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Response from H.J.N. Andreyev, A.R. Norman, J. Oates and D. Cunningham

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WE ARE pleased that Professor Bozzetti, who is distinguished by his research into nutritional support for patients with cancer, should wish to comment on our observational study which found that patients with weight loss receiving chemotherapy for metastatic gastrointestinal cancer suffer more toxicity, receive less treatment and do less well than patients who have not lost weight [1].

We agree that his study in patients with lymphoma may suggest that those with nutritional deficit have more aggressive disease. However, there is no such large and adequate study in patients with metastatic gastrointestinal malignancy and as we state in our paper, to prove for certain whether weight loss promotes tumour aggressiveness or whether tumour aggressiveness leads to weight loss in humans requires a prospective study.

However, we cannot agree with him that the role of supplemental glutamine has been settled by the findings of the three trials cited in his letter. As is so often the case with nutritional studies, there are problems with the number of patients included, patient selection, the methodology used and the dose of nutritional supplement given. The one study which looked at glutamine in patients receiving 5-fluorouracil-based chemotherapy with gastrointestinal cancer [2] included only 28 patients, of whom 21% died after just a single cycle of chemotherapy, the dose of 5-fluorouracil was not reduced when patients developed toxicity, the dose of glutamine was only half that used with benefit in an earlier small study in bone marrow transplant patients [3] and, most concerning of all, in 80% of the patients studied, the expected, transient increase in serum glutamine levels was not seen after dosing, suggesting that either the dose taken or the bioavailability of the preparation was inadequate [4].

Nutritional support is of proven benefit in reducing toxicity in some laboratory animals treated with chemotherapy. There is a dearth of high quality, clinically relevant nutritional support studies in human patients. We believe that our data decisively defines a subgroup of patients who might benefit from nutritional intervention; those who present with metastatic gastrointestinal malignancy, have lost weight and are suitable for treatment with chemotherapy.

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3. Ziegler TR, Young LS, Benfell K, *et al.* Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. *Ann Internal Med* 1992, **116**, 821–828.
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Double Modulation of 5-Fluorouracil with Interferon Alpha-2a and High-dose Leucovorin in Advanced Neuroendocrine Tumours

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THE CLINICAL course of patients with advanced neuroendocrine tumours (NET) is quite often indolent, although unresectable metastatic disease is incurable and ultimately fatal. Chemotherapy for metastatic NET has generally achieved objective tumour response rates of 10–15% [1]. Both 5-fluorouracil (5-FU) and interferon-alpha (IFNα) have demonstrated independent activity in NET [2, 3]. Non-randomised studies of the combination have shown promising activity in other gastrointestinal malignancies [4]. With this background, we set out to investigate the combination of 5-FU, leucovorin (LV) and IFNα in patients with advanced NET.

15 chemotherapy naïve patients with advanced, histologically confirmed NET, not amenable to surgery, were treated

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