Table 1. Patient's characteristics

Median age (years) (range)	63 (41–71)
Median ECOG PS (range)	1 (0–3)
Hystological type	
Squamous cell	13
Site of primary	
Nasopharynx	2/13
Oral cavity	1/13
Oropharynx	5/13 (1)
Larynx	3/13 (1)
Hypopharynx	2/13 (1)
Previous treatments	
CT + RT	8/13 (1)
S → CT + RT	2/13
CT + RT → S	1/13
S → RT → CT	2/13 (2)
Site of relapse	
T	6/13 (2)
N	3/13
TN	1/13
M	3/13 (1)

S, surgery; CT, chemotherapy; RT, radiotherapy.
The number of patients who responded to carboplatin and 5-FU are in parentheses.

characteristics of the patients who responded to carboplatin and 5-fluorouracil are shown in the table.

The overall antitumour activity (23% response rate) observed with carboplatin and 5-fluorouracil at the doses employed in the present study can be considered satisfactory considering that in these chemotherapy-pretreated patients, the possibility of reaching a response with a second-line regimen is generally extremely low [1] and that this combination, in pretreated but chemotherapy-naive patients, gives an average response rate of 26% [2]. Moreover, in our experience, the efficacy of a second-line chemotherapy is particularly low when given to patients already treated with cisplatin. In a previous trial, with a methotrexate-based regimen, all 10 patients who had previously responded to cisplatin and 5-FU progressed [3], while in the present study only 2/13 patients progressed under treatment.

In conclusion, our experience suggests that, in clinical practice, when previous responsiveness to cisplatin and the long chemotherapy-free interval lead the physician to offer a second-line chemotherapy to heavily pretreated patients, a further platinum-based chemotherapy can be considered. In this line, a carboplatin/5-FU combination may be a reasonable choice in terms of toxicity/activity ratio.

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Oral Glutamine in the Prevention of Chemotherapy-induced Gastrointestinal Toxicity

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GLUTAMINE (GLN) is the most abundant amino acid in the body [1] and the main energy fuel for enterocytes [2, 3]. Catabolic stress markedly increases the needs for GLN [2, 4] which becomes an essential substrate for damaged intestinal mucosa. The observation that the mucosal brush border doubles GLN uptake in neoplastic diseases, while GLN extraction from blood is significantly reduced [5], prompted us to test oral administration of GLN in adult acute myelogenous leukaemia patients in an attempt to reduce intestinal toxicity induced by combined intensive chemotherapy. The morbidity (nausea, vomiting, abdominal pain, severe diarrhoea, ileus, ileotyphlitis) and mortality secondary to chemotherapy-induced gastro-intestinal toxicity are relatively high [6] and warrant new, cost-effective supportive care measures.

Based on previous clinical studies, in which the administration of 16–30 g/day of GLN was proven safe [7–9], a dose of 18 g of GLN (6 g three time daily, orally in water during meals) was started on day 3 prior to chemotherapy initiation and discontinued if neutrophils recovered (polymorphonuclear leucocytes >500 ml) or parenteral nutrition was initiated. 14 patients (9 M, 5 F), admitted to the Hematology, Department of Human Biopathology of the University of Rome 'La Sapienza', from September 1994 to January 1995 for first intensive remission induction, receiving the EORTC-GIMEMA AML10 protocol (containing either idarubicin or mithoxantrone or daunorubicin in combination with etoposide and cytarabine) were studied. Three patients discontinued GLN early, 2 (14%) because of nausea, 1 for psychological problems, and withdrew from the study. Of the 11 evaluable patients (6 M, 5 F, age range 25–54 years), 5 (45%) continued GLN until neutrophil recovery (median 31 days, range 27–39); 6

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Table 1. Clinical outcomes in the two groups of patients studied

	GLN-supplemented	Unsupplemented	*P*
Patients evaluated	11	22	
Incidence of abdominal distension	2/11 (18%)	4/22 (18%)	n.s.
Incidence of abdominal pain	3/11 (27%)	7/22 (32%)	n.s.
Duration of diarrhoea, days, median	7	12	<0.05
Incidence of diarrhoea*	5/11 (45%)	9/22 (41%)	n.s.
Incidence of mild diarrhoea (3–6 evacuations/day)	5/5 (100%)	3/9 (33%)	n.s.
Incidence of severe diarrhoea (>6 evacuations/day)	0/5	6/9 (67%)	<0.03
Incidence of ileus	0/11	0/22	n.s.
Incidence of ileotyphlitis	2/11 (18%)	7/22 (32%)	n.s.
Time to resolution of ileotyphlitis, days, mean (S.D.)	8.5 (3.54)	11.67 (4.46)	n.s.
Cyprofloxacin prophylaxis	11 (100%)	22 (100%)	n.s.
Fever during neutropenia	11 (100%)	22 (100%)	n.s.
Antibacterial treatment	11 (100%)	22 (100%)	n.s.
Systemic antifungal treatment	5/11 (45%)	18/22 (82%)	0.04
Length of hospital stay, days, median	36	39	n.s.

*Three evacuations/day at least, for 3 consecutive days.

patients (55%) discounted GLN before neutrophil recovery because they needed total parenteral nutrition either for diarrhoea (5 patients) or oral mucositis and minimal food intake (1 patient) (median GLN treatment 17.5 days, range 11–24).

A case–control comparison was performed using a group of patients (12 M, 10, F, aged 24–62 years) (1:2 case:control) with the same underlying disease and matched for sex and chemotherapy, randomly selected by a computer program among a larger cohort of patients enrolled in the same chemotherapeutic protocol between November 1993 and February 1995. During neutropenia, both groups received the same antibacterial and antifungal prophylaxis, and the same broad spectrum antibiotherapy in case of fever. Treatment-related differences in clinical outcome parameters were evaluated by the Student's *t*-test and Fisher's exact test, as appropriate. A P value <0.05 was considered significant.

GLN supplements did not significantly influence the incidence of diarrhoea, as shown in Table 1. This is not surprising, since all patients had received cytarabine, which can induce diarrhoea in up to 32% of patients [10]. However, both duration and severity of diarrhoea were significantly reduced in GLN-supplemented patients ($P < 0.05$ and $P < 0.03$, respectively): none had severe diarrhoea. Moreover, the incidence and time to resolution of ileotyphlitis were reduced although not significantly, and severe diarrhoea during this infectious event was not observed. The use of parenteral nutrition was also significantly reduced in the GLN-supplemented patients. No difference was observed in the incidence of febrile neutropenia and/or the need for antibacterial combinations between GLN supplemented patients and controls. The use of systemic antifungal therapy was significantly reduced in the GLN group, but the relevance of this observation remains uncertain, considering the small number of patients studied.

Based on this limited experience, we conclude that oral administration of GLN in acute leukaemia patients before, during and after chemotherapy is feasible and possibly associated with better tolerance to antineoplastic treatments. The clinical efficacy of this relatively inexpensive nutritional substrate must be confirmed by a larger placebo-controlled, double-blind, randomised trial.

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