CORRESPONDENCE

Protracted Treatment with Tegafur and Low Dose Oral Leucovorin in Patients with Advanced Colorectal Carcinoma

As has been reported previously, leucovorin (LV) modulation increases the response rate of 5-fluorouracil (5-FU) in patients with advanced colorectal carcinoma, but overall survival does not appear to be modified significantly.[1,2] In an attempt to improve results in the treatment of such patients, several trials have been designed to test the efficacy of 5-FU administered as a continuous intravenous infusion. A recent meta-analysis shows a benefit for continuous compared with rapid infusion with regard to response rate with little increase in overall survival.[3] According to pharmacokinetic studies,[4] several investigators have tried to demonstrate the same effects using 5-FU as a protracted continuous infusion by the maintained oral administration of 5-FU derivatives such as tegafur or tegafur plus uracil (UFT). A majority of these Phase II trials are designed to include LV because they assume it can also be a potential modulator of tegafur or UFT.[5–7] However, it remains unproven in prospective randomized trials whether the therapeutic benefit of LV is independent of the schedule of administration of 5-FU (rapid vs. protracted continuous infusion).[8,9] In the same way the results of treatment with maintained continuous infusion of 5-FU are not changed significantly by the concomitant administration of LV in a prospective comparative study; nevertheless, in this trial different doses of 5-FU are included and the schedule of LV is not standard (Table 1).[10] If we accept the validity of these results by assuming a similar effect for the protracted continuous infusion of 5-FU and oral tegafur or UFT, a possible conclusion is that before including LV we should first know the activity of tegafur or UFT alone in patients with advanced colorectal carcinoma. Subsequent studies must be aimed at assessing the effect of the simultaneous administration of LV and 5-FU. Eventually, prospective randomized trials should be designed to compare both tegafur or UFT with or without LV. Meanwhile, before adding other drugs to the regimen, we must select tegafur or UFT alone as the experimental arm for comparison with a rapid infusion 5-FU plus LV (standard therapy) in prospective controlled studies.

TABLE 1
Results of a SWOG Seven-Arm Comparative Trial of Different 5-FU Modulations (Presented Data are Limited to 5-FU as Continuous Infusion with or without LV[10])

Schedule	No. of patients	Confirmed responses	Median survival (mos)
5-FU, 300 mg/m^2 Days 1–28, every 35 days	88	18%	15
5-FU, 200 mg/m^2 Days 1–28, every 35 days + LV 20, mg/m^2 IV, every 7 days	86	17%	14

SWOG: Southwest Oncology Group; 5-FU: 5-fluorouracil; LV: leucovorin.

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Alvaro S. Rubiales, M.D.
M. Luisa del Valle, M.D.
Oncology Department
Hospital Universitario
de Valladolid
Valladolid, Spain

Author Reply

To our knowledge, the only controlled trials of oral fluoropyrimidines versus 5-fluorouracil (5-FU) are those referring to tegafur. These studies show that in patients with advanced colorectal carcinoma the response rate, response duration, and mean survival are similar when comparing oral tegafur with 5-FU as an intravenous bolus.[1–3]

Therefore, we accept that oral tegafur in the recommended doses (1 g/m^2/day) is similar to 5-FU in intravenous bolus. To our knowledge there are no comparative studies of oral tegafur versus 5-FU in continuous infusion, nor are their comparative studies of tegafur plus uracil versus 5-FU.

If what we are trying to do is offer an easily orally administered treatment in an ambulatory setting, to increase the activity of oral tegafur we have two choices. The first is to increase the total dose of oral tegafur similar to 5-FU in continuous infusion, in which the total dosage is greater than the bolus administration. With this option gastrointestinal toxicity is the dose-limiting factor.[4] The other option is to increase the activity of tegafur by modulating it. Based on the lower dose recommended in monotherapy, as advised in the continuous infusion regimens or the 5-FU regimen modulated with leucovorin, we have obtained activity indices and a toxicity pattern that can be superimposed on intravenous modulation schedules.

The consistency of the results of controlled studies of intravenous modulation that show an activity greater than 5-FU in bolus makes it necessary that 5-FU and leucovorin be the control arm of the study. In that case, if we have an oral treatment plan available with a possible efficacy similar to that of intravenous modulation regimens and we want to show its contribution in the treatment of colorectal carcinoma, which regimen will we compare it with? Would it be ethical to include a treatment arm of tegafur as monotherapy? Currently we have a randomized study in progress comparing oral modulation with the Mayo Clinic schedule.

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Miquel Nogué, M.D.
Miquel A. Seguí, M.D.
Eugeni Saigi, M.D.
Oncology Unit
Consorci Hospitalari
Parc Taulí
Barcelona, Spain

A Clinicopathologic Study of Mucinous Gastric Carcinoma Including Multivariate Analysis

We read with great interest the recent article by Dr. Wu et al.[1] The authors referred to our study[2] and stated in the "Discussion" section that: ". . .Adachi et al. chose only advanced gastric carcinoma cases for the NGC [nonmucinous gastric carcinoma] control group to compare with *all* [italics authors'] MGC [mucinous gastric carcinoma] cases, including early gastric carcinoma." However, Wu et al. misinterpreted our study, and this statement is not accurate. They compared the data of 22 patients with MGC with the data of 46 patients with NGC who were selected as controls from 905 NGC patients. The 5-year survival rate for the MGC cases was lower than that for the NGC cases, but the frequency of Stage I and II disease was significantly less frequent in MGC cases (0% and 18%, respectively) compared with NGC cases (11% and 33%, respectively) ($P < 0.05$).

If MGC was considered to be more aggressive it would be because MGC was detected most often in an advanced stage and rarely in an early stage. Therefore, to clarify the biologic behavior of MGC clinicopathologic characteristics and treatment results must be compared among the same stages. In our previous study,[2] we investigated 42 patients with MGC and, after excluding 1 patient with early stage MGC, we compared the surgical outcome of 41 patients with advanced MGC with that of 73 patients with advanced NGC. The results indicated that the MGC cases and NGC cases were not different with regard to the frequencies of serosal invasion (76% vs. 77%), lymph node metastases (85% vs. 79%), Stage III and IV disease (78% vs. 86%), overall 5-year survival rate (39% vs. 30%), and 5-year survival rate after curative resection (58% vs. 56%). Thus, we concluded that when comparing advanced tumors, the biologic behavior of MGC did not differ from that of NGC.

To confirm the results of our previous study in Kyushu University Hospital, pathologic and follow-up data from Oita Medical University Hospital were analyzed. A total of 630 patients underwent gastrectomy for gastric adenocarcinoma and 17 patients (2.7%) had MGC; all were cases of advanced MGC and there was no case of early MGC. The 10-year survival rate for the 17 MGC patients (45%) was lower than that for the 613 NGC patients (72%) ($P < 0.05$), whereas the 10-year survival rate for the 17 patients with advanced MGC (45%) was not different from that for the 326 patients with advanced NGC (49%). Therefore, if MGC was considered clinically more malignant, it would be because advanced MGC predominates over early MGC.

Again we would like to emphasize that the biologic behavior of advanced MGC is similar to that of advanced NGC, and that histologic subtype (well differentiated and poorly differentiated types) is useful for predicting metastases and the recurrence pattern of MGC.[2] We hope this letter will contribute to the further understanding of MGC.

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Yosuke Adachi, M.D.
Seigo Kitano, M.D.
First Department of Surgery
Oita Medical University
Oita, Japan

Masaki Mori, M.D.
Medical Institute of Bioregulation
Kyushu University
Kyushu, Japan

Author Reply

We would like to thank Dr. Adachi et al. for their comments regarding our recently published article.[1] In their interesting study,[2] they chose all mucinous gastric carcinoma (MGC) cases for their study, including early gastric carcinoma. However, they excluded the only early gastric carcinoma case when comparing with MGC cases with cases of advanced nonmucinous gastric carcinoma (NGC). We misinterpreted their study significantly.

Although the majority of MGCs were diagnosed at an advanced stage, we were interested in both early (18%) and advanced (82%) cases. In the univariate analysis, we observed the more aggressive biologic behavior of MGC. However, multivariate analysis disclosed the worse prognosis of MGC when correlated with more frequent serosal invasion and more advanced stage at diagnosis, *not* with the mucinous histologic type. The conclusion was compatible with the study of Adachi et al. regarding advanced MGC and NGC. However, our study results also could be applied

to early stage MGC. We hope the article will be helpful in providing a more complete understanding of MGC.

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Chun-Ying Wu, M.D., M.P.H.
Section of Gastroenterology
Department of Internal Medicine
Taichung Veterans General Hospital;
China Medical College
Taichung, Taiwan
Republic of China

Hong-Zen Yeh, M.D.
Section of Gastroenterology
Department of Internal Medicine
Taichung Veterans General Hospital
Taichung, Taiwan
Republic of China
Rocky Tai-Ping Shih
Department of Pathology
Taichung Veterans General Hospital
Taichung, Taiwan
Republic of China
Gran-Hum Chen, M.D.
Section of Gastroenterology
Department of Internal Medicine
Taichung Veterans General Hospital
Taichung, Taiwan
Republic of China