Table 1. Quantity, onset and duration of vomiting and the experience of chemotherapy in controls and cases

Indicator of effect	Controls n	Controls %	Cases n	Cases %
Any vomiting	6	25	16	37
Onset of vomiting ≤ 4 h	3	13	10	21
Duration of vomiting ≥ 3 h	3	13	8	19
Patient rating chemotherapy intolerable	2	8	6	14

duration of vomiting. The tolerability of vomiting and chemotherapy were assessed according to the patient's report.

There were no differences between 43 cases and 24 controls by age, sex, diagnosis, chemotherapy schedule or duration of schedule. One third of the patients had more or less severe vomiting. Cases vomited more frequently but the difference was not statistically significant (Table 1). Most commonly vomiting began within 4 h of the infusion and it lasted more than 3 h (13% in controls and 19% in cases). The correlation to self-reported and observer-rated information was good. Cases found chemotherapy to be intolerable more commonly but there was no significant difference.

Differences in emesis occurred between patients receiving the same type of chemotherapy and between similar treatment courses in the same patient. Many individual factors contribute to the differences in gastrointestinal distress associated with chemotherapy. Earlier experience, susceptibility to nausea in the past, anxiety and the information on side-effects given to the patient may contribute. If the preparation of a patient for chemotherapy is too careful this can induce unnecessary anxiety and may increase emesis. On the other hand patients cannot cope with side-effects if they do not get practical advice about them [2].

In some studies systemic desensitisation and other behavioral interventions, such as relaxation or hypnosis were observed to be useful in the management of chemotherapy-related emesis [3, 4].

The failure in this study to demonstrate any benefit does not prove that non-pharmacological methods have no other beneficial effects on patients.

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Tauromustine (TCNU) Combined with 5-Fluorouracil and Leucovorin in the Treatment of Advanced Colon Cancer

Babs G. Taal, W.W. Ten Bokkel Huinink and S. Rodenhuis

ALTHOUGH 5-FLUOROURACIL (5-FU) was introduced more than 30 years ago, it is still the mainstay of treatment for advanced colorectal carcinoma, achieving response rates of 10–20% [1–3]. Tauromustine (TCNU), a novel nitrosurea derivative, has also shown antitumour activity: a response rate of 14% which including a single complete remission has been observed in 57 patients [4]. We have previously reported that a combination of 5-FU and TCNU yielded only a 10% response rate in 31 patients [5]. At that time, this disappointing outcome was difficult to explain. *In vitro* experiments with the human colon cancer cell line HT 29 by Hartley-Asp and Alenfall [6] have shown that simultaneous exposure to both TCNU and 5-FU produced less-than-additive cytotoxicity. In contrast, enhanced tumour cell kill was achieved when TCNU was added 24 h before the 5-FU. To determine whether this sequence dependence can also be shown to be present in patients, we studied a combination of TCNU with one of the most effective regimens available in colon cancer, 5-FU and leucovorin (LV) [7]. Because of its convenience and its suitability for administration in the out-patient setting, a weekly schedule with an intermediate dose of leucovorin was selected [8] to which tauromustine was added [9].

Patients with symptomatic advanced colorectal adenocarcinoma and no prior history of chemotherapy were treated. All patients had measurable lesions, a WHO performance status ≤ 2, were under 75 years of age, and had adequate bone marrow, renal and hepatic functions. The chemotherapy was administered every week as a 1-h infusion of LV (80 mg/m^2), followed by an intravenous (i.v.) push of 5-FU (400 mg/m^2) during weeks 1–8. TCNU was administered as a weekly oral dose of 40 mg/m^2, 24–28 h before the 5-FU/LV administration during weeks 1–4 [9]. Dose modifications and/or treatment delay depended on haematological and gastrointestinal toxicity. Patients were considered evaluable for both toxicity and efficacy when they had received at least one full treatment cycle of 8 weeks. Toxicity grades and responses were defined according to WHO criteria.

Between January 1989 and August 1991, 18 patients were entered (Table 1). All were evaluable for both toxicity and response. Toxicity consisted mainly of myelosuppression. Four of 31 courses had to be delayed and in three courses dose reductions were applied because of thrombocytopenia. Grade

Correspondence to B.G. Taal.
The authors are at the Department of Medical Oncology, Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
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Table 1. Patients' pretreatment characteristics

	5-FU/LV + TCNU
Sex (M/F)	10/8
Median age, years (range)	51 (24–66)
Median performance status (range)	1 (0–2)
Primary tumour *in situ*	5
Local recurrence	1
Sites of metastatic disease	
Liver	11
Lung	3
Peritoneal carcinosis	2
Bone	1
No. of tumour sites	
1	11
2	7
3	–

M, male; F, female.

III and IV leucopenia was present in two cycles (6%), grade III and IV thrombocytopenia in 6 (19%) and 2 (6%) courses, respectively. No haemorrhage was observed and platelet transfusions were not required. 1 patient was hospitalised during the first cycle of 5-FU/LV + TCNU because of grade 4 leucopenia and fever which resolved with antibiotics. Nausea and vomiting in 10 cycles (32%) were associated with tauromustine and responded favourably to 10–20 mg (oral) metoclopramide. Diarrhoea and mucositis were not seen and alopecia did not occur.

Among the 18 patients, there were 2 complete remissions (CR), 5 partial remissions, 6 patients with stable disease and 5 patients with progressive disease. Thus, the overall response was 39% (95% confidence interval: 17–65%). 1 complete responder had presented with bilateral lung metastases, which disappeared completely on the chest X-ray. A solitary lung metastasis recurred 3 months after discontinuation of treatment, and responded (partially) to retreatment. The other complete responder had peritoneal carcinosis and a subcutaneous nodule, the latter of which disappeared at clinical examination. The peritoneal carcinosis was not re-evaluated. The median survival of all patients was 12 months (range 3–22). Both CR patients survived for 22 months.

It is tempting to speculate that the antagonism between TCNU and 5-FU that has been demonstrated to exist *in vitro* [6] when the agents are employed simultaneously, may have caused the discouraging outcome of our previous 5-FU/TCNU trial [5]. It is of interest that a similar antagonism has never been observed in combinations of 5-FU with the nitrosurea derivative methyl-CCNU, despite the fact that over 700 patients have taken part in clinical trials [10]. Provided that the agents are applied in the proper time setting, TCNU does not appear to antagonise the activity of 5-FU and LV. Further study will be required to demonstrate any synergism in the clinic.

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Combination IL-2 and Cisplatinum: a Promising Treatment for Bronchioloalveolar Carcinoma?

V. Trillet-Lenoir, D. Arpin, A. Mercatello, R. Oskham, P.A. Palmer, P.J. Souquet, F. Champel, J. Boyer, J.F. Cordier, C.R. Franks, J.F. Moskovtchenko, J. Brune and T. Philip

RECOMBINANT INTERLEUKIN 2 (IL2) has an anti-tumoral effect in some chemoresistant carcinomas including non-small cell lung cancer (NSCLC) [1, 2]. Possible synergy of IL2 and chemotherapy has been reported in several tumours including NSCLC [3]. Similar immunoaugmenting effects have been reported *in vitro* [4] and *in vivo* [5] with cisplatinum, one of the most active drugs in NSCLC. We investigated the feasibility and efficacy of combined cisplatinum and IL2 in patients with

Correspondence to V. Trillet-Lenoir.
V. Trillet-Lenoir, D. Arpin, J.F. Cordier and J. Brune are at the Lung Department, Hopital Louis Pradel, 28 Avenue Doyen Lepine 69394 Lyon; A. Mercatello and J.F. Moskovtchenko are at the Immunotherapy Department, Hopital Edouard Herriot; P.J. Souquet is at the Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, France; R. Oskham, P. Palmer and C.R. Franks are at the Eurocetus, Amsterdam, The Netherlands; F. Champel is at the P.A.R.O.T., Lyon; J. Boyer is at the Lung Department, Centre Hospitalier de Vienne; and T. Philip is at the Centre Léon Bérard, Lyon, France.
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