Intraperitoneal 5-fluoro-2′-deoxyuridine with escalating doses of leucovorin: Pharmacology and clinical tolerance

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Summary

In a preceding study, we established the tolerance and pharmacokinetic behavior of 5-fluoro-2′-deoxyuridine (FdUrd) given by the intraperitoneal (IP) route. A dose of 3 g daily x 3 days was found satisfactory for Phase II study and exploration of biochemical modulation. Therefore, the current study was conducted to study the tolerance and pharmacokinetics of such a dose-schedule and route of FdUrd combined with escalating doses of leucovorin (LV). Fourteen patients were entered and 13 were evaluable for tolerance determination. Pharmacologic determinations of IP FdUrd and 5-Fluorouracil (FuRa) derived from it and LV were obtained by HPLC methods on 11 occasions. Findings were compared with the preceding study of FdUrd alone. LV did not appear to alter the tolerance of IP FdUrd even in the four patients receiving the highest dose of LV (640 mg). Toxicities included nausea, vomiting, and rarely neutropenia and diarrhea. Pharmacokinetic parameters indicate a parallel rate of egress of FdUrd and LV from the peritoneal cavity. The pharmacologic advantage for FdUrd is at least 3 logs as previously reported and one log for LV. Evidence of antitumor effect was noted particularly among untreated patients with gastrointestinal primaries. We conclude that IP FdUrd 3 g and LV in doses of up to 640 mg x 3 days are well tolerated. Since FdUrd is more potent, has an even greater hepatic clearance and shows greater potential for modulation with LV than FuRa, it may be the preferred fluoropyrimidine for subsequent studies via the IP route in the treatment of carcinomas with prominent peritoneal spread. The pharmacologic advantage for leucovorin is limited but it is a good marker for peritoneal clearance since it parallels FdUrd clearance.

Abbreviations: FdUrd, 5-fluoro-2′-deoxyuridine; FuRa, 5-fluorouracil; LV, leucovorin or 6(R,S)-5-formyl tetrahydrofolate; IP, intraperitoneal therapy; CHexUP, cyclophosphamide; Hexalen®, 5-fluorouracil, Platinol® (cisplatin)

Introduction

Initial trials of intraperitoneal (IP) therapy were directed against minimal residual disease documented at second-look laparotomy following platinum-based systemic therapy for epithelial ovarian cancer. Studies appearing during the past decade focused on drug pharmacology and on the pharmacologic advantages that could be achieved as defined by the ratio of concentration x time curves for IP versus plasma (AUC peritoneal fluid/AUC plasma). Although antitumor effects have been documented, the role of IP cisplatin alone or in combination remains controversial [1,2], and awaits the outcome of randomized trials. Results of IP platinum trials do not necessarily apply to other
drugs. For example, fluoropyrimidines achieve ‘pharmacologic advantages’ often exceeding three logs [3-6] compared to less than 20-fold for cisplatin or carboplatin. However, unlike platinum compounds, therapeutic systemic levels are not consistently achieved because the doses of FUra and FdUrd when given IV must be kept just below levels where life-threatening toxicities become common. Such unpredictable events are a result of saturation kinetics in hepatic clearance of fluoropyrimidines. In a previous study we established the pharmacokinetic and clinical profile of IP FdUrd and concluded that 3 g daily x 3 resulted in cytotoxic concentrations on peritoneal surfaces and were safe for phase II studies [6]. In addition to the millimolar IP concentrations achieved with FdUrd, other potential advantages of this fluoropyrimidine are favorable subjective patient tolerance, antitumor activity regardless of multidrug resistance, and greater potency than FUra upon direct exposure, along with greater suitability for biochemical modulation [7,8]. The expectation is that this form of therapy could play a role principally in the treatment of gynecologic and gastrointestinal malignancies with a propensity to spread within the peritoneal cavity. Accordingly, a phase II study in epithelial ovarian cancer was begun within the Southwest Oncology Group for patients with small volume (< 1 cm) disease documented at second-look laparotomy following failure of the initial platinum-based regimen.

In the current study we have sought to optimize fluoropyrimidine IP therapy through biochemical modulation with leucovorin (LV). The millimolar concentrations of FdUrd in the peritoneal cavity achieved by IP administration [6] are already extremely cytotoxic; however, modulation may maximize effects for disease just beyond the peritoneal surfaces, and in areas supplied by the portal venous blood and by the systemic circulation. At these sites, the effects of an exposure to substantially lower concentrations of FdUrd, may be enhanced by LV modulation in accordance with preclinical models [7-9]. Concurrent IP administration of LV was considered both more practical and more advantageous for modulation than IV LV since the prolonged half-life of LV in the peritoneal cavity would enhance IP exposure and also prolong plasma half-life of LV. This study, therefore, sought to establish the tolerance of combined IP FdUrd and LV and make preliminary observations on antitumor effects. Initially, dose escalations were made cautiously because of concerns that IP administration of both drugs could lead to the hepatobiliary toxicity associated with intraarterial hepatic artery infusions of FdUdR. Once this concern proved groundless we confined the study to 3 dose-levels within the same patient. We wished to study the pharmacology of these two drugs when given together IP and determine the effect of escalating dose-levels of LV on the disposition and pharmacokinetics of FdUrd, and whether LV exhibited dose-dependent pharmacokinetics.

Patients and methods

Clinical protocols

Soon after completion of a phase I and pharmacologic study of IP FdUrd and selection of an appropriate dose-schedule for modulation [6], we initiated in November 1988 a study of IP FdUrd plus escalating doses of LV. The study was approved by the Institutional Review Board of the University of Southern California for patients with histologically confirmed residual, recurrent, or metastatic malignant disease predominantly confined to the peritoneal cavity, and no symptomatic disease elsewhere. Ovarian cancer patients had to have failed prior systemic therapy with platinum compounds. The design of the new study was to administer FdUrd (fluorouridine, Roche) at a fixed dose of 3 g (total dose and not per m2 in order to provide fixed IP drug concentrations) in 2 L of normal saline on day 1, and in 1.5 L on days 2 and 3 – this slight reduction in volume aimed at avoiding cumulative retention of fluid. The dose-schedule of FdUrd selected had proven to have optimal tolerance and well defined pharmacokinetic parameters in the preceding study [6]. After proving stability in normal saline with FdUrd and calcium leucovorin (KKC, unpublished, 10) LV (calcium leucovorin for IV use, Lederle) was added to the fluid, initially in 5 mg amounts, doubling within patients after tolerating completion of each cycle consisting of three consecutive days of IP drug administration every 3 weeks. When two patients had progressed through the initial three dose escalations, the start-