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## Letters to the Editor

# Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer

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#### Sir,

In the March 8 issue, Ohwada et al (2004) reported a randomised study of patients with stage II or III colorectal cancer, treated with either UFT alone or the combination of UFT and PSK. The benefit obtained by PSK seems impressive, with a decrease by 43.6% in the risk of recurrence and 5-year disease-free survival of 73%, especially as there were only 139 patients in the investigational group and 68 in the control group. Nevertheless, several aspects must be discussed. The first point is the choice of the control arm. The combination of 5-FU and leucovorin currently is the standard adjuvant chemotherapy of colorectal cancer in most countries. There is currently no evidence that UFT, even when modulated by leucovorin, is superior to this regimen. On the contrary, a large phase III trial comparing UFT/ leucovorin with 5-FU/LV (Mayo Clinic regimen) in 816 patients with metastatic disease resulted in an increase by 22% in the risk of disease progression in the investigational arm (Douillard et al, 2002). Another randomised study showing some benefit in terms of survival for cancer death only used oral 5-FU in the control arm (Ito et al, 2004). Of note is the high proportion of patients with rectal cancer, reaching 50% in the control group. Given the impact of the quality of surgery and radiotherapy in this location, a confusing factor might have been introduced especially as preoperative radiotherapy has not been administered. The study design introduces several variables in chemotherapy such as early start, long duration, sequential administration of MMC and UFT, introducing other confusing factors. The early start of chemotherapy might be interesting since surgery provokes the circulation of neoplastic cells (Yamaguchi et al, 2000) and angiogenesis and potentially the development of micrometastasis. Intravenous chemotherapy usually starts 4-8 weeks after surgery. Nevertheless, the poor results of the control arm do not support this approach. On a psychological viewpoint, the impact of a very long treatment should not be neglected since it may enforce the idea that cancer can relapse any time. The results in stage III patients in the control arm are poor and question about the efficacy of UFT and

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\*Correspondence: Dr C Alliot; E-mail: alliotcfr@yahoo.fr Published online 10 August 2004 MMC. Indirectly, the mediocrity of UFT alone minimises the impact of PSK. The authors largely invoke indirect comparisons with studies published more than 10 years before while many procedures, including surgery, improve over time and promising trials of combination chemotherapy with either oxaliplatin or irinotecan are ongoing. The impact of secondary surgery as well as second-line chemotherapy in well-followed patients may be important in terms of overall survival. The issue of the mechanism of action of PSK, in particular its synergy with a fluoropyrimidine, is intriguing. Since decades, a tremendous number of studies regarding immunotherapy have been reported. Although extracts of microbial agents can logically induce demonstrable production of interleukin-2, interferon, or activated immune cells, evidence of a clinical impact remains extremely limited. Even high-dose interleukin-2 or interferon result only in a modest efficacy in subgroups of patients with cancers partially dependant on immunesurveillance such as advanced renal cancer or melanoma. The efficacy of interferon in the adjuvant therapy of melanoma is highly debated (Sabel and Sondak, 2003). Recent randomised studies have shown that neither interferon (Messing et al, 2003) nor interleukin-2 (Clark et al, 2003) improve survival in the adjuvant treatment of high-risk renal carcinoma. Consequently, the impact of 'soft' immunotherapy is difficult to advocate in colorectal cancer. In addition, several recent randomised studies have called into question the efficacy of levamisole (QUASAR Collaborative Group, 2000; Dencausse et al, 2002; Cascinu et al, 2003). Probably, an alternative mechanism should be considered. Inhibition of metastases by protection of vascular membrane basement has also been evoked (Kudo et al, 2002). In conclusion, although PSK remains a good candidate for convenient adjuvant therapy, this study is not definitively convincing. The challenge remains crucial since oral therapy is particularly adapted to the vast concerned population, particularly in the elderly, given the relatively heavy procedure of combination chemotherapy with FOLFOX or FOLFIRI regimen.

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# Reply: Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer

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Sir,

We thank Dr C Alliot for his comments and critique in the editorial accompanying our article (Ohwada et al, 2004). Regarding the choice of the control arm, we agree that the standard adjuvant treatment for stage III colon cancer since 1990 has been 5fluorouracil plus leucovorin (5-FU/LV) (NIH, 1990; IMPACT, 1995; Wolmark et al, 1999). Now, FOLFOX has become a standard regimen for stage II or III colorectal cancer (Andre et al, 2004). Nevertheless, the Ministry of Health and Welfare of Japan did not approve LV for colorectal cancer until June 16, 1999. This study was conducted between October 1994 and March 1997, 2 years before official permission. Therefore, LV was unavailable as a randomised control. As you indicated, there is currently no evidence that UFT is superior to the standard regimen, even when modulated by LV. In a large phase III trial that compared UFT/LV with 5-FU/LV for untreated metastatic colorectal cancer, UFT/LV was found to be a safer, more convenient oral alternative to a standard bolus IV 5-FU/LV regimen, while producing equivalent survival; however, it was associated with an inferior time to disease progression and 22% increase in the risk of disease progression (Douillard et al, 2002). Recently, the efficacy of UFT has been determined. In randomised, controlled trials, adjuvant chemotherapy with UFT alone improved the survival of patients with completely resected pathological stage III rectal cancer (Akatsu *et al*, 2004) and stage I adenocarcinoma of the lung (Kato *et al*, 2004), compared with surgery alone.

Dr Alliot was concerned with the high proportion of patients with rectal cancer in the control arm, the impact of the quality of surgery, and the fact that no preoperative radiotherapy was administered. The 5-year disease-free survival for rectal cancer was 69.4% (95% CI: 56.5-82.3%) with PSK and 52.9% (95% CI: 36.2-69.7%) in the controls (P=0.133). The difference was not significant, but the high proportion of patients with rectal cancer in the control arm may have pushed the survival for all the patients downward. Therefore, we reanalysed the 5-year disease-free survival adjusted for histologic type and tumour location and found that the survival remained significantly better for the PSK group (stratified logrank; P=0.031). The result suggests that the high proportion of patients with rectal cancer did not affect the survival significantly.

As Dr Alliot indicated, the quality of surgery is an important point when conducting any randomised, controlled trial in a surgical field. The recognition that tumour cell involvement in the circumferential margin is important in local recurrence has led to the general use of total mesorectal excision (MacFarlane *et al*,

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