Letters to the Editor

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 colorectal cancer since 1990 has been 5-fluorouracil 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, 2002). The development of less invasive surgical procedures has produced more patients with a positive circumferential margin and a greater proportion of patients with local recurrence. In our study, the rate of local recurrence was 19% (22/114) in the control arm and 9% (2/23) in the PSK arm, which was significantly different (stratified logrank; P = 0.003). The difference was due to the surgical procedure. Therefore, we believe that the primary cause of the different survival between the control and PSK arms was due to differences in surgical technique. It is possible that local recurrence might be a more important factor than the quality of surgery. Further studies are warranted to evaluate the role of surgery and the influence of tumour cell involvement in the circumferential margin in colorectal cancer.

Determining the survival benefit for those patients in whom the cancer has been resected is important. In our study, the 5-year disease-free survival of patients with local recurrence was significantly better in the PSK arm compared with the control arm (stratified logrank; P = 0.012). The 5-year disease-free survival of patients with local recurrence in the control arm was 11% (2/19) and 33% (7/21) in the PSK arm, which was significantly different (stratified logrank; P = 0.012). The difference was due to the surgical procedure. Therefore, we believe that the primary cause of the different survival between the control and PSK arms was due to differences in surgical technique. Further studies are warranted to evaluate the role of surgery and the influence of tumour cell involvement in the circumferential margin in colorectal cancer.

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1993; Kapiteijn et al, 2001), in which the entire mesorectum is enveloped and resected using a precise, sharp dissection. Therefore, suitably qualified chief surgeons were trained in the Second Department of Surgery, Gunma University Hospital, in order to standardise surgical quality. We applied total mesorectal resection for Rb or Rab tumours, and tumour-specific mesorectal resection for Ra tumours (at least 4 cm of the anal mesorectum was dissected). Lateral node dissection was performed, while groin dissection was not added. In our study of rectal cancer, the rate of local recurrence was 4.8% in all patients, 2.9% in the control, and 6.1% in the PSK group. The low rate of local recurrence in our study with no preoperative radiation therapy (4.8% at 5 years) is similar to the excellent results achieved using preoperative radiochemotherapy (4.1% at 5 years) for stage II colon cancer (Kapiteijn et al, 2001).

Oncologists agree that an early start for chemotherapy is rationally correct, because surgery provokes the circulation of neoplastic cells (Yamaguchi et al, 2000), angiogenesis, and, potentially, the development of micrometastasis, as Dr Alliot indicated. In his editorial, Dr Alliot does not focus on the superior results in the PSK arm, but emphasises the poor results in the control arm. The benefits of an early start for chemotherapy are supported by the significantly superior disease-free survival in the PSK arm. The survival of UFT/MMC in pathologic stage III patients was poor and was similar to that of untreated controls in standard regimens (Francini et al, 1994; IMPACT, 1995). This may be explained by the difference in the dose intensity of UFT. The UFT doses used in positive randomised trials include 600 mg/m$^2$/day$^{-1}$ (Malik et al, 1990), 300 or 350 mg/m$^2$/day$^{-1}$ with LV (Douillard et al, 2002), 400 mg/m$^2$ for 5 of 7 days (Akatsu et al, 2004), and 250 mg/m$^2$/day$^{-1}$ (Kato et al, 2004), which are all higher than the 300 mg/m$^2$/day$^{-1}$ used in our study, despite the lack of LV modulation. The development of more effective agents or regimens should prove that an early start with chemotherapy benefits disease-free survival.

Invoking recently published data from randomised, controlled trials, the survival with PSK/UFT treatment is comparable or superior to standard 5-FU/LV regimens. The 5-year disease-free and overall survival rates were 73.0 and 81.8% for the PSK group, respectively, while 5FM/LV and 78.2% for FOLFOX, while we achieved 77.8% for PSK/UFT. When limited to stage III, the 3-year disease-free survival rates of stage II or III patients were 72.9% for 5FU/LV and 78.2% for FOLFOX, while we obtained 70.9% for PSK/UFT.

I agree that disease-free survival is more meaningful than overall survival, at least in the case of adjuvant chemotherapy for colorectal cancer (Elfenbein, 2003; Andre et al, 2004); second-line therapies for recurrence, including chemotherapy and salvage surgery, can prolong the survival of colorectal cancer patients (de Gramont et al, 2000; Saltz et al, 2000; Choti et al, 2002).

There is no consensus on the optimal duration for adjuvant chemotherapy after colorectal cancer. Currently, a standard adjuvant treatment for stage III colon cancer, is 5-FU/LV for 6 – 12 months (Francini et al, 1994; O’Connell et al, 1998; IMPACTB2, 1999; Wolmark et al, 1999; QUASAR, 2000; Andre et al, 2004). Recurrences generally occur within 2 years after surgery. Indeed, in our study, 71% of cancers recurred during the first 2 years after surgery, and 85% recurred within 2 years. The mean time to recurrence was 1.9 ± 1.4 years in the PSK group and 1.6 ± 1.1 years in the control group (O’Connell et al, 2001) reported that the median time to relapse was 15 months with 5FU/LV treatment and 12 months with 5FU/levamisole treatment. Fluorouracil is a time-dependent agent, and a daily regimen of UFT is an effective way to maintain the blood fluorouracil level. Therefore, the daily, long-term administration of UFT may be beneficial. In addition, oral use of adjuvant chemotherapy with PSK and UFT is less toxic and less complex, as it avoids frequent treatment-related visits and thereby allows patients to receive long-term treatment.

PSK has a wide range of biological activity, remarkable immune-enhancing activity, and a broad antineoplastic scope (Wasser, 2002). Therefore, therapy with PSK differs from therapy with cytokines, such as interferon (IFN) and interleukin (IL)-2. PSK activates NK cells independent of IFN and the IL-2/IL-2 receptor system, and activates lymphokine-activated killer (LAK) cells (Ebina and Murata, 1992; Algarda et al, 1997; Harada et al, 1997; Pedrinaci et al, 1999; Garcia-Lora et al, 2001; Garcia-Lora et al, 2003). PSK also functions as a specific biochemical modulator of antitumour agents, such as mitomycin C, 5-fluorouracil, cyclophosphamide, bleomycin, CPT-11, cisplatin, and docetaxel (Zhang et al, 2003). PSK upregulates the IL-1, IL-6, and IL-8 genes in peripheral mononuclear cells (Hirose et al, 1990), as well as the genes for TNF and macrophage chemotactic factors in tumour cells (Ebina and Murata, 1992), and induces apoptosis (Yefenof et al, 1995; Zhang et al, 2003). In addition, PSK induces differentiation-related genes and produces leukemic cell differentiation in vitro (Yefenof et al, 1995). Furthermore, PSK suppresses tumour cell invasiveness via the downregulation of several invasion-related factors, which include TGF-β1, urokinase plasminogen activator, and the matrix metalloproteinase (MMP)-2 and -9 (Zhang et al, 2000). These activities of PSK are varied and differ from those of levamisole. Although the efficacy of levamisole in a randomised, controlled trial was questionable (QUASAR, 2000), the results for levamisole did not represent those for PSK.

Finally, I thank Dr C Alliot for his comments again. This study shows that PSK is a good candidate for convenient therapy with less toxicity, better compliance, and comparable survival to FOLFOX or 5FU/LV regimens, although our results are not definitive.

REFERENCES

Akatsu T, Moiry S, Yoshida S, Shirao K, Ohashi Y, Kodaira S (2004) Adjuvant oral uracil and tegafur (UFT) improves survival after complete mesorectal excision (ME) of pathologic TNM stage III rectal cancer. In Proc Am Soc Clin Oncol, Vol. 23, pp 251, New Orleans
Algarra I, Collado A, Garrido F (1997) Protein bound polysaccharide PSK abrogates more efficiently experimental metastases derived from H-2 negative than from H-2 positive fibrosarcoma tumor clones. J Exp Clin Cancer Res 16: 373 – 380
André T, Boni C, Mounedj-Boudiaf L, Navarro M, Tabernerio J, Hickish T, Topham C, Zaninelli M, Clingen P, Bridgewater J, Tabah-Fisch I, de Gramont A (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350: 2343 – 2351
Choti MA, Sitzmann JV, Tiburi MF, Sunetchothimetha W, Rangsin R, Schulik RD, Lillemoe KD, Yeo CJ, Cameron JL (2002) Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 235: 759 – 766
de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Poźniak I, de B. N, Louvet C, Hendler D, de Braud F, Wilson C, Morfan V, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938 – 2947
Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE (2002) Multicenter phase III study of uracil/tegafur and oral leucovorin vs...
