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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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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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Table 1. *Clinical characteristics*

	Carcinoid group	Non-carcinoid neuroendocrine tumours
No. of patients	12	3
Male:Female	8:4	3:0
Age range (years)	40–77	38–71
Performance status (ECOG)		
1	6	1
2	6	2
Primary tumour site		
Pancreas	2	2
Small bowel	6	–
Colorectum	1	–
Adrenals	–	1†
Unknown*	3	–
Metastatic site		
Liver	10	2
Lung	2	–
Heart	2	1
Local	1	–
Other	1	–
Hormone secretion		
5-HIAA	10	–
VIP	–	1

*Considered to be of gastrointestinal origin. †None of the tumours were poorly differentiated. ‡Phaeochromocytoma. 5-HIAA, 5-hydroxy-indole-acetic acid. VIP, vasoactive intestinal peptide.

in a phase II study (Table 1). All patients had radiologically measurable disease, and 11 had raised biochemical markers at presentation 5-hydroxy-indole-acetic acid (5-HIAA), vasoactive intestinal peptide (VIP). All had progressive disease (PD) or symptoms not responsive to pharmacological manipulation. Study endpoints, were radiological and hormonal responses. The treatment schedule was based on a phase I–II study carried out in our institution, in patients with gastrointestinal malignancies [5]. It comprised LV 200 mg/m^2 intravenous (i.v.) infusion over 2 h then 5-FU 400 mg/m^2 i.v. over 5 min, followed by 400 mg/m^2 over 22 h on day 1, all repeated on day 2, of a 2 week cycle (maximum 12). IFNα2a (Hoffman-La Roche, Basel, Switzerland) was given at 6×10^6 IU subcutaneously (s.c.) every 48 h throughout.

In the case of an objective response or stable disease (SD), IFNα was continued until PD or the development of toxicity. Response was assessed 3 monthly. Standard WHO criteria were used for the evaluation of radiological response and toxicity [6]. Hormonal response was defined as a greater than 50% reduction from baseline, sustained for two assessments 1 month apart.

A median of five courses was administered (range 1–12). 4 patients were withdrawn from the study after just one cycle; 2 with grade IV diarrhoea, 2 with grade III–IV neutropenia and sepsis. 4 patients required a 50% dose reduction of IFNα because of fatigue. There was no dose limiting stomatitis, or clinically significant neurotoxicity or hepatotoxicity. Responses were as follows: 2/11 assessable patients achieved a radiological partial response (PR) (18%; 95% confidence interval (CI) 0–33.7%) of 3 and 4 months' duration, 5/11 achieved SD (45%) associated with symptomatic improvement for a median of 8 months (range 4–22); 5/11 (45%; 95% CI 16–74%) achieved a reduction of 5-HIAA (4 patients) or VIP (1 patient).

Accrual stopped after 15 patients; it was felt that the combination of 5-FU/IFNα did not confer an advantage over the use of these agents individually and was associated with excessive toxicity. The small number of patients make the interpretation of responses difficult. Our results are consistent with those reported in two other studies [7, 8], although in contrast with another, which reported encouraging results with a combination of infusional 5-FU and IFNα, with a good toxicity profile [9]. Since initiating this study in NET, several phase III randomised studies in advanced colorectal cancer have not confirmed a clinical benefit for the addition of IFNα to standard 5-FU based regimens [10, 11]. In conclusion, the combination of 5-FU/LV/IFNα in the doses and schedule described cannot be recommended for routine use in this group of patients.

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