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CLINICAL TRIAL REPORT

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5-Fluorouracil plus 5-methyltetrahydrofolate in advanced pancreatic cancer

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Abstract A total of 20 patients with advanced pancreatic adenocarcinoma were enrolled in a phase II trial testing the activity of 5-fluorouracil given at 370 mg/m^2 as a rapid i.v. bolus for 5 consecutive days, preceded by a rapid i.v. bolus of 200 mg/m^2 5-methyltetrahydrofolic acid. The treatment was repeated every 4 weeks. The median age of the patients was 68 years and their median Eastern Cooperative Oncology Group (ECOG) performance status was 1. There were 7 patients with locally advanced disease and 13 with distant metastases (median, 2 sites). A median of 3 monthly cycles of treatment (range, 1–7) were given, with a corresponding dose intensity of 396 mg/m^2 per week (86% of that planned). No complete response, 1 partial response, and 8 cases of disease stabilization were obtained. In general the regimen was well tolerated, with only 2 patients suffering from grade 3 stomatitis or diarrhea; the most common toxicity was nausea, which was experienced by almost 50% of the patients. The combination of 5-methyltetrahydrofolate plus 5-fluorouracil appears as little effective in this disease as 5-fluorouracil plus 5-formyltetrahydrofolate (leucovorin). It is suggested that bolus 5-fluorouracil is so inactive as an "effector agent" against pancreatic cancer that its biochemical modulation with exogenous high-dose reduced folates cannot improve the therapeutic outcome produced by the fluoropyrimidine in these patients.

Key words 5-Fluorouracil · Pancreatic cancer
Reduced folates

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Abbreviations FUra 5-fluorouracil
LV 5-formyltetrahydrofolic acid
ME-THF 5-methyltetrahydrofolic acid

Introduction

Pancreatic carcinoma is among the most lethal of human malignancies its overall survival being 10% at 2 years and no more than 5% at 5 years [7]. Fewer than 25% of patients undergo resection with radical intention. The median survival varies from approximately 2–6 months for patients with metastatic disease, to 5–12 months for those with locally advanced disease, to 10–20 months for radically resected cases. Radiation therapy alone and chemotherapy alone have no impact on survival at any stage of this disease [6, 13]. Only in the adjuvant setting does the combination of chemotherapy and radiation therapy appear promising [5, 9]. Considering that (a) there is no evidence of a dose-response curve for external-beam radiotherapy exceeding 40 Gy [13], (b) intraoperative radiation therapy trials indicate no prolongation of survival as compared with the figures mentioned above [3], and (c) the time to distant failure in locally advanced disease is extremely short, it is clear that efforts should primarily be directed at identifying new active drugs or drug combinations to be used alone in metastatic disease and, perhaps, in combination with radiation therapy in the locally advanced or radically resected stages.

A recent survey of the medical oncology literature on advanced pancreatic cancer [21] indicated that 22 studies have been performed, 17 on patients with metastatic disease and 5 on those with locally advanced disease. Apart from a few exceptions [4, 6, 10, 11, 13], no drug or drug combination appears effective, with objective response rates being lower than 20% in most instances. Doxorubicin, mitomycin C, cisplatin, fluorouracil (FUra), and streptozotocin are the drugs that have most frequently been used in these studies, but none of these represents a sine qua non, either alone or in combination.

On the wave of partial clinical successes obtained with the biochemical modulation of FUra by 5-formyltetrahydrofolic acid (leucovorin, LV) in colon cancer [15], this combination has recently been tested in advanced pancreatic cancer with discouraging results [1, 2]. We thus sought an alternative way of biochemically modulating the fluoropyrimidine in this disease. FUra was combined with a different source of exogenous reduced folate, 5-methyltetrahydrofolate (ME-THF). The rationale of this combination is the same as that of FUra + LV: enhanced inhibition of thymidylate synthesis via stabilization of the ternary complex 5-fluorodeoxyuridylate–5-10-methylene-tetrahydrofolic acid–thymidylate synthase [14, 19]. However, the differences in the metabolic pathways responsible for the activation of ME-THF and LV to the active compound 5-10-methylene-tetrahydrofolic acid, or its polyglutamylated derivatives [16], might afford activity and selectivity greater than that of the FUra + LV combination, which has been clinically tested in this disease.

Patients and methods

Patients were eligible for the study if they had all the following conditions: (1) histologically or cytologically proven adenocarcinoma of the pancreas, (2) metastatic or locally advanced disease that was bidimensionally measurable by computerized tomography (CT) scan or ultrasound, (3) an ECOG performance status of 0, 1 or 2, (4) a total bilirubin level of <3.0 mg/dl and a serum creatinine level of <2.0 mg/dl, and (5) adequate bone marrow function (WBC, $>3{,}000/\mu l$; platelet count, $>100{,}000/\mu l$). Furthermore, no prior chemotherapy or radiation therapy was allowed except for patients with measurable metastatic disease who had received prior radiotherapy on their primary tumor.

Chemotherapy was given on an outpatient basis and consisted of cycles of FUra given at 370 mg/m^2 as a rapid i.v. bolus for 5 consecutive days; each administration was preceded by a rapid i.v. bolus of 200 mg/m^2 ME-THF (Prefolic, supplied by Bioresearch, Milan, Italy). The treatment was repeated every 4 weeks. It was delayed if WBC or platelet counts were below $3{,}000/\mu l$ and $100{,}000/\mu l$, respectively, on the day of re-cycling, and the dose of FUra was reduced by 50% in case of WHO grade 2 or 3 diarrhea or mucositis. No dose reduction was planned for the folate.

The objective response was assessed monthly by CT scan or ultrasound. A complete response required total resolution of all detectable tumor. A partial response required at least a 50% reduction in the product of the two maximal tumor diameters lasting a minimum of 2 months and the absence of new lesions.

The protocol followed a two-stage design [17]. Alpha and beta errors were set at 0.05 and 0.20, respectively; P0 was 0.10 and P1, 0.25. A total of 18 patients were admitted to the 1st stage; since only 1 response was observed, the study was closed without extension to the 2nd stage (43 patients). The protocol was approved by the Human Investigation Committee of the Istituto Nazionale per la Ricerca sul Cancro, and verbal informed consent had to be obtained from each patient before the beginning of the treatment.

Results

Between April 1991 and October 1992, 20 patients from the area around Genova were accrued. Their characteristics are shown in Table 1. The diagnosis was confirmed histocytologically in all of the 20 patients registered: 10 during laparotomy, 8 via fine-needle aspiration of pancreatic masses under ultrasound guidance, and 2 by means of endoscopic retrograde brush cytology. There was no carcinoma arising from the endocrine pancreas, and the histological type was ductal adenocarcinoma in all patients. A median of 3 cycles of treatment (range, 1–7) were given, and the dose intensity of FUra actually delivered was 86% of that planned, i.e., 396 mg/m^2 per week.

Table 2 illustrates the therapeutic outcome. In all, 3 registered patients never received the treatment, and 2 additional patients died within 1 month of the beginning of chemotherapy of rapidly progressive disease, before the response assessment. The responding patient, who had metastatic liver disease, responded after the second cycle and progressed after 6 months. Of the 5 patients with locally advanced disease, 2 had disease stabilization and 3 progressed. The median survival of the 17 treated patients was approximately 7 months, and this figure was similar for patients with locally advanced (5) and metastatic disease

Table 1 Patients' characteristics (*ERCP* Endoscopic retrograde cholangiopancreatography)

Number of patients registered	20
Histologic diagnosis	20
Median age, years (range)	68 (42–79)
M:F ratio	11:9
ECOG performance status (range)	1 (0–2)
Primary location:	
Head	8
Head/body	1
Body	3
Body/tail	8
Locally advanced: metastatic disease	7:13
Number of metastatic sites: 1:2:>2	5:7:1
Prior surgery:	
None	7
Exploratory laparotomy only	6
Biliary bypass	3
Biliary stent via ERCP	3
Partial pancreatectomy	1

Table 2 Therapeutic outcome

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Patients registered	20
Treatment refusal	1
Progression before start of treatment	2
Patients treated:	17
Locally advanced disease	5
Metastatic disease	12
Complete response	0
Partial response	1
Stable disease	10
Progressive disease	4
Median survival, days (range)	225 (67–336)

Table 3 Toxicity encountered, expressed as the percentage of patients with toxicity according to the worst grade observed in the present trial (FUra+ME-THF) as compared with the toxicity observed in patients with colorectal cancer treated with FUra+6-S-LV (daily × 5 schedule) [18]

Toxicity	Grade	FUra+ME-THF (n = 17)	FUra+6-S-LV (n = 79)
Stomatitis	1–2	27	55
	3–4	5	14
Diarrhea	1–2	22	35
	3–4	5	17
Nausea/vomiting	1–2	44	41
	3–4	0	6
Leucopenia	1–2	11	49
	3–4	0	2
Thrombocytopenia	1–2	0	2
	3–4	0	0
Alopecia	1–2	16	14
	3–4	0	1

(12). In general the regimen was well tolerated, with only 2 patients suffering from grade 3 stomatitis or diarrhea; the most common toxicity was nausea, which was experienced by 44% of the patients (Table 3).

Discussion

The biochemical modulation of FUra with LV or methotrexate has improved the activity and, in some instances, the efficacy of the fluoropyrimidine against advanced colorectal cancer [12, 15]. In addition, the highly active FUra-Adriamycin-methotrexate (FAMTX) regimen for gastric cancer [22] is strongly based upon the potentiation of FUra by methotrexate in the sequence methotrexate→FUra. Finally, FUra + LV is a promising combination in advanced head and neck [20] and breast cancer [19]. The biochemical modulation of FUra might thus be expected to improve the therapeutic results in those neoplasms against which the fluoropyrimidine has some activity. Unfortunately, such is not the case for pancreatic cancer; the conclusion of our study with FUra + ME-THF, together with the results of two other recent phase II studies with FUra + LV [1, 2], is that enhancing the DNA effect of FUra by high doses of reduced folates does not improve the clinical activity of the drug against this disease. The source of exogenous folates as modulators of FUra does not appear to be a determinant of activity, since the results we obtained with ME-THF are equivalent to those reported for LV [1, 2].

Of interest is the limited toxicity of the FUra + ME-THF regimen. Only 3 of 60 cycles produced grade 3 toxicity. This figure contrasts with the toxicity of the FUra + LV regimens, which are known to produce severe toxicity in approximately 20% of patients, regardless of whether the fluoropyrimidine is given on the weekly schedule or the 5-day schedule [15]. While doing this trial on pancreatic cancer, our group conducted a phase II study of FUra + 6-S-LV (given daily for 5 days every 4 weeks) in patients with advanced colorectal cancer [18]. Thus, toxicity data from the same investigators at the same institution are available for the comparison of FUra + 6-S-LV with FUra + ME-THF (daily × 5 schedule). Table 3 reports these data.

Many fewer episodes of severe stomatitis and diarrhea were observed in the present study with ME-THF, indicating that FUra + ME-THF given by the present schedule is less toxic than FUra + 6-S-LV. The explanation for this difference may be sought in the metabolic pathways responsible for the activation of ME-THF and LV to the active cofactor 5-10-methylene-tetrahydrofolate. The former is converted to tetrahydrofolate and then to 5-10-methylene-tetrahydrofolate and the latter, to the intermediate metabolite 5,10-methenyl-tetrahydrofolate [16]. The efficiency of these conversions, as well as the extent of polyglutamylation of these cofactors [8], may be tissue-specific and may account for the differing toxicity observed.

These observations may be useful in the design of trials based upon the biochemical modulation of FUra by reduced folates for the treatment of neoplasms that are responsive to fluoropyrimidines such as colon, breast, gastric, and head and neck cancer; however, the present data suggest that FUra given as a bolus is inactive as an effector agent against pancreatic cancer and, therefore, its biochemical modulation cannot be expected to improve the therapeutic outcome in this disease.

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