eficacia y efectos adversos de leucovorina y levoleucovorina demostraron que levoleucovorina es tan efectivo como leucovorina en términos de respuesta, toxicidad

dad, y supervivencia. Seis estudios clínicos aleatorizados de fase 3 demostraron la seguridad y eficacia de levoleucovorina como modulador del fluoracilo en combinación con o sin otros agentes antitumorales en los pacientes con cáncer colorrectal. Levoleucovorina ha sido objeto de estudio para otros tipos de cáncer. Estos estudios clínicos de fase I, II, y III demostraron la eficacia y seguridad de levoleucovorina en combinación con regímenes de quimioterapia que incluyan fluoracilo y otros agentes antitumorales.

**CONCLUSIONES:** Los resultados de los estudios clínicos sugieren que I-LV es eficaz y puede emplearse de forma segura en combinación con 5-FU y otros agentes antitumorales. I-LV puede emplearse de forma intercambiable con LV para la modulación de 5-FU. El recorte actual del suministro de LV centrado en Norteamérica convierte a I-LV en una alternativa razonable en términos de eficacia y perfil de toxicidad, pero desde la perspectiva del coste el fármaco de elección seguiría siendo LV.

Traducido por Enrique Muñoz Soler

## RÉSUMÉ

Le Lévoleucovorin Pourrait-il Remplacer le Leucovorin en Oncologie

VTG Chuang et M Suno

*Ann Pharmacother* 2012;46:1349-57.

**OBJECTIF:** Évaluer les données probantes quant à l'efficacité, l'innocuité, et les coûts associés à l'utilisation du levoleucovorin dans le traitement de différents cancers et évaluer si ce nouvel agent représente une option raisonnable à l'utilisation du mélange racémique de leucovorin.

**SOURCES D'INFORMATION:** Une recherche de littérature a été effectuée dans la banque de données MEDLINE (entre les mois de janvier 1980 et avril 2012) en utilisant les mots-clés suivants: levoleucovorin, isomère lévogyre du leucovorin, mélange racémique de leucovorin, acide folinique, folinate, 5-formyltétrahydrofolate, acide folique, folates, méthotrexate, 5-fluorouracil, et essais cliniques.

**SÉLECTION DE L'INFORMATION ET EXTRACTION DES DONNÉES:** Tous les essais cliniques de phase I, II, et III ayant évalué l'efficacité, l'innocuité du levoleucovorin et son interchangeabilité avec le leucovorin ont été revus.

**RÉSULTATS:** Les informations provenant des essais cliniques et des études pharmacocinétiques ayant documenté l'utilisation du levoleucovorin comme un agent modulant l'activité du 5-fluorouracil ou en association avec d'autres agents anti-tumeur sont présentées et discutées. Les résultats de 2 essais cliniques de phase III à répartition aléatoire suggèrent que le levoleucovorin démontre une efficacité, une réponse clinique, une toxicité, et des données de survie similaires à celles du leucovorin. L'efficacité et l'innocuité du levoleucovorin comme un agent de modulation possible dans le traitement par le 5-fluorouracil, en association ou non avec d'autres agents antitumoraux chez les patients souffrant de cancer colorectal, ont aussi été documentés dans 6 essais cliniques de phase III. Finalement, l'utilisation du levoleucovorin dans d'autres types de cancer, en association avec des traitements à base de fluorouracil et d'autres agents antitumoraux, est décrites dans différentes publications de phase I, II, et III.

**CONCLUSIONS:** Le levoleucovorin est efficace et peut être utilisé de façon sécuritaire en combinaison avec le 5-fluorouracil et d'autres agents anti-tumeur. Le levoleucovorin semble pouvoir être interchangeable avec le leucovorin pour moduler l'activité du 5-fluorouracil. Considérant son profil d'efficacité et d'innocuité, le levoleucovorin pourrait s'avérer une alternative raisonnable durant la pénurie nord-américaine de leucovorin. Son coût est toutefois plus élevé que le leucovorin.

Traduit par Sylvie Robert

# THE ANNALS OF PHARMACOTHERAPY®

is pleased to offer **free** online access to all **Case Reports, Letters, and Book Reviews**, in addition to selected articles that are found under the **Articles Ahead of Print** and **Current Issue** headings of the Web site.

**theannals.com**