CORRESPONDENCE

# Elimination of Dose Limiting Toxicities of Cisplatin, 5-Fluorouracil, and Leucovorin Using a Weekly 24-Hour Infusion Schedule for the Treatment of Patients with Nasopharyngeal Carcinoma

The recent article by Chi et al.[1] employs a mixture of cisplatin, 5-fluorouracil, and leucovorin in a single infusion solution.

I do not know how the authors obtained a compatible mixture in 10–40 mL with the doses they recommend.[1] Furthermore, mixtures of leucovorin calcium and 5-fluorouracil have, in several studies, been shown to be chemically incompatible. Ardalan and Flores showed calcite occlusion of in-dwelling catheters.[2] Immunex, a major producer of leucovorin calcium, distributed a letter on August 19, 1994, that warned of "the incompatibility of the parenteral admixture combination of leucovorin calcium with and fluorouracil. Precipitation may occur when leucovorin calcium and fluorouracil are mixed in the same intravenous solution. . . . We advise that leucovorin calcium for injection should not be mixed in the same infusion with fluorouracil." The Immunex letter states that "there are conflicting reports on the physical compatibility . . ." and that they were evaluating another study. Trissel et al. recently published another study that described color and turbidity changes that occurred in leucovorin calcium and fluorouracil mixtures.[3] It is worth noting their opening statement: "The combination of fluorouracil and leucovorin calcium has generally been regarded by pharmacists in the institution as being compatible and stable" as well as their conclusion: "Fluorouracil admixed with leucovorin calcium or levoleucovorin calcium frequently generated unacceptable crystalline precipitates in the solutions."[3]

One is left to wonder whether the elimination of "dose limiting toxicities" cited by Chi et al. may have resulted from the elimination of the medicinal agents themselves through precipitation or other chemical changes. The clinical responses in the article by Chi et al. are not the cure rates (complete or partial) but only the adverse effect responses. We need to know 1) if this regimen is at least as effective against nasopharyngeal carcinoma as standard therapy and 2) if cisplatin alone might be any more toxic than this combination and equally effective against the disease. One cannot discount the possibility that 5-fluorouracil and leucovorin were not active.

## REFERENCES


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2. Ardalan B, Flores MR. A new complication of chemotherapy administered via permanent in-dwelling central venous catheter. *Cancer* 1995;75:2165–8.
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## Author Reply

We wish to further clarify the efficacy and safety of using cisplatin, 5-fluorouracil (5-FU), and leucovorin (PFL) chemotherapy in a single infusion solution.[1]

5-FU and leucovorin chemotherapy given in single infusion solution have been reported as feasible and effective.[2-5] Our weekly PFL chemotherapy was prepared from 60–80 mL of 5-FU (supplied as 50 mg/mL by Roche-Hoffman Ltd, Basel, Switzerland), 18–22 mL of leucovorin (supplied as 10 mg/mL by David Bull Laboratories, Victoria, Australia), 30–45 mL of cisplatin (supplied as 1 mg/mL by David Bull Laboratories), plus 10–40 mL normal saline to make a total volume of approximately 150 mL in a polyvinyl chloride bag for 24-hour infusion therapy with the aid of a portable pump.[1,5] The final concentration of 5-FU was $< 25$ mg/mL and leucovorin, $< 1.5$ mg/mL in the admixture. These were within the stability recommendations from the American Pharmaceutical Association, in which 5-FU $> 25$ mg/mL and leucovorin $\geq 2$ mg/mL were considered incompatible.[6] We did not observe any color or turbidity changes or in-dwelling catheter calcite blockage[1,5] as reported by Trissel et al.[7] and Ardalan et al.[8] Some of the reported incompatibility of 5-FU and leucovorin might be related to drug concentrations given that were above those recommended by the American Pharmaceutical Association.[6]

The possibility that elimination of dose-limiting toxicity resulted from the elimination of 5-FU and leucovorin through precipitation or other chemical changes is extremely unlikely clinically. We used the same preparation of PFL chemotherapy every 3 weeks and observed an 80% incidence of moderate to severe (Grade 2 or higher) oral mucositis,[5] which was obviously related to the action of 5-FU and leucovorin and not due to cisplatin alone. Despite a doubled 5-FU dose intensity, when we changed the same PFL chemotherapy from every 3 weeks to weekly, a dramatic reduction of oral mucositis, from 80% to 7%, was observed.[1] This is most likely related to the change in the PFL chemotherapy schedule and not due to inactivation of 5-FU and leucovorin.

Both PFL chemotherapy schedules are effective in the treatment of nasopharyngeal carcinoma (NPC), with a response rate of up to 100%.[1,5] The 30% complete response rate and 60% partial response rate in localized NPC from weekly PFL chemotherapy indicate this regimen is at least as effective as most other chemotherapy regimens reported.

PFL chemotherapy appears to be more effective than the response rate of approximately 40% achieved using cisplatin alone in the treatment of NPC.[9] The relatively higher response rate of PFL chemotherapy compared with cisplatin alone suggests 5-FU and leucovorin remain active in the PFL regimen.

In summary, PFL chemotherapy given in a single infusion may be clinically safe and effective. The drug concentration recommendations of the American Pharmaceutical Association should be followed to avoid 5-FU and leucovorin incompatibility or precipitation.[6]

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