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Phase II Study of Cisplatin, 5-Fluorouracil and Folinic Acid in Patients with Carcinoma of Unknown Primary Origin

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THE OBJECTIVE of this study was to evaluate the efficacy and toxicity of cisplatin (CDDP), 5-fluorouracil (5-FU) and folinic acid (FA) in patients with metastatic carcinomas of unknown primary. A number of chemotherapy regimens have been used for these tumours [1–3], with cisplatin, doxorubicin and mitomycin being among the most commonly used agents. Unfortunately, an effective treatment regimen has not yet been established for the majority of patients who present with this syndrome.

The drug combination used in this study was chosen on the basis of laboratory and clinical observations including the recent finding that intracellular levels of 5–10 methyltetrahydrofolic acid are increased following exposure to CDDP, suggesting that cytotoxicity would be enhanced by exogenous folates in the form of FA [4].

All patients had histological proof of carcinoma with no evidence of a primary after an evaluation that included history and physical examination, chest X-ray, mammogram (in females), and computed tomography (CT) scan of the abdomen and pelvis. The gastrointestinal (GI) tract was evaluated radiologically or by endoscopy when indicated. Subgroups of patients with specific clinical presentations known to be associated with a more favourable prognosis [5] were excluded.

Additional requirements were performance status (PS) of < 3 (Zubrod), granulocyte count $\geq 1500/mm^3$, platelet count $\geq 100\,000/mm^3$, bilirubin level ≤ 1.5 mg/dl and creatinine level ≤ 1.5 mg/dl. All patients were previously untreated with chemotherapy.

CDDP, 75 mg/m^2, was administered intravenously (i.v.) on day 1 over 1 h with appropriate hydration, FA (500 mg/m^2) was given i.v. over 2 h on days 1–5, and 5-FU (375 mg/m^2) over 20 min starting 1 h after the initiation of FA infusion (days 1–5). These doses were based on a previously reported phase I trial of this combination [6]. The treatment was repeated every 21–28 days. Toxicity and responses were evaluated according to published criteria [7]. Patients who completed a minimum of two courses of treatment were evaluable for response.

31 patients were entered into the study. Patients' characteristics are shown in Table 1. 27 patients were evaluable for response. Reasons for exclusion were: primary found (1 patient), no evaluable disease (2 patients), lost to follow-up after one course of treatment (1 patient). One complete and seven partial responses were observed, for a response rate of 30% (95% confidence interval, 30 ± 8). The median duration of response was 21 weeks (range 14–92). Median overall survival was 18 months. Median survival for responders was 24 months. Median survival for non-responders was 17 months. Survival was longer than in other reported series, probably reflecting the good performance status (0 or 1) in evaluable patients [1].

Table 1. Patients' characteristics

No. of patients entered	31
No. evaluable for response	27 (87%)
Median age (range)	60 (30–71)
Performance status	
0	9 (29%)
1	21 (68%)
2	1 (3%)
Sex	
Female	17 (55%)
Male	14 (45%)
Prior therapy	
None	29 (94%)
Radiation	2 (6%)
Cell type	
Adenocarcinoma	21
Carcinoma, poorly differentiated	3
Carcinoma, unclassified	1
Clear cell carcinoma	1
Squamous	2
Neuroendocrine	2
Seminoma*	1

* This patient was removed from the study before treatment was started.

Haematological toxicity was modest with an average platelet nadir of 182 000/mm^3 (range 24 000–466 000) and a mean granulocyte nadir of 2000/mm^3 (range 0–10 000). Although there were six instances of neutrophil counts $< 500/mm^3$, none of the patients developed infections.

1 patient experienced an increase (reversible) in the serum creatinine level over the baseline. There were no instances of neurological toxicity above grade 1. Nausea and vomiting were almost universal side-effects. In no instance did chemotherapy have to be discontinued because of excessive toxicity.

Given the low rate of severe complications and response rate similar to other platinum-based combinations [2, 8], this appears to be a reasonable alternative to other proposed regimens in the management of unknown primary carcinomas. Efforts are presently focused on the development of regimens with greater activity.

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