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Short communication

Activity of continuous-infusion 5-fluorouracil in patients with advanced colorectal cancer clinically resistant to bolus 5-fluorouracil

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Abstract. We have recently demonstrated that continuous-infusion (CI) 5-fluororacil (FU) eradicates human colon carcinoma cells made resistant to bolus FU in vitro. In addition, in the same experimental system, the mechanisms of resistance to pulse and CI FU were found to be different. These observations led us to test the clinical activity of a standard regimen of CI FU (300 mg/m^2 per day) in a cohort of 15 patients with advanced measurable colorectal cancer who were in progression after having failed to respond to bolus treatment with FU alone (3 patients) or FU combined with high-dose 6-S-leucovorin (LV) (12 patients). The median age of the patients was 68 years, and their median Eastern Cooperative Oncology Group performance status (ECOG PS) was 1. No myelotoxicity was observed. Mild diarrhea, mucositis, and vomiting occurred in 32%, 26%, and 19% of the patients, respectively, with no WHO grade 3 or 4 episodes being noted. In all, 6 of 15 patients complained of hand-foot syndrome, which was severe in 2 instances, lasting approximately 1 week. Overall, 1 partial response and 6 instances of disease stabilization, including 3 minor responses, were obtained both in patients who had been pretreated with pulse FU alone and in patients who had failed first-line treatment with FU + LV. Finally, 8 patients failed CI FU. In conclusion, these results, obtained in patients who were clearly progressing after having failed first-line treatment, support our experimental finding that resistance to bolus FU may be overcome by CI FU and extend this possibility to patients who are resistant to bolus treatment with FU + LV.

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Introduction

We have recently demonstrated that human colon carcinoma cells that are repetitively exposed in vitro to clinically relevant concentrations of 5-fluorouracil (FU) for short periods (4 h), acquire resistance via reduced incorporation of FU nucleotides into RNA, whereas cells exposed continuously to the same drug develop resistance via a DNA-oriented mechanism [1]. This observation, coupled with the evidence that continuous-infusion (CI) FU eradicates human colon carcinoma cells that are resistant to bolus treatment with FU [6], led us to test the clinical activity of a standard regimen of CI FU (300 mg/m^2 per day) [4] in a cohort of 15 patients with advanced measurable colorectal cancer who were in progression after having failed to respond to bolus treatment with FU alone or FU combined with high-dose 6-S-leucovorin (LV). Progression was defined as an increase of greater than 25% in the sum of the products of the longest perpendicular diameters of measurable lesions and/or the appearance of new lesions after a minimum of 2 months of treatment with bolus FU.

Patients and methods

In all, 12 patients had received a median of 4 monthly cycles of 370 mg/m^2 bolus FU daily × 5 every 4 weeks preceded by 100 mg/m^2 bolus LV and 3 patients had completed a median of 2 monthly cycles of bolus FU given alone at 500 mg/m^2 daily × 5 every 4 weeks. Overall, 2 partial responses (lasting 6 and 7 months, respectively), 2 instances of disease stabilization (lasting 2 months), and 8 failures had been observed in the former group of patients, whereas 3 failures had occurred in the latter group. CI FU was given using CADD 1 Pharmacia portable pumps and Port-a-Cath devices surgically implanted in the subclavian vein. The patients' characteristics are shown in Table 1.

Results and discussion

The treatment was continued for a median of 14 weeks (range, 3–50 weeks), and the median dose intensity actually delivered during the first 3 months of treatment was

Table 1. Patients' characteristics

Total number of eligible patients	15
Sex:	
M	8
F	7
Median age (years)	68
Median ECOG PS	1
Site of primary disease:	
Colon	12
Rectum	3
Site of metastatic disease:	
Liver	8
Pelvis	2
Lung	5
Peritoneum	1
Lymph nodes	3
Bone	1
Prior treatment with bolus FU	3
Prior treatment with bolus FU + LV	12

ECOG PS, Eastern Cooperative Oncology Group performance status

1650 mg/m^2 per week (79% of that planned). No myelotoxicity was observed. Mild diarrhea, mucositis, and vomiting occurred in 32%, 26%, and 19% of the patients, respectively, with no WHO grade 3 or 4 episodes being noted. In all, 6 of 15 patients complained of hand-foot syndrome, which was severe in 2 instances, lasting approximately 1 week.

Only 1 partial response of 7-month duration (indicator lesions in the liver and lung) was obtained in a patient who had progressed after receiving 3 monthly cycles of full-dose FU + LV. In addition, 6 instances of disease stabilization occurred, lasting 3, 4, 5, 8, 8, and 9 months, respectively; 3 of these were minor responses, defined as a decrease of more than 25% but less than 50% in the tumor mass. It is interesting that 5 of 6 cases of disease stabilization, including 2 minor responses, were obtained in patients who had progressed after failing FU + LV. The third minor response occurred in a patient who had been pretreated with pulse FU alone. Finally, 8 patients failed salvage treatment with CI FU.

These results are encouraging in four respects: first, they support our in vitro data showing that resistance to bolus FU may be overcome by CI FU [6]; second, they further extend this concept, showing that even the addition of LV to front-line chemotherapy with bolus FU does not preclude the possibility of successful salvage treatment with CI FU; third, they confirm a recent anedoctal report on the lack of clinical cross-resistance between the two schedules of FU [2]; and finally, they encourage the use of CI FU as a more adequate FU schedule to be biochemically modulated by LV.

The clinical responses (1 partial response, 2 minor responses, and 3 cases of disease stabilization) obtained in this study on patients who were resistant to the combination FU + LV indicate that the folate cofactor failed to modulate bolus FU biochemically, at least in half of these patients. In general, given a percentage of colon cancer cells in the S phase of only 3% [5] and an FU plasma half-life of only a few minutes for pulse FU, the addition of LV may not suffice to target bolus FU to thymidylate synthase and the folate cofactor may exert only a marginal effect on the overall cytotoxicity.

This DNA-directed effect may thus be greatly enhanced by a better match between the tumor growth kinetics and the pharmacokinetics of FU achievable by CI. CI FU and weekly bolus LV have given promising results as front-line chemotherapy for advanced colorectal cancer [3], and our group is now completing a phase II study of bolus FU preceded by methotrexate, given in alternation with CI FU modulated by LV.

References

1. Aschele C, Sobrero A, Faderan MA, Bertino JR (1992) Novel mechanism(s) of resistance to 5-fluorouracil in human colon cancer (HCT-8) sublines following exposure to two different clinically relevant dose schedules. Cancer Res 52: 1855–1864
2. Izzo J, Zarba J, Rougier P (1992) Low dose 5-FU continuous infusion (FU CI) in advanced colorectal cancer (ACC): clinical evidence for reversal for acquired/intrinsic resistance to 5-FU or 5-FU folinic acid (FUFO) (abstract 1298). Proc Am Assoc Cancer Res 33: 217
3. Leichman CG, Leichman L, Spears CP, Rosen P, Jeffers S, Groshen S (1993) Prolonged continuous infusion of fluorouracil with weekly bolus leucovorin: a phase II study in patients with disseminated colorectal cancer. J Natl Cancer Inst 85: 41–44
4. Lokich JJ, Ahlgren JD, Gullo JJ (1989) A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. J Clin Oncol 7: 425–432
5. Shackney SE (1985) Cell kinetics and cancer chemotherapy. In: Calabresi P, Shein PS, Rosenberg SA (eds) Medical oncology. MacMillan, New York, pp 41–60
6. Sobrero A, Rosso R, Aschele C, Guglielmi A, Mori A, Bertoglio S, Tixi L, Bolli E, Bertino JR (1993) Sequential bolus and continuous infusion 5-fluorouracil: experimental and clinical studies (abstract 667). Proc Am Soc Clin Oncol 12: 219