Treatment of Advanced Adenocarcinomas of the Exocrine Pancreas and the Gallbladder with 5-Fluorouracil, High Dose Levofolinic Acid and Oral Hydroxyurea on a Weekly Schedule

Results of a Multicenter Study of the Southern Italy Oncology Group (G.O.I.M.)

Vittorio Gebbia, M.D. Ph.D.[1]
Evaristo Majello, M.D.[2]
Antonio Testa, M.D.[1]
Giuseppe Pezzella, M.D.[3]
Serravezza Giuseppe, M.D.[4]
Francesco Giotta, M.D.[2]
Fernando Riccardi, M.D.[5]
Santo Fortunato, M.D.[6]
Giuseppe Colucci, M.D.[2]
Nicolò Gebbia, M.D., Ph.D.[1]
for the Southern Italy Oncology Group

[1] Service of Chemotherapy, Policlinico, University of Palermo Palermo, Italy.

[2] Division of Medical Oncology, Oncological Institute, Bari, Bari, Italy.

[3] Service of Medical Oncology, "SS Annunziata" Hospital, Taranto, Italy.

[4] Oncology Unit, Civil Hospital, Casarano, Italy.

[5] Division of Medical Oncology, "Caldarelli" Hospital, Naples, Italy.

[6] Oncology Center Analisi, Catania, Catania, Italy.

Preliminary data have been presented at the 19th Congress of the European Society of Medical Oncology, Lisbon, Portugal, November 18–22, 1994; and published as abstract in *Ann Oncol* 1994; 5(Suppl 8):84.

BACKGROUND. To date there is no established chemotherapeutic treatment for patients with unresectable locally advanced and/or metastatic carcinomas of the exocrine pancreas or the gallbladder. A multicenter Phase II trial has been performed by the Southern Italy Oncology Group with the aim of evaluating the clinical effectiveness and tolerability of weekly 5-fluorouracil (5-FU) in modulation with intravenous (i.v.) high dose levofolinic acid and oral hydroxyurea.

METHODS. A total of 70 patients fulfilling the standard eligibility for a Phase II study were enrolled in the trial. Forty patients had advanced pancreatic adenocarcinoma and 30 had advanced gallbladder carcinoma. The treatment schedule was: levofolinic acid, 100 mg/m^2, in 500 mL of normal saline over 2-hour infusion followed by 5-FU, 600 mg/m^2 i.v. bolus, and oral hydroxyurea, 1000 mg/m^2, for 1 day every week for 6 consecutive weeks followed by 15 days of rest.

RESULTS. Among the 40 patients with pancreatic adenocarcinoma, 5 (12.5%; 95% confidence level [CL], 8.5–16.5%) showed a partial response with a median duration of 5.6+ months, and 13 had stable disease. Twenty-two patients progressed. Median survival was 5.8 months. Among patients with advanced gallbladder carcinoma, 9 of 30 had a partial response (30%; 95% CL, 26–34%) with a median duration of 6.5 months, and 8 (27%) had stabilization of disease. Thirteen patients showed progressive disease. Median overall survival was 8 months. Toxicity was mild, with Grade 1 to 2 leukopenia and gastrointestinal toxicity the most frequent side effects. No chemotherapy-related deaths were observed.

CONCLUSIONS. 5-FU in modulation with i.v. levofolinic acid and oral hydroxyurea on a weekly schedule is well tolerated by the vast majority of patients with locally advanced and/or metastatic carcinoma of the pancreas or the gallbladder. Although response rate and overall survival for patients with pancreatic adenocarcinoma are far from acceptable, the 30% overall response rate achieved in patients with advanced gallbladder carcinoma suggests that 5-FU in modulation with levofolinic acid and hydroxyurea is active in this neoplasm. The combination of modu-

Other members of the Southern Italy Oncology Group include: Ernesto Durini, M.D., Oncology Service, Civil Hospital, Tricase, Italy; Francesco Giuliani, M.D., Unità Operativa Medicina, Oncological Institute, Bari, Italy; Giuseppe Pisconti, M.D., Medical Oncology, Hospital "SS Annunziata, Taranto, Italy; Roberto Valenza, M.D., Service of Chemotherapy, Policlinico, Palermo, Italy; and Rosalba Cifarelli, M.D., Unità Operativa Medicina, Oncological Institute, Bari, Italy.

Address for reprints: Vittorio Gebbia, M.D., Ph.D., Service of Chemotherapy, Institute of Pharmacology, Policlinico—via del Vespro n. 129; 90127 Palermo, Italy.

Received February 9, 1996; revision received May 13, 1996; accepted May 13, 1996.

lated 5-FU with other antineoplastic drugs seems worthy of clinical testing in further controlled trials. *Cancer* **1996; 78:1300–7.** © *1996 American Cancer Society.*

KEYWORDS: pancreatic carcinoma, gallbladder carcinoma, levofolinic acid, 5-fluorouracil, hydroxyurea, chemotherapy.

In the last two decades, the prognosis of exocrine pancreatic adenocarcinoma has remained dismal because most patients at diagnosis still present with distant metastatic involvement (any T-N, M 1; Stage IV) or locally advanced tumors (T3 N0 M0 [Stage II] or T1-3 N1 M0 [Stage III]), which often are not ameneable for radical surgery.[1–3]

Although evaluation of the activity of chemotherapeutic treatments against pancreatic carcinoma is often hampered by patients' poor performance status and by difficulties in measuring the extension of disease, pancreatic adenocarcinoma is generally considered a chemotherapy-resistant malignant neoplasm.[1–3] Among single agents most commonly employed in advanced pancreatic carcinoma, only 5-fluorouracil (5-FU) and mitomycin C have been reliably shown to induce a nearly 20% overall response rate.[1,2,4] However, this borderline activity of 5-FU has been documented in several Phase II trials performed more than two decades ago when strict radiologic monitoring with imaging techniques was not routinely employed for the assessment of objective responses.[5,6] Combination chemotherapy regimens, such as the 5-fluorouracil, doxorubicin, and mitomycin C (FAM) and streptozotocin, mitomycin C, and 5-fluorouracil (SMF), were shown to induce a nearly 30% overall response rate with a largely unsatisfactory overall median survival of fewer than 6 months.[1,7–11] Subsequent Phase III trials failed to confirm this activity of combination chemotherapy, reporting lower response rates with a similar duration of response.[12–15] However, in the Phase III trial by Mallinson et al.[16] polychemotherapy was reported to significantly improve median survival over untreated controls. Unfortunately, this latter trial and a subsequent study by Cullinan et al.[17] also suggested that more aggressive polychemotherapy was not better than monochemotherapy with 5-FU alone.

Clinical reports on the chemotherapeutic treatment of patients with advanced gallbladder carcinoma and cholangiocarcinomas are almost anedotical.[18] 5-FU and mitomycin C have been shown to induce a nearly 20% overall response rate, but its should be stressed that these results have been obtained in 2 very small series of 15 and 17 patients, respectively.[19] Similar results have been reported by the Eastern Cooperative Oncology Group (ECOG) with 5-FU in advanced bile tract carcinomas[20] and by the European Organization for the Research and Treatment of Cancer (EORTC) with mitomycin C in advanced gallbladder and bilary tree carcinomas.[21] The FAM regimen has also been tested in a series of 13 patients, achieving a 30% overall response rate and a median duration of response of 8.5 months.[22] Similar response rates have been obtained by Harvey et al.[23] with the FAM regimen and by Rougier et al.[24] and Walzymer et al.,[25] who combined 5-FU with cisplatin alone or plus mitomycin C and methotrexate. Although there is not a standard treatment for patients with advanced gallbladder carcinoma and cholangiocarcinomas, the FAM regimen may represent a possible therapy, as suggested by others.[18]

Recently there has been much interest in the possibility of increasing 5-FU activity and therapeutic selectivity by the use of biochemical modulators such as folinic acid, interferons, and cisplatin.[26,27] Folinic acid strengthens the binding of the 5-FU active metabolite 5-FdUMP (deoxyuridine monophosphate) to its target enzyme, thymidylate synthase, forming a stable ternary complex that dissociates very slowly.[28] This biochemical interaction increases the fluoropyrimidine cytotoxic activity. The 5-FU-induced inhibition of thymidylate synthase leads to a progressive increase in the intracellular deoxyuridine monophosphate pool, which thus may more effectively compete with FdUMP for binding sites on thymidylate synthase.[29,30] The intracellular production of dUMP is mediated by the enzyme ribonucleotide reductase, which reduces uridine triphosphate (UTP), and by deoxycytidine deaminase, which catalyses the deamination of 2′-deoxycytidine monophosphate. The administration of hydroxyurea (HU), a well known inhibitor of ribonucleotide reductase, may thus deplete the intracellular pool of dUMP, allowing FdUMP to compete more effectively for thymidylate synthase binding sites.[31–33] The combination of 5-FU and HU with or without levofolinic acid has been employed in advanced colorectal and head/neck carcinomas with interesting preliminary clinical results.[34–37]

Based on the above reported preclinical data and on the interesting results achieved in the treatment of patients with advanced colorectal carcinoma, we performed a multicentric Phase II study of 5-FU modulated with high dose levofolinic acid and oral HU in

a series of patients affected by chemotherapy-naive advanced pancreatic or gallbladder carcinomas.

MATERIALS AND METHODS

Elegibility Criteria

After approval from the Ethical Committee of the Southern Italy Oncology Group, a multicenter Phase II trial was begun in October 1992 and closed in July 1995. To be eligible for the study, all patients were required to meet the following entry criteria: histologic confirmation of exocrine pancreatic adenocarcinoma or gallbladder carcinoma; written informed consent; bidimensionally measurable disease according to the World Health Organization (WHO) criteria,[38] performance status according to Karnofsky index $\geq$ 60; life expectancy $>$ 2 months; age $\leq$ 75 years; no sign of clinically detectable brain metastases; absence of a second malignancy other than adequately treated cutaneous basalioma or in situ uterine carcinoma; no major concomitant infective, cardiovascular, neurologic, or respiratory disease; and geographical accessibility to the participating centers to guarantee a correct follow-up. Patients also had to meet the following laboratory criteria: leukocyte count of $\geq$4,000/mm^3 with an absolute neutrophil count $\geq$ 1500/mm^3; platelets $\geq$ 120,000/mm^3; hemoglobin $\geq$ 10 g/dL; serum billirubin $<$ 2 m/dL; serum creatinine $\leq$ 1.2 mg/dL; and blood urea nitrogen $\leq$ 50 mg/dL.

Study Design and Treatment Plan

Pretreatment evaluation included complete medical history and physical examination, standard chest X-ray, abdominal sonogram, bone ^{99}TC scan, routine chemistry tests and hemocromocytometric analysis, carcinoembryonic antigen and CA 19-9. Computed tomography scan of the abdomen was mandatory to precisely define disease extension.

Chemotherapy was given on an outpatient basis to all patients. The treatment plan included: levofolinic acid, 100 mg/m^2 in 500 mL of normal saline, over 2-hour infusion followed by 5-FU, 600 mg/m^2 intravenous bolus. HU, 1000 mg/m^2, was given orally in 3 refracted doses for 24 hours starting 6 hours after 5-FU administration. Because HU dosage is commercially available as 500-mg capsules, dosages were adjusted according to a body surface area (BSA) cutoff arbitrarily established as follows: if BSA $\leq$ 1.7 m^2, 3 capsules (1500 mg) were given; if BSA $>$ 1.7 m^2, 4 capsules (2000 mg) were given. This treatment was repeated weekly for 6 consecutive weeks followed by a 15-day rest period, during which time patients were restaged. Chemotherapy was continued until progression of disease or unacceptable toxicity ensued. Accordingly to Gehan's formula[39] for an estimated therapeutic effectiveness of 20% and a 10% rejection error, 11 patients with pancreatic carcinoma were initially enrolled into the trial within 2.8 months. The same calculation was applied to patients with gallbladder carcinoma. If at least one major objective response was observed in this group, then patient accrual had to be continued to reach approximately 45 patients to confirm a 20% therapeutic effectiveness with a 5% standard error.

Response Criteria

After at least 1 complete cycle of chemotherapy (8 weeks), patients were restaged. Objective responses were classified according to the WHO criteria.[38] Briefly, the complete disappearance of all signs of disease was defined as complete response (CR); partial response (PR) was defined as a $\geq$50% reduction in the sum of the products of the major perpendicular greatest dimensions of all measurable lesions without the appearance of any new lesions; stabilization (SD) was defined as a $<$50% or $<$25% increase in the size of tumoral deposits; and progressive disease (PD) was defined as the appearance of new metastases or a $\geq$25% increase in the size of tumoral lesions. Objective responses were reported as relative rates with their 95% confidence limits (95% CL) according to an intent-to-treat analysis.

Statistics

The product limit analysis according to Kaplan–Meier was employed for analysis of response duration and survival.[40] These variables were calculated from the first day of chemotherapeutic treatment until progression or death.

Toxicity

Toxicity was reported according to the WHO criteria.[38] Patients were closely monitored for gastrointestinal toxicity, especially diarrhea, which was promptly treated with oral loperamide, and in severe, refractory, or unresponsive cases with parenteral electrolyte and fluid repletion and subcutaneous octreotide, as previously reported.[41] With this procedure, it is generally possible to prevent severe diarrhea by vigorously treating patients as soon as diarrhea is reported. In the case of Grade 3 diarrhea or oral mucositis, treatment was stopped until recovery and then restarted with a 25% reduction in 5-FU dosage. A complete hematologic analysis and serum chemistry tests were obtained every 3 weeks during chemotherapy. In the case of Grade 2 leukopenia and/or Grade 1 thrombocytopenia, chemotherapy was delayed by 1 week. If $>$2 episodes of Grade 2 leukopenia occurred during 1 cycle of chemotherapy, 5-FU dosage was reduced to 450 mg/m^2/week.

TABLE 1
Clinical Characteristics of Patients

Characteristics	Pancreatic carcinoma	Gallbladder carcinoma
No. of enrolled patients	40 (100%)	30 (100%)
Median age (yrs)	64	60
Range	53–74	45–75
Males/females	23/17	5/25
Median performance status (KI) range	80	80
	60–100	60–100
Histology		
Adenocarcinoma	38 (95%)	28 (93%)
Undifferentiated ca	2 (5%)	2 (7%)
Previous treatments		
Surgery	6 (15%)	20 (67%)
Palliative	2 (5%)	14 (41%)
Radical	4 (10%)	6 (20%)
Radiotherapy	2 (5%)	0 (—)
Stent		
Chemotherapy	None	None
Stage		
Stage III (T2-3 N1)	11 (28%)	Stage III 3 T3N0 1 T3N1 2
Stage IV	29 (72%)	Stage IVA 3 Stage IVB 24 (M1 or recurrent)
Sites of disease		
Locoregional	37	12
Liver	20	16
Lung	2	2
Distant nodes	4	2
Bone	1	0
Peritoneum	3	4
Soft tissue	1	0

KI: Karnofsky index; ca: carcinoma.

RESULTS

Patient Population

A total of 70 consecutive eligible patients with advanced adenocarcinoma of the exocrine pancreas or gallbladder were enrolled in this clinical trial. The main demographic and clinical characteristics of enrolled patients are presented in Table 1.

Pancreatic Adenocarcinoma

The 40 enrolled patients had locally advanced unresectable (T2-3N1M0) or metastatic (anyTN,M1) adenocarcinoma of the pancreas with a median age of 64 years (range, 53–74 years) and a median performance status according to Karnofsky index of 80 (range, 60–100). There were 23 males (57%) and 17 females (43%). Four patients (10%) had previous radical surgery, 2 patients (5%) had palliative surgery, and another 2 patients had received radiotherapy. No patient had been previously treated with chemotherapy. Sites of disease mainly included locoregional tumor and/or metastatic liver involvement. Eleven patients (28%) had Stage III carcinoma, and 29 patients (72%) had Stage IV disease.

Gallbladder Carcinoma

The 30 enrolled patients, with a median age of 60 years (range, 45–75 years) and a median performance status of 80 (range, 60–100), had metastatic Stage IVB disease (80%) or locally unresectable Stage III–IVA carcinoma of the gallbladder (20%). Histologically, most patients (93%) had adenocarcinoma of the gallbladder and 2 had an undifferentiated carcinoma. Among these patients, most of whom were females (83%), 6 patients had undergone previous radical surgery (20%), and 14 had palliative surgery (41%). No patient had previous chemotherapy. Sites of disease mainly included both locoregional unresectable or recurrent neoplasm and metastatic involvement of the liver. Two patients had tumoral deposits at the lungs, and an additional four patients had metastatic disease into the peritoneum.

Objective Response and Survival

Pancreatic Carcinoma

All enrolled patients with advanced pancreatic carcinoma were considered evaluable for response according to an intent-to-treat analysis. Two patients did not complete the last week of therapy of the first chemotherapy cycle due to clinically PD. These two patients were restaged and considered as progressions. No CR was observed. A PR was recorded in 5 patients (12.5%; 95% CL, 8.5–16.5%) with a median duration of 5.6+ months (range, 4–6.2+ months), SD in 13 patients (32.5%) with a median duration of 4 months, and 22 patients progressed (55%). Two patients did not complete the sixth week of therapy of first cycle due to PD. These two patients were considered as progressions. Responses were observed at liver metastatic deposits in three patients and at the primary tumor in two patients. The median survival was 5.8 months (range, 2.3–12+ months). Despite the low response rate, 8 patients (20%) reported a symptomatic improvement in terms of reduction of subjective sense of pain, analgesic drug consumption, and energy. Such improvement was recorded in four patients with PR and in an additional four patients with objective SD, even in patients who did not show an objective response.

Gallbladder Carcinoma

Among the 30 patients with advanced and/or metastatic gallbladder carcinoma, 9 patients showed a PR (30%; 95% CL, 26–34%) with a median duration of 6.5

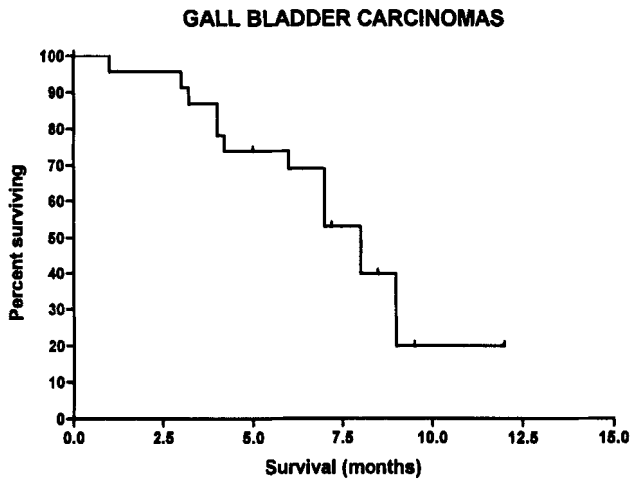

FIGURE 1. Overall survival.

months (range, 5–9+ months). SD was observed in 8 patients (27%), and PD in 13 patients (43%). All responses were recorded at liver metastases, but one was recorded at lymph node metastases. The median overall survival (Fig. 1) was 8 months (range, 1–11+ months).

Toxicity

As shown in Table 2, this regimen has been well tolerated by most patients. No chemotherapy-related deaths were observed. The 70 patients enrolled into the study received a total of 126 cycles (1.8 cycles/patient) for a total of 754 weeks of therapy (10.8 weeks/patient). The most frequent toxicity was leukopenia (37%); however, it was mild in all cases (Grade 1-2). Thrombocytopenia was sporadically observed. Mild Grade 1-2 vomiting was recorded in 33% of patients, and Grade 1 stomatitis in 10%. Grade 3 gastrointestinal toxicities were virtually absent, with the exception of Grade 3 diarrhea recorded in 6% of patients. Only one patient required hospitalization due to the simultaneous occurrence of fever and diarrhea.

DISCUSSION

To date, there is no standard polychemotherapeutic regimen for advanced pancreatic adenocarcinoma and 5-FU monochemotherapy is still considered the routinary palliative treatment for advanced pancreatic carcinomas by many oncologists.[1–6] In this study, a 12.5% PR rate (95% CL, 8.5–16.5%) was achieved in a series of 40 patients with locally advanced and/or metastatic pancreatic adenocarcinoma with a median duration of response of 5.6+ months, and a median overall survival of 5.8 months. Thirteen other patients had SD of short duration. A subjective improvement of symptoms and analgesic consumption was recorded in approximately 20% of cases.

In our opinion, these results were largely unsatisfactory and demonstrated that 5-FU modulated by levofolinic acid and oral hydroxyurea is poorly effective against locally advanced and/or metastatic pancreatic adenocarcinoma, at least using the weekly schedule and the standard WHO criteria for definition of response. Moreover, overall survival is far from acceptable.

These results are consistent with the clinical results achieved by other authors with 5-FU monochemotherapy modulated by interferon,[42] levofolinic acid,[43–45] or interferon plus folinic acid.[46–48] In fact, all these studies reported response rates lower than 20% and confirmed the observation that the biochemical modulation of 5-FU does not yield better results than 5-FU alone, even though no prospective randomized Phase III study has directly addressed this issue and most articles have been retrospectively compared with data achieved before the 1980s, when imaging techniques were not routinely employed for definition of objective response. Some discrepancies between the above-reported results and those achieved in other studies[49] may well be explained by differences in patients series and the difficulty in measuring pancreatic carcinoma, even with the newest imaging techniques, because any enlarged pancreatic area may not necessarily be equivalent to a pancreatic neoplasm. Gallbladder carcinoma is a relatively uncommon cancer in the West, but it represents a major challenge for oncologists due to its high mortality rate and the difficulty in obtaining an early diagnosis.[50,51] In fact, most patients are diagnosed at a very advanced stage, and are often unresectable and with metastatic disease.[18–20] Gallbladder carcinoma shows a female to male ratio of 3:1, with peak incidence at the age of 70 years.[50] To our knowledge, the series reported in our study is one of the largest ever published regarding the chemotherapeutic treatment of locally advanced and/or metastatic gallbladder carcinoma with a uniform regimen in a controlled trial. Our series is totally consistent with the above-mentioned demographic data showing a mean age and a male/female ratio superimposable to those reported in the medical literature.[50,51]

Medical literature concerning the chemotherapeutic management of metastatic gallbladder carcinoma is scarce.[18–20] The FAM regimen[18,20,23] and the combination of 5-FU + cisplatin with[24] or without[25] methotrexate and mitomycin C have been reported to yield a nearly 30% overall response rate with significant gastrointestinal toxicity in approximately one-third of patients and a median survival of 6 to 10 months. In the current study, the combination of 5-FU plus levofolinic acid and oral hydroxyurea on a

TABLE 2
Toxicity

	WHO score			
Type of toxicity	Grade 1	Grade 2	Grade 3	Overall
Nausea/vomiting	16 (23%)	7 (10%)	None	23 (33%)
Diarrhea	7 (10%)	5 (7%)	4 (6%)	16 (23%)
Stomatitis	7 (10%)	None	None	7 (10%)
Leukopenia	16 (23%)	10 (14%)	None	26 (37%)
Platelets	3 (4%)	None	None	3 (4%)
Anemia	2 (3%)	1 (2%)	None	3 (4%)
Fever	2 (3%)	None	None	2 (3%)
Cutaneous	3 (4%)	None	None	3 (4%)
Conjunctivitis	2 (3%)	None	None	2 (3%)

WHO: World Health Organization.

weekly schedule has yielded a 30% partial response rate (95% CL, 26–34%) with a median duration of 6.5 months and a median overall survival of 8 months. These results are quite significant because 5-FU modulated by levofolinic acid and oral hydroxyurea appears to be as active as the FAM regimen or cisplatin + 5-FU, even if such a comparison is not conclusive because of the lack of a head to head comparison and the scarcity of medical literature concerning the chemotherapeutic management of advanced gallbladder carcinoma.

The possibility that biochemical modulation of 5-FU may represent an active therapy for gallbladder carcinoma is partially confirmed by the data of Patt et al.,[52] who reported 39% overall response rate in a series of 18 patients with biliary tract carcinoma treated with continuous venous infusion 5-FU plus interferon-α. These data are further strengthened by Colleoni et al.,[53] who reported a 25% overall response rate in 27 patients treated with oral folinic acid and doxifluridine. However, Ellis et al.[54] have recently reported a significant 40% overall response rate with a 10-month duration in a well conducted trial employing an aggressive schedule with epirubicin, cisplatin, and infusional 5-FU as first-line chemotherapy for biliary system carcinoma. These latter data could suggest a role of infusional 5-FU in the management of biliary system carcinomas. Recently, a 48% overall response rate has been reported in a Phase II trial of superselective intraarterial chemotherapy with mitomycin C.[55] Unfortunately, this technique is not useful in those patients with peritoneal implants or metastatic disease.

The reported toxicity is similar to that observed with the same schedule in other gastrointestinal malignances. However, the incidence of severe Grade 3 diarrhea was lower than expected from studies on colorectal carcinoma. This observation may be due to clinical differences between patients with advanced colorectal carcinoma and those with metastatic pancreatic or gallbladder carcinoma or to the improved management of diarrhea consequent to the increased awareness by both oncologists and patients of the problem and its prompt treatment.

In conclusion, the combination of 5-FU with levofolinic acid and oral hydroxyurea on a weekly schedule is poorly active against locally advanced unresectable and/or metastatic pancreatic adenocarcinoma and surely no better than historic data reported for 5-FU alone. The 12.5% objective response rate, the short duration of response, and the moderate subjective improvement observed in 20% of patients are not satisfactory. Moreover, data recently achieved with gemcitabine in 5-FU-resistant patients with advanced pancreatic adenocarcinoma, especially in terms of objective improvement rather than objective response, appear to be superior to those reported with 5-FU alone or in combination with several modulators, even if a direct head to head comparison is lacking.[56] Conversely, this weekly combination appears to be quite active in advanced and/or metastatic gallbladder carcinoma, and may be considered a useful palliative treatment for such a neoplasm. However, the low number of patients and the Phase II nature of this study do not permit clinicians to draw any significant conclusion as to the duration of response and the possible impact of such treatment on patient survival. In both pancreatic and gallbladder carcinoma, this regimen has been very well tolerated in most patients and may be safely given on an outpatient basis.

REFERENCES

1. O'Connell MJ. Current status of chemotherapy for advanced pancreatic and gastric cancer. *J Clin Oncol* 1985;3:1032–9.

2. Wagener DT, de Mulder PHM, Wils JA. Multimodality treatment of advanced pancreatic cancer. *Ann Oncol* 1994;5 (Suppl 3):81–6.
3. Kelly DM, Benjamin IS. Pancreatic carcinoma. *Ann Oncol* 1995;6:19–28.
4. Arbruck SG. Overview of chemotherapy for pancreatic cancer. *Int J Pancreatol* 1990;12:209–22.
5. Carter SK. The integration of chemotherapy into a combined modality approach for cancer treatment. VI. Pancreatic adenocarcinoma. *Cancer Treat Rev* 1975;2:193–214.
6. Moertel CG. Chemotherapy for gastrointestinal cancer. *Clin Gastroenterol* 1976;5:777–93.
7. Bitran JD, Desser RK, Kozloff MF, Billings AR, Shapiro CM. Treatment of metastatic pancreatic and gastric adenocarcinoma with 5-fluorouracil, adriamycin, and mitomycin C (FAM). *Cancer Treat Rep* 1979;63:2049–51.
8. Smith FP, Hoth DF, Levin B, Coombs A, Walker A, McDonald F. 5-fluorouracil, adriamycin, and mitomycin C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. *Cancer* 1980;46:2014–8.
9. Wiggans RG, Wooley PV, MacDonald JS, Smythe T, Ueno W, Schein PS. Phase II trial of streptozotocin, mitomycin C, and 5-fluorouracil (SMF) in the treatment of advanced pancreatic cancer. *Cancer* 1978;44:387–91.
10. Bukowsky RM, Abderhalden RI, Hewlett JS. Phase II trial of streptozotocin, mitomicyn C, and 5-fluorouracil in adenocarcinoma of the pancreas. *Cancer Clin Trials* 1980;3:321–4.
11. Smith FP, Stablein DM, Schein PS. Phase II combination chemotherapy trials in advanced measurable pancreatic cancer. *Proc Am Soc Clin Oncol* 1984;3:150.
12. Bukowsky RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chen TT. Randomized trial of 5-fluorouracil and mitomycin C with or without streptozotocin for advanced pancreatic cancer. *Cancer* 1983;52:1577–82.
13. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric adenocarcinoma:fluorouracil versus fluorouracil and doxorubicin versus fluorouracil, doxorubicin, and mitomycin C. *JAMA* 1985;253:2061–7.
14. Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma:fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin C plus fluorouracil. *J Clin Oncol* 1986;4:1794–8.
15. Oster MW, Gray R, Panasci L, Perry MC, for the Cancer and Leukemia Group B. Chemotherapy for advanced pancreatic cancer:a comparison of 5-fluorouracil, adriamycin, and mitomycin C (FAM) with 5-fluorouracil, streptozotocin, and mitomycin C (FMS). *Cancer* 1986;57:29–33.
16. Mallinson CN, Rake MO, Cocking JB. Chemotherapy in pancreatic cancer:results of a controlled, prospective, randomized multicenter trial. *BMJ* 1980;281:1589–91.
17. Cullinan S, Moertel CG, Wieand HS, Schutt AJ, Krook JA, Foley JF, et al. A phase III trial on the therapy of advanced pancreatic carcinoma. *Cancer* 1990;65:2207–12.
18. Macdonald JS, Gunderson LL, Adson MA. Cancer of the hepatobiliary system. In:De Vita VT, Hellman S, Rosenberg SA, editors. Cancer principles and practice of oncology. Philadelphia: JP Lippincott Co, 1982: 590–615.
19. Haskell CM. Cancer of the liver. In:Haskell CM, (editor.) Cancer treatment. Philadelphia: WB Saunders, 1980: 319–57.
20. Falkson G, MacIntyre JM, Moertel CG. Eastern Co-Operative Oncology Group experience with chemotherapy for inoperable gall-bladder and bile duct cancers. *Cancer* 1984;54:965–9.
21. Taal BG, Audisio RA, Bleiberg H, Blijham GH, Neijt JP, Veenhof CHN, et al. Phase II trial of mitomycin C (MMC) in advanced gallbladder and bilary tree carcinoma. An EORTC Gastrointestinal Tract cancer Cooperative Group Study. *Ann Oncol* 1993;4:607–9.
22. Cambareri RJ, Smith FP, Kales A, Stablein DM, Schein PS. 5-Fluorouracil, adriamycin, and mitomycin C in cholangiocarcinoma. *Proc Am Soc Clin Oncol* 1980;21:418.
23. Harvey JH, Smith FP, Schein PS. 5-Fluorouracil, mitomycin C and doxorubicin (FAM) in carcinoma of the biliary tract. *J Clin Oncol* 1984;2:1245–8.
24. Rougier P, Fandi A, Ducreux M, Fandi L, Fabri MC, Zarba J, et al. Demontrated efficiency of 5-fluorouracil (5FU) continuous infusion (CI) and cisplatin (P) in patients with advanced biliary tract carcinoma. *Proc Am Soc Clin Oncol* 1995;14:205.
25. Walzymer A, Caponero R, Donato EW, Feriancic CV, Bacchella T, Cuhna JEW, et al. FALP-M Chemotherapy in nonresetable biliary tract adenocarcinoma. *Ann Oncol* 1992; 3(Suppl 5):25.
26. Peters GJ, van Groeningen CJ. Clinical relevance of biochemical modulation of 5-fluorouracil. *Ann Oncol* 1991;2:469–80.
27. Doroshow JH, Newman EM. Fluoropyrimidine biochemical modulation in colon cancer:pharmacology relevant both in the laboratory and the clinic. *J Clin Oncol* 1991;9:365–7.
28. Lockshin A, Danneberg A. Biochemical factors affecting the tightness of 5-fluorodeoxyuridylate binding to human thymidylate synthetase. *Biochem Pharmacol* 1981;30:247–57.
29. Klubes P, Connelly K, Cerna I. Effects of 5-fluorouracil on 5-fluorodeoxyuridine 5′-monophosphate and 2-deoxyuridine 5′-monophosphate pools and DNA synthesis in solid mouse L1210 and rat Walker 256 tumors. *Cancer Res* 1978;38:2325–31.
30. Myers CE, Young RC, Johns DG, Chabner BA. Assay of 5-fluorodeoxyuridine 5′-monophosphate pools following 5-fluorouracil. *Cancer Res* 1974;34:2682–8.
31. Moran RG, Danenberg PV, Heidelberger C. Therapeutic response of leukemic mice treated with fluorinated pyrimidines and inhibitors of deoxyuridylate synthesis. *Biochem Pharmacol* 1982;31:2929–35.
32. Frankfurt OS. Enhancement of the antitumor activity of 5-fluorouracil by drug cobinations. *Cancer Res* 1973;33:1043–7.
33. Kobayashi S, Hoshino T. Combined cytotoxic effect of low dose fluorouracil and hydroxyurea on 9L cells in vitro. *Cancer Res* 1983;43:309–13.
34. Lokich J, Anderson N, Bern M. Dual modulation of 5-fluorouracil using leuovorin and hydroxyurea. *Cancer* 1991; 68:744–6.
35. Di Costanzo F, Bartolucci R, Piccinnini L, Sabbatini R, Leonardi F, Corgna E, et al. High dose folinic acid (FA) and 5FU alone or combined with hydroxyurea (HU) in advanced colorectal cancer (CRC):a randomized trial of the Italian Oncology Group for Clinical Research (GOIRC). *Proc Am Soc Clin Oncol* 1992;11:162.
36. Gebbia V, Valenza R, Testa A, Cipolla C, Latteri M, Curto G, et al. Weekly levofolinic acid and 5-fluorouracil plus hydroxyurea in metastatic gastrointestinal adenocarcinomas. *Am J Clin Oncol* 1994;17:485–9.
37. Gebbia V, Gebbia N, Russo A, Testa A, Valenza R, Zerillo G, et al. Hydroxyurea modulates 5-fluorouracil antineoplastic activity in advanced head and neck carcinomas pretreated with chemotherapy. *Anticancer Drugs* 1992;3:347–9.

38. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting of results of cancer treatment. *Cancer* 1981;471:207–14.
39. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chron Dis* 1961;14:346–53.
40. Kaplan EL, Meier P. Non parametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
41. Gebbia V, Carreca I, Testa A, Valenza R, Curto G, Cannata G, et al. Subcutaneous octreotide versus oral loperamide in the treatment of diarrhea following chemotherapy. *Anticancer Drugs* 1993;4:443–5.
42. Pazdur R, Ajani JJ, Abbruzzese JL, Belt RJ, Dakhil SR, Dubovsky D, et al. Phase II evaluation of fluorouracil and recombinant alpha-2a-interferon in previously untreated patients with pancreatic adenocarcinoma. *Cancer* 1992;70:2073–6.
43. Bruckner HW, Crown J, McKenna A. Leucovorin and 5-fluorouracil as a treatment for disseminated cancer of the pancreas and unknown primary tumors. *Cancer Res* 1988; 48:5570–2.
44. Crown J, Casper ES, Botet J, Murray P, Kelsen DP. Lack of efficacy of high doe leucovorin and 5-fluorouracil in patients with advanced pancreatic adenocarcinoma. *J Clin Oncol* 1991;9:1682–6.
45. De Caprio JA, Mayer RJ, Gonin R, Arbuck G. Fluorouracil and high dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas:results of a phase II trial. *J Clin Oncol* 1991;9:2128–33.
46. Scheithauer W, Pfeffel F, Kornek G, Marczell A, Wiltschke C, Funovics J. A phase II trial of 5-fluorouracil, leucovorin, and recombinant alpha-2b interferon in advanced adenocarcinoma of the pancreas. *Cancer* 1992;70:1864–6.
47. Cascinu S, Fedeli A, Luzi Fedeli S, Catalano G. 5-Fluorouracil, leucovorin and interferon alpha 2b in advanced pancreatic cancer:a pilot study. *Ann Oncol* 1993;4:83–4.
48. Bernhardt H, Jager-Arand E, Bernhard G, Heike M, Klein O, Riemann JF, et al. Treatment of advanced pancreatic cancer with 5-fluorouracil, folinic acid and interferon alpha-2A: results of a phase II trial. *Br J Cancer* 1995;71:102–5.
49. Moore DF, Pazdur R, Abbruzzese JF, Ajani J, Dubowsly DW, Wade III JL, et al. Phase II trial of edatrexate in patients with advanced pancreatic adenocarcinoma. *Ann Oncol* 1994; 5:286–7.
50. Millward-Sadler GH, Wright R. Uncommon tumors of the hepatobilary system. In: Williams CJ, Krikorian JC, Green MR, Raghavan D, editors. Textbook of uncommon cancer. New York: John Wiley & Sons, 1988: 471–90.
51. Al-Hadeedi SY, Moorehead RJ, Leaper DJ, Wong J. Carcinoma of the gall-bladder: a diagnostic challenge. *J Rl Coll Surg Edinb* 1991;36:174–7.
52. Patt YZ, Jones D, Markoviwitz A, Charnsangavej C. Phase II trial of 5FU and alpha-interferon in biliary tract cancers. *Proc Am Soc Clin Oncol* 1995;14:203.
53. Colleoni M, Nolè F, Di Bartolomeo M, Nelli P, Pandolfi A, La Monica G, et al. Oral chemotherapy with doxifluridine and L-leucovorin for unresectable biliary tract carcinomas. *Proc Am Soc Clin Oncol* 1994;13:192.
54. Ellis PA, Norman A, Hill A, O'Brien MER, Nicolson M, Hickish T, et al. Epirubicin, cisplatin and infusional 5-fluorouracil (5FU) (ECF) in hepatobiliary tumors. *Eur J Cancer* 1995; 31:1594–8.
55. Makela JT, Kairaluoma MI. Superselective intra-arterial chemotherapy with mitomycin C for gall-bladder cancer. *Br J Surg* 1993;80:912–5.
56. Rothenberg ML, Burris III HA, Andersen JS, Moore M, Green MR, Portenoy RK, et al. Gemcitabine: effective palliative therapy for pancreas cancer failing 5-FU. *Proc Am Soc Clin Oncol* 1995;14:198.