[Frontiers in Bioscience 3, e214-225, November 1, 1998]

TREATMENT OF ADVANCED AND METASTATIC PANCREATIC CANCER

Lawrence Blaszkowsky

Department of Medicine, The New England Medical Center, Boston, MA

Received 7/8/98 Accepted 8/5/98

TABLE OF CONTENTS

1. ABSTRACT

The majority of adenocarcinoma of the pancreas are non-resectable at diagnosis due to locally advanced or metastatic disease. There will be an estimated 28,900 new cases of pancreatic cancer diagnosed in the United States in 1998. In data collected from 1986-1993, the five year survival of all stages combined was 4%. Realizing that most patients present with advanced disease, and there are no acceptable screening methods to detect early stage disease, efforts to develop active anti-cancer agents with minimal toxicity are essential in order to improve the quality of life and survival. Several 5-fluorouracil based regimens have been tried without a significant impact on palliation or survival. Recently, the anti-metabolite gemcitabine has been approved for use in individuals with locally advanced and metastatic disease, primarily on the basis of improved functional status. Many cytotoxic agents have proven ineffective in the treatment of this disease. There are several ongoing studies investigating the role of new cytotoxic and biologic agents.

2. INTRODUCTION

There will be an estimated 564,800 cancer deaths in the United States in 1998, of which 28,900 will be due to pancreatic cancer, making it the fifth leading cause of cancer deaths (1). During that same period, 29,000 cases of pancreatic cancer will be diagnosed. Needless to say, our current therapy appears not to have a major role in curing this disease. In fact, the five year survival for all stages between 1986-1993 was 4%. The 5 year survival for localized disease was 14%, for regional disease 5%, and for distant disease 2% (1). The majority of patients, more than 80%, are diagnosed with either locally advanced or distant disease, deeming them unresectable.

Although gemcitabine was recently approved and is the standard therapy for locally advanced and metastatic adenocarcinoma of the pancreas, it appears to marginally prolong survival, having its major impact on improvement of functional status. Many combination chemotherapy regimens have been published, but none have been demonstrated in phase III randomized trials to be superior to single agent therapy with 5-FU, but are associated with greater toxicity.

3. SINGLE AGENT CHEMOTHERAPY

Few single agents have demonstrated more than a 15% response rate in phase II clinical trials (table 1). As is the case for most gastrointestinal tumors, 5-fluorouracil has been the most commonly used agent as the first line therapy for pancreatic cancer until recently. Gemcitabine is now widely accepted to be the most active commercially available agent for this disease.

3.1 Gemcitabine

Gemcitabine (difluorodeoxycytidine) is a deoxycytidine analog resembling cytosine arabinoside (ARA-C), that requires intracellular phosphorylation by deoxycytidine kinase to become active. The active agent, difluorodeoxycytidine triphosphate (dFdCTP), accumulates within the cell and inhibits DNA synthesis by competing with deoxycytidine triphosphate (dCTP) for incorporation into DNA (2, 3). Gemcitabine also appears to stimulate the activity of deoxycytidine kinase and inhibits ribonucleotide reductase, which reduces the pools of deoxynucleoside triphosphate, and inhibits deoxycytidine monophosphate (dCMP) deaminase, the primary enzyme responsible for degradation of gemcitabine (4, 5).

Table 1. Single Agent Therapy in Advanced and Metastatic Pancreatic Cancer

Agent	Responses/Total Patients	Median Survival (mos.)	Reference
Amonafide	0/36 (0%)	-	106
Aziridinylbenzoquinolone	0/21 (0%	2	107
Brequinar Sodium	0/17 (0%)	-	110
Carmofur	1/31 (3.2%)	8.3	116
Cisplatin	7/33 (21%)	-	75
Dihydroanthracenedione	0/29 (0%)	2.5	107
Docetaxel	9/42 (21%)	-	41
Docetaxel	0/16 (0%)	3.8	42
Docetaxel	2/33 (6%)	-	43
Doxorubicin (liposomal)	0/16 (0%)	-	109
Edatrexate	0/17 (0%)	3	36
Edatrexate	2/40 (5%)	3.5	37
Epirubicin	8/34 (24%)	5	108
Epirubicin/Quinidine	0/18 (0%)	-	25
Etoposide	0/25 (0%)	-	112
Fazarabine	0/14 (0%)	-	113
Fludarabine	0/20 (0%)	-	114
FUDR	7/17 (41%)	-	11
5-FU	0/57 (0%)	4.41	8
5-FU (PVI)	3/16 (19%)	-	123
5-FU/Leucovorin	0/20 (0%)	2.5	12
5-FU/Leucovorin	3/42 (7%)	6.2	14
5-FU/PALA	5/35 (14%)	5.1	115
5-FU/PALA	1/21 (5%)	-	118
Gemcitabine	5/44 (11%)	5.6	6
Gemcitabine	2/32 (6.3%)	6.3	7
Gemcitabine	3/56(5.4%)	5.7	8
Irinotecan	3/34 (9%)	5.2	34
Ifosfamide	6/27 (22%)	6	30
Ifosfamide	2/30 (6.7%)	3	31
Ifosfamide	4/25 (16%)	5	121
Iproplatin	3/32 (9.4%)	-	102
Menogaril	2/38 (5.2%)	3.1	120
Merbarone	2/29 (6.9%)	-	111
MGBG	2/32 (6.3%)	7.6	107
Mistletoe (Eurixor)	0/16 (0%)	5.6	104
Mitomycin-C	12/44 (27%)	-	10
Mitoxantrone	0/24 (0%)	-	29
Octreotide	0/22 (0%)	5	53
Paclitaxel	3/39 (8%)	5	39
Pibenzimol	0/23 (0%)	-	119
Pirarubicin	0/18 (0%)	-	103
Piroxantrone	0/35 (0%)	-	105
6-thioguanine	1/30 (3.3%)	-	117
Thymitaq	1/25 (4%)	-	101
Tomudex	2/42 (4.8%)		100
Topotecan	0/27 (0%)	4.4	33
Topotecan	3/30 (10%)	4.8	122
Topotecan	0/15 (0%)	-	32
Trimetrexate	0/14 (0%)	3.3	38

The initial phase II study evaluated gemcitabine in 44 patients with advanced pancreatic cancer at doses of 800-1,250 mg/M2/week, and reported a partial response rate of 11% with a median response duration of 13 months, and a 23% one year survival (6). Interestingly, not only the patients with objective tumor response, but also the patients with stable disease experienced symptomatic improvement (6). In another phase II study of 32 patients, an objective response rate of 6.3% was obtained (7). In both of these studies, patients appeared to have improvement of symptoms without objective tumor response. In a multi-center randomized trial by Burris, *et al*., the concept of symptomatic improvement or "clinical benefit", was analyzed. In addition, objective response and survival in previously untreated patients was examined (8). Clinical benefit was determined by monitoring three variables: pain (quantitated by an MPAC visual analog scale and an analgesic diary), Karnofsky Performance Status, and weight (6). One hundred twenty six patients were randomized equally to receive gemcitabine 1,000 mg/M2 weekly x 7 weeks followed by a one week break, then weekly for 3 of 4 weeks per cycle, versus 5-fluorouracil 600 mg/M2 weekly (8). Gemcitabine treated patients experienced a 23.8% clinical benefit response

compared to 4.8% of the 5-FU treated patients (P=0.0022) (8). The median survival was 5.65 versus 4.41 months (P=0.0025) for the gemcitabine and 5-FU arm, respectively, and the 1 year survival was 18% versus 2% (8). All patients progressed within 14 months of starting therapy, and none survived beyond 19 months (8). An objective tumor response rate of 5.4% for gemcitabine and 0% for 5-FU was reported (8). Both treatments were well tolerated, with neutropenia, liver function abnormalities, nausea and vomiting being the most commonly reported grade 3/4 toxicities (8). Rothenberg, *et al.* found the clinical benefit to extend to patients who were 5-FU refractory as well, with a response rate of 27% in 63 patients (9).

3.2 5-Fluorouracil

Prior to the approval of gemcitabine, 5-fluorouracil (5-FU) was the most commonly administered agent for adenocarcinoma of the pancreas, and has been the most frequently studied. Response rates of 0-67% have been reported for single agent bolus 5-FU, with an overall response rate of 28% (10). Recent trials have shown the objective response rate to be less than 15%. Earlier studies showing higher response rates may be due to the parameters of response evaluated, such as physical examination or laboratory indices. There is no standard way of administering 5-FU for this disease: bolus, 24 hour continuous infusion, protracted venous infusion or chronotropically. In a phase II study presented in abstract form, Ardalan and colleagues demonstrated a 41% response rate to a weekly 24 hour infusion of FUDR (5-fluorodeoxyuridine) in patients with unresectable pancreatic cancer who previously failed 5-FU or gemcitabine (11).

3.3 5-Fluorouracil Modulation

Several studies have examined the effect of modulation of 5-FU, but have not yielded significant improvement over 5-FU alone. Modulation of 5-FU by leucovorin, resulting in improved response by enhancing the inhibition of thymidylate synthetase in colorectal cancer, is well accepted. Crown and colleagues failed to demonstrate a single response to leucovorin 500 mg/M2/day for 6 days by continuous infusion, with 5-FU 370 mg/M2/day by bolus for 5 days, in 20 patients studied (12). There was no impact on survival, with a median survival of 10 weeks. The Mayo regimen of 5-FU and leucovorin daily for 5 days every 4-5 weeks has demonstrated no objective responses in 31 patients, with a median survival of 5.7 months (13). DeCaprio, *et al.* reported a 7% partial response rate in 42 patients treated with weekly leucovorin 500 mg/M2 and 5-FU 600 mg/M2 for 6 of 8 weeks, with a median survival of 6.2 months (14). Other modulators of 5-FU such as PALA (N-{phosphonacetyl}-L-aspartic acid), methotrexate, hydroxyurea and interferon have also been studied, and show no significant benefit over 5-FU alone, but do show a greater toxicity (15-24).

3.4 Other cytotoxic agents

Single agent epirubicin has a reported response rate of 0-37% and doxorubicin a response rate of 13% (10, 25-28). Mitoxantrone was studied in 24 patients and yielded no responses (29). Mitomycin-C has a reported response in 12 of 44 patients (27%), based on 4 phase II studies performed prior to 1970 (10). The nitrosoureas BCNU, CCNU, methyl-CCNU and streptozotocin have single-agent responses of 0%, 16%, 0%, and 11%, respectively, based on CTEP (Cancer Therapy Evaluation Program) data (10). Although ifosfamide at a dose of 1.25-2 g/M2/d x 5 days every 3 weeks in 29 patients initially showed a response rate of 22%, including one complete response, another study using a similar dose and schedule obtained a 7% response rate, including one complete response (30, 31). The topoisomerase I inhibitors, topotecan and irinotecan, have demonstrated minimal response rates of 0% in 2 studies, and 9%, respectively (32-34). RFS 2000 (9-Nitro-20(S)-Camptothecin-9NC) was evaluated in 53 patients, with a reported response rate of 32%. The responses in these cases were based not only on decrease in tumor volume on CT scan, but also by tumor markers and symptoms (35). The antifolate edatrexate has shown 0 and 5% response rates in 2 phase II studies, while trimetrexate had a 0% response rate (36-38). The taxanes have shown minimal activity in pancreatic cancer. Paclitaxel at a dose of 225 mg/M2 by 24 hour infusion, with prophylactic G-CSF, yielded a response rate of 8%, including one complete response, with a median survival of 5 months (39). Paclitaxel has also been studied in combination with radiation therapy for locally advanced disease (40). Docetaxel was initially reported to have a response rate of 21% in 42 patients with metastatic and locally advanced disease (41). Okada and Taguchi reported no objective responses in 16 patients who received Docetaxel 60 mg/M2 every 3 weeks (42). Kouroussis and colleagues reported an overall response rate of 6%, including 1 complete response, but interestingly, 58% of their patients had stabilization of disease (43). Similar to the findings with gemcitabine, 27% of patients had improvement in performance status and symptoms (43).

4. HORMONAL THERAPY

Pancreatic tumors express receptors to sex hormones (44). Several studies have suggested activity of tamoxifen in pancreatic cancer, but a randomized double-blind trial showed essentially no difference between the two groups: median survival was 115 days for the tamoxifen arm and 122 days for the placebo group, with a 1 year survival of 8% in both (45-47). Studies evaluating the LH-RH inhibitor goserelin, with or without hydrocortisone, have failed to demonstrate activity (48, 49).

The somatostatin analog octreotide has anti-proliferative effects in the AR42J pancreatic cell line *in vitro*. Weckbecker *et al.* have demonstrated synergistic effects when cells are also treated with doxorubicin, mitomycin-C and paclitaxel (50). Octreotide has demonstrated *in vitro* inhibition of human adenocarcinoma cell lines, but showed no significant responses or effect on survival in two studies of 34 and 32 patients with metastatic pancreatic cancer (51-53). Octreotide has also been administered in combination with goserelin, resulting in a response rate of 7% (54). The long acting somatostatin analog, SMS 201-995 pa LAR (SMS pa LAR), was recently evaluated in two studies. In the first study, 185 patients were randomized to receive either SMS pa LAR or placebo. No objective responses were observed, and the median survival was 16 weeks versus 16.9 weeks, respectively (55). In another randomized study, 281 patients received 5-FU 225 mg/M2/day by continuous infusion for 8 weeks followed by a one week break, and were randomized to receive monthly SMS pa LAR versus placebo. One complete and one partial response was seen in the SMS pa LAR group, and one partial response in the

placebo group, with a median survival of 22.6 and 21.6 weeks, respectively (56).

An antagonist to the cholecystokinin receptor, MK 329, showed no responses in 18 patients (57). The CCK-A receptor antagonist loxiglumide was studied in a randomized trial versus placebo in patients with advanced disease, and also showed no significant impact (58).

5. COMBINATION CHEMOTHERAPY REGIMENS

For most malignancies, the first line treatment for a patient with a good performance status is combination chemotherapy. Individual drugs are chosen based on their known single agent activity and ideally synergistic activity, and complimentary, not overlapping toxicity. Such strategies have been successful for malignancies such as acute leukemia, non-Hodgkin's lymphoma, breast, head and neck, and lung cancer. Although several regimens have been tested in pancreatic cancer, none have reproducibly shown a benefit to single agent therapy in randomized phase III trials (table 2). The development of new and more active agents against this disease may ultimately result in more potent and hopefully less toxic combinations. Nearly all combination regimens studied for pancreatic cancer include 5-FU.

5.1 FAM regimen

The combination regimen FAM (5-FU 600 gm/M2 weeks #1, 2, 5, and 6, doxorubicin 30 mg/M2 on weeks #1 and 5, and mitomycin-C 10 mg/M2 on week #1, repeated every 8 weeks), was initially evaluated in patients with gastric cancer, resulting in a median survival of 5.5 months and partial remission rate of 50%, in 36 patients studied (59). This same regimen was then studied in 39 patients with metastatic pancreatic cancer. The median survival of all patients was 6 months, with a partial response rate of 37% (60). In those that responded, the median survival was 12 months compared to 3.5 months in non-responders (60). In a small study by Bitran, *et al*., 40% of the 15 patients treated with FAM experienced a response, with a median survival of 12 months (61). The North Central Cancer Treatment Group (NCCTG) performed a randomized study in 305 patients evaluating three regimens: 5-FU, 5-FU with doxorubicin (FA), and 5-FU with doxorubicin and mitomycin-C, in patients with gastric and pancreatic cancer (62). There were 144 patients with pancreatic cancer in this study, and 33 were evaluated for response. The objective response rates for this group were 24%, 29% and 23%, respectively, for the 5-FU, FA and FAM arms, and the median survival for the entire group was 22 weeks (62). Both combination regimens proved to be more toxic and costly. Other studies have reported similar survival (63).

5.2. 5-FU + Nitrosoureas

The earliest studies of combination therapy evaluated the contribution of the nitrosoureas to 5-FU. In a Veterans Administration study, 5-FU and CCNU resulted in a median survival of 3 months (64). In a trial comparing the combination 5-FU and methyl CCNU versus 5-FU and mitomycin-C, the response rate was 5% and 22%, respectively, again without a survival advantage (65). Abderhalden and colleagues initially studied the combination of SF (Streptozotocin 300 mg/M2/day x 5 days and 5-FU 500 mg/M2/day x 5 days every 4 weeks) with and without mitomycin-C 10 mg/M2 every 8 weeks in 26 patients (66). The three drug regimen yielded a slightly higher response rate of 31% versus 21% (66). Wiggans *et al*. evaluated the regimen SMF (streptozotocin 1 g/M2 weeks #1, 2, 5 and 6, mitomycin-C 10 mg/M2 on week #1, and 5-FU 600 mg/M2 on weeks #1, 2, 5 and 6, repeated every 8 weeks), in 23 previously untreated patients with advanced and metastatic pancreatic cancer. They reported a response rate of 43%, which included one complete response and a median survival of 6 months (67). Measure of response was either by palpation (hepatomegaly), x-ray, ultrasound or by CT scan, which may have, at least to some extent, over-estimated the responses. The Southwest Oncology Group (SWOG) performed a prospective randomized trial of streptozotocin, mitomycin-C and 5-FU versus mitomycin-C and 5-FU (68). In 116 patients evaluated, the response rate to SMF was 34% and to MF 8%, with no difference in overall survival: 18 versus 17 weeks (68).

5.3. FAM versus 5-FU + Nitrosourea combinations

Several studies were initiated to evaluate FAM with combinations including streptozotocin. Bukowski *et al*. studied a new regimen, FAM-S (5-FU, doxorubicin, mitomycin-C and sreptozotocin). Twenty-five patients with metastatic disease were enrolled, with 48% of patients experiencing a response, 4 with stable disease, and a median survival for the entire group of 6.75 months (69). FAM was compared with two different regimens of SMF by the Gastrointestinal Tumor Study Group (GITSG). They found no difference in the response rates or survival of the 133 patients studied. The response rate for the FAM arm was 14% with a median survival of 3 months, compared to 14% and 15%, with a median survival of 4.5 months for the SMF arms (70). Leucovorin has also been added to the SMF regimen. Douglass, *et al* recently reported a 27% response rate, including 2 complete responses, with a median survival of 7.5 months, in a phase II study of 28 patients (71). The Cancer and Leukemia Group B (CALGB) randomized 196 patients with advanced pancreatic cancer to receive FAM versus FSM (5-FU, streptozotocin and mitomycin-C). The response rate and median survival for the FAM arm was 14% and 26 weeks, respectively, and for the FSM arm, 4% and 18 weeks, respectively (72).

5.4. Mallinson Regimen

The Mallinson regimen includes 5-FU, cyclophosphamide, methotrexate, and vincristine, followed by 5-FU and mitomycin-C as maintenance chemotherapy. In a randomized phase II study of this regimen versus supportive care, the median survival of the treated group was 44 weeks versus 9 weeks in the supportive care group (73). The study group consisted of 40 patients who were found to be unresectable at the time of surgery. A follow-up study randomized 187 patients to one of 3 arms: 5-FU, the Mallinson regimen, or 5-FU, doxorubicin and cisplatin. The response rates of the 3 arms in the 41 patients with measurable disease were 7%, 21% and 15%, with a median survival of 4.5, 4.5, and 3.5 months, respectively (74).

5.5. Platinum regimens

Cisplatin (CDDP) has demonstrated moderate activity in in advanced pancreatic cancer (75). Cisplatin 100 mg/M2 with 5-FU 1,000 mg/M2/day by continuous infusion for 5 days in 40 patients, resulted in a response

Table 2. Combination Chemotherapy Regimens (Randomized Trials)

Regimen	N	Responses/Total Patients	Median Survival	Reference
Observation	152	-	3.9 months	64
5-FU + CCNU		-	3 months	
5-FU + Mito-C	140	10/45 (22%)	19 weeks	65
5-FU + meCCNU		2/43 (5%)	17 weeks	
5-FU	144	3/10 (30%)	~22 weeks	62
FA		3/10 (30%)	"	
FAM		1/13 (7.7%)	"	
5-FU +Mito-C	181	5/60 (8%)	17 weeks	68
SMF		19/56 (34%)	18 weeks	
5-FU	71	1/25 (4%)	6.2 months	63
FAM (modified)		0/0/26 (0%)	6 months	
FAM	196	9/90 (14%)	26 weeks	72
FSM		3/94 (4%)	18 weeks	
FA	133	4/29 (14%)	3 months	70
SMF-1		4/28 (14%)	4.5 months	
SMF-2		4/27 (15%)	-	
5-FU	187	7%	4.5 months	74
Mallinson Reg.		21%	4.5 months	
FAP		15%	3.5 months	
CAC	82	4/49 (5%)	5 months	83
SMF		2/38 (10%)	10 months	
5-FU	127	0/57 (0%)	4.4 months	8
Gemcitabine		3/56 (5.4%)	5.65 months	

Abbreviations:C:cisplatin, doxorubicin and caffeine, FA: 5-Fluorouracil and doxorubicin, FAM: 5-Fluorouracil, doxorubicin, mitomycin-C, SMF:streptozotocin, mitomycin-C and 5-Fluorouracil, FSM:5-Fluorouracil, streptozotocin and mitomycin-C, Mallinson, Regimen:5-Fluorouracil, cyclophosphamide, methotrexate and vincrisitine, induction, followed by 5-Fluorouracil and mitomycin-C maintenance, FAP:5-Fluorouracil, doxorubicin and cisplatin

rate of 26.5%, with a median survival of 7 months (76). Other studies utilizing a protracted venous infusion of 5-FU with CDDP have demonstrated similar benefit (77, 78). A 21% response rate was observed with the addition of leucovorin to 5-FU and CDDP (79). Both epirubicin and doxorubicin have been combined with 5-FU and CDDP, but have resulted in no significant impact on survival, but with increased toxicity (80, 81). A non- 5-FU containing regimen, CAC (CDDP, cytosine arabinoside and caffeine), yielded a 39% response rate in 18 patients (82). A randomized trial comparing CAC to SMF was not as encouraging, with a response rate of 7% versus 10%, and a median survival of 3.5 versus 5.3 months, respectively, in 82 patients studied (83). The Mid-Atlantic Oncology Program studied carboplatin administered weekly with 5-FU by protracted venous infusion in 54 patients with advanced disease. Of the 47 patients who were evaluable, 17% responded, including 2 complete responses, with a median overall survival of 22 weeks (84). Although modulation of 5-FU by interferon has not proven beneficial in this disease, Sporn and colleagues evaluated the addition of leucovorin and CDDP to this regimen, in 16 patients. They reported a partial response rate of 37.5%, resulting in a survival for the responders of greater than 8 months, but an overall median survival of 5 months, similar to most other single agent studies (85).

5.6. 5-FU and Gemcitabine

Gemcitabine appears to be the most active single agent available for the treatment of pancreatic cancer, with an acceptable toxicity profile, which is predominantly neutropenia. It is not surprising that several combinations evaluating gemcitabine with 5-FU have been studied. As was the case for the single agent studies of gemcitabine, these studies have examined the clinical benefit response. In the first study, 54 patients received gemcitabine 1,000 mg/M2 and 5-FU 600 mg/M2 weekly for 3 of 4 weeks each cycle. A clinical benefit response was reported in 51%. Two patients had a partial response and 34 stable disease, with a median survival of 7 months (86). In a dose-escalation study of gemcitabine starting at 700 mg/M2/week for 3 weeks of a 4 week cycle, and fixed dose 5-FU 200 mg/M2/day by protracted venous infusion, a clinical benefit response was reported in 55% of 26 patients studied, with an overall response rate of 16% and median survival of 10.4 months (87). The recommended dose for further studies was gemcitabine 900 mg/M2/week with the 5-FU at 200 mg/M2/day (87). The Eastern Cooperative Oncology Group (ECOG) completed a phase II study evaluating 37 patients who received gemcitabine 1,000 mg/M2 and 5-FU 600 mg/M2 weekly for 3 of 4 weeks per cycle. The combination was well tolerated, but the results have not yet been published. ECOG recently launched a phase III study

comparing the same regimen to gemcitabine 1,000 mg/M2 alone. A phase I study of weekly gemcitabine at a fixed dose of 1,000 mg/M2 with leucovorin 200 mg/M2 followed by a 24 hour infusion of 5-FU starting at 750 mg/M2 administered weekly for 4 of 6 weeks, found the maximum tolerated dose of 5-FU to be 1,000 mg/M2 (8). Of the 13 patients enrolled on the study, 6 achieved stable disease (88).

5.7. Other 5-FU Combinations

In a phase II trial of sequential high-dose methotrexate, 5-FU and doxorubicin, 4 of 25 evaluable patients demonstrated a response, with an overall median survival of 6.7 months (89). The anthracycline epirubicin, when added to bolus 5-FU, resulted in a 14% response rate with a median survival of 4 months (90). The addition of CDDP to epirubicin and 5-FU resulted in a response rate of 17.3%, but with considerable toxicity (80).

6. BIOLOGICAL AND GENE THERAPY

Several monoclonal antibodies have been used in the treatment of pancreatic cancer. The 17-1A monoclonal antibody recognizes a glycoprotein on many gastrointestinal adenocarcinomas. In one study, evaluating the 17-1A monoclonal antibody, 1 of 28 patients responded (91). In another study, 30 patients received the antibody with gamma interferon. Only one of the 25 patients experienced a response (complete) (92).

Interferon alpha in combination with 13-cis-retinoic acid failed to show a single response (93). There have been many studies evaluating interferon with 5-FU, with or without leucovorin. Although response rates and survival may be comparable to 5-FU alone, the toxicity is significantly higher (17, 18, 21-24).

Giantonio and colleagues completed a phase I study of a recombinant E. Coli derived fusion protein of Staphylococcal enterotoxin A and the Fab-fragment of the C242 monoclonal antibody in patients with advanced colorectal and pancreatic carcinomas (94). The aim of this approach is to generate a local cytokine release at the site of the tumor, with ultimate regression of tumor (94). The majority of pancreatic cancers possess K-ras mutations. In a small phase I/II study of 5 patients, 2 patients exhibited an immune response against synthetic peptide loaded antigen presenting cells from the patient (95).

Gene therapy is an active area of investigation, but at present, there have been little data generated in humans. The herpes simplex virus thymidine kinase gene (HSV-TK), when transduced into pancreatic carcinoma cells, makes these cells susceptible to ganciclovir, resulting in tumor regression. Delivery systems have been created with adenovirus and liposomes (96-99).

7. PERSPECTIVE

Although many active combination regimens have improved response rates and prolonged survival in several tumor sites, chemotherapy for metastatic pancreatic cancer has had little impact. It is encouraging that after more than 30 years, a new drug is now part of the armamentarium for this disease. Combination regimens, when taken to phase III studies, have consistently resulted in minimal activity with moderate toxicity. There are already several phase II studies of gemcitabine with 5-FU that appear to yield improved response rates and marginal survival advantage, in the absence of significant toxicity. Phase III studies, as is on ongoing in ECOG at this time, will determine whether this regimen should become the new standard for advanced and metastatic disease. Presently, gemcitabine should be considered the standard regimen by which other agents are compared. There is urgent need for the development of new agents with significant impact on the course of this disease. These agents may not be standard cytotoxic chemotherapy, but instead gene therapy or anti-angiogenesis agents. All eligible patients with advanced pancreatic cancer should be encouraged to participate in clinical trials. In addition to objective response and survival data, such trials must evaluate the impact of therapy on quality of life, and report a clinical benefit response,. In the absence of a clinical trial, the medical oncologist should base therapy on the patient's performance status and symptoms, and choose an appropriate therapy based on available data, keeping in mind that combination therapy has not consistently resulted in a significant prolongation of survival. It is essential to maintain a reasonable quality of life, which a toxic regimen can easily disturb.

8. REFERENCES

1. Landis, S. H. Murray, T. Bolden, S. Wingo, P. A.: Cancer Statistics, 1998. *CA - Cancer J Clin* 48, 6-29 (1998)

2. Heinemann, V. Hertel, L. W. Grindey, G. B. Plunkett, W.: Comparison of the cellular pharmacokinetics and toxicity of 2', 2'-difluorodeoxycytidine and 1-b-D-aribinofuranosylcytosine. *Cancer Res 48*, 4024-31 (1988)

3. Huang, P. Chubb, S. Hertel, L. W. Grindey, G. B. Plunkett, W.: Action of 2', 2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res* 51, 6110-7 (1991)

4. Ghandi, V. Plunkett, W.: Modulatory activity of 2', 2'-difluorodeoxycytidine on the phosphorylation and cytotoxicity of arabinosyl nucleosides. *Cancer Res* 50, 3675-80 (1990)

5. Hertel, L. W. Boder, G. B. Kroin J. S. Rinzel S. M. Poore, G. A. Todd, G. C. Grindey, G.B.: Evaluation of the antitumor activity of gemcitabine. *Cancer Res* 50, 4417-22 (1990)

6. Casper, E. S. Green M. R. Kelsen, D. P. Heelan, R. T. Brown, T. D. Flombaum, C. D.Trochanowski, B. Tarassoff, P. G.: Phase II trial of gemcitabine (2', 2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 12, 29-34 (1994)

7. Carmichael, J. Fink, U. Russell R. C. G. Spittle, M. F. Harris, A. Spiessi, G. Blatter, J.: Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer* 73, 101-5 (1995)

8. Burriss, H. A. Moore, M. J. Anderson, J. Green, M.R. Rothenberg, M. L. Modiano, M. R.Cripps, C. C. Portenoy, R. K. Storniolo, A. M. Tarassoff, P. Nelson, R. Dorr, F. A. Stephens, C. D.von Hoff, D. D.: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for

patients with advanced pancreas cancer- a randomized trial. *J Clin Ocol* 15, 2403-2413 (1977)

9. Rothenberg, M. L. Burris, H. A. Andersen, J. S. Moore, M. Green, M. R. Portenoy, R. K.Casper, E. S. Tarassoff, P. G. Storniolo, A. M. von Hoff, D. D.: Gemcitabine-effective palliative therapy for pancreas cancer patients failing 5-FU. *Proc Am Soc Clin Oncol* 14, 198a (1995)

10. Carter, S. K. Comis, R. L.: The integration of chemotherapy into a combinedmodality approach for cancer treatment- VI. pancreatic adenocarcinoma. *Cancer Treat Rev* 2, 193-214 (1975)

11. Ardalan, B. Sparling, L. Livingstone, A. Francheschi D. Sridhar, K. S. Feun, L. G.Richman, S. P. Triplett, N.: Phase II trial of high-dose 24 hour infusion of 5 - fluorodeoxyuridine (FUDR) in patients with inoperable pancreatic cancer. *Proc Am Soc Clin Oncol* 16, 282a (1997)

12. Crown, J. Casper, E. S. Botet, J. Murray, P. Kelsen, D. P.: Lack of efficacy of high-doseleucovorin and fluorouracil in patients with advanced pancreatic adenocarcinoma. *J Clin Oncol* 9, 1682-1686 (1991)

13. Rubin, J. Gallagher, J. G. Schroeder, G. Schutt, A. J. Dalton, R. J. Kugler, J. W. Morton,R. F., Mailliard, J. A. Burch, P. A.: Phase II trials of 5-fluorouracil and leucovorin in patients with metastatic gastric or pancreatic carcinoma. *Cancer* 78, 1888-91, (1996)

14. DeCaprio, J. A. Mayer, R. J. Gonin, R. Arbuck, S. G.: Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of thepancreas- results of a phase II trial. *J Clin Oncol* 9, 2128-33 (1991)

15. Morrell, L. M. Bach, A. Richman, S. P. Goodman, P. Fleming, T. R. MacDonald, J. S.: A phase II multi-institutional trial of low-dose N-(phosphonacetyl)-L-aspartate and high -dose 5-fluorouracil as a short-term infusion in the treatment of adenocarcinoma of the pancreas. *Cancer* 67, 363-7 (1991)

16. Ardalan, B. Sridhar, K. S. Benedetto, P. Richman, S. Waldman, S. Morell, L. Feun, L.Savaraj, N. Fodov,M. Livingstone, A.: A phase I, II study of high-dose 5-fluorouracil and high-dose leucovorin with low-dose phosphonacetyl-L-aspartic acid in patients with advanced malignancies. *Cancer* 68, 1242-1246 (1991)

17. 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* 70, 1864-6 (1992)

18. Pazdur, R. Ajani, J. J Abbruzzese, J. L. Belt, R. J. Dakhil, S. R. Dubovsky, D. Graham, S. Pilat, S. Winn,R. Levin B.: Phase II evaluation of fluorouracil and recombinant alpha-2a-interferon in previously untreated patients with pancreatic adenocarcinoma. *Cancer* 70, 2073-6 (1992)

19. Harstrick, A. Kohne, C. H. Hiddemann, W. Preusser, P. Strumberg, D. Berns, T. Seeber, S. Wilke, H. Schmoll H. J.: Modulation of 5-fluorouracil with methotrexate and low doseN- (phosphoanacetyl)-L-aspartate (PALA) is inactive in advanced pancreatic carcinoma. *Ann Oncol* 8, 917-8 (1997)

20. Gebbia, V. Majello, E. Testa, A. Pezella, G. Giuseppe, S. Giotta, F. Riccardi, F.Fortunato, S. Colucci,G. Gebbia, N.: Treatment of advanced adenocarcinoma 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.). *Cancer* 78, 1300-7 (1996)

21. John, W. J. Flett, M. Q.: Continuous venous infusion 5-fluorouracil and interferon-alpha in pancreatic carcinoma. *Am J Clin Oncol* 21, 147-50 (1998)

22. Sparano, J. A. Lipsitz, S. Wadler, S. Hansen, R. Bushunow, P. W. Kirkwood, J. Flynn, P.J. Dutcher, J. P. Benson, A, B.: Phase II trial of prolonged continuous infusion of 5-fluorouracil and interferon-alpha in patients with advanced pancreatic cancer, Eastern Cooperative OncologyGroup protocol 3292. *Am J Clin Oncol* 19, 546-51 (1996)

23. Moore, M. J. Erlichman, C. Kaizer, L. Fine, S.: A phase II study of 5-fluorouracil, leucovorin and interferon-alpha in advanced pancreatic cancer. *Anti-Cancer Drugs* 4,555-7 (1993)

24. Cascinu, S. Fedeli, A. Fedeli, S. L. Catalano G.: 5-fluorouracil, leucovorin and interferon -alpha 2b in advanced pancreatic cancer, a pilot study. *Ann Ocol* 4, 83-4 (1993)

25. Abad, A. Massuti, B. Blanco, E. Carrato, A. Maurel, J. Cervantes, A. Aranda, E. Anton, A. Vincent, J. M. Dorta, J. Garcia de Paredes, M. L. Ariza, A.: Seventy-two hour epirubicin infusion plus quinidine in unresectable and metastatic adenocarcinoma of the pancreas, a phase II trial. *Am J Clin Oncol* 21, 151-4 (1998)

26. Cerosimo, R. J. Hong, W. K.: Epirubicin, a review of the pharmacology, clinical activity,and adverse effects of an adriamycin analogue. *J Clin Oncol* 4, 425-39 (1986)

27. Gastrointestinal Tumor Study Group: Phase II trials of the single agents baker's antifolate diaziquone,and epirubicin in advanced pancreatic cancer. *Cancer Treat Rep* 71, 865-7 (1987)

28. Schein, P. S. Lavin, P. T. Moertel, C. G. Frytka, K. S. Hahn, R. G., O'Connell, M. J.Reitemeier, R. J. Rubin, J. Schutt, A. J. Weiland, L. H. Kalser, M. Barkin, J. Lessner, H. Mann-Kaplan, R. Redlhammer, D. Silverman, M. Trovier, M. Douglass, H. O. Jr. Milliron, S. Lokich, J. Brocks, J. Chaffe, J. Like, A. Zamchek, N. Ramming, K. Bateman, J. Spiro, J. Livstone, E. Knowlton, A.: Randomized phase II clinical trial of adriamycin, methotrexate and actinomycin-D in advanced measurable pancreatic carcinoma. *Cancer* 42, 19-22 (1978)

29. Taylor, S. A. Fleming, T. von Hoff, D. D., McCracken, J. D. Bukowski, R. M. Talley, R.W. Natalie, R. B. Guy, J. T. Samlowski, W. E. Costanzi, J. H.: Phase II evaluation of mitoxantrone in advanced pancreatic carcinoma: a Southwest Oncology Group study. *Invest New Drugs* 8, 77-80 (1990)

30. Loehrer, Sr. P. J. Williams, S. D. Einhorn, L. H. Ansari, R.: Ifosfamide: an active drug in the treatment of adenocarcinoma of the pancreas. *J Clin Oncol* 3, 367-72 (1985)

31. Ajani, J. A. Abbruzzese J. L. Goudeau, P. Faintuch, J. S. Yeomans, A. C. Bowman, B.M. Nicaise, C. Levin, B.: Ifosfamide and mesna, marginally active in patients with advanced carcinoma of the pancreas. *J Clin Oncol* 6, 1703-7 (1988)

32. Sugarman, S. M. Pazdur, R. Daugherty, K. Evans, D. Winn, R. Dubovsky, D. Goodwin,J. W. Abbruzzese,J. L.: A phase II trial of Topotecan for the treatment of unresectable pancreatic cancer. *Proc Am Soc Clin Oncol* 13, 224 (1994)

33. O'Reilly, S. Donehower, R. C. Rowinsky, E. K. Ord, S. Grochow, L. B.: A phase II trial of topotecan in patients with previously untreated pancreatic cancer. *Anti-Cancer Drugs* 7, 410-4 (1996)

34. Wagener, D. J. Verdonk, H. E., Dirix, L. Y. Catimel, G. Siegenthaler, P. Buitenhuis, M. Mathieu-Boue,A. Verweij, J.: Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC Early Clinical trials Group study. *Ann Oncol* 6, 129-32 (1995)

35. Stehlin, Jr. J. S. Giovanella, B. C. Natelson, E. A. Coil, D. R. De Ipolyi, P. D. Fehir, K. M.Wallace, P. J. Trojacek A. Griswold, J. Wolk, D.: Clinical investigations of RFS 2000 (9-nitro-20(s)-camptothecin-9NC) in patients with advanced pancreatic carcinoma. *Proc Am Soc Clin Oncol 17*, (1998)

36. Casper, E. S. Schwartz, G. K. Johnson, B. Kelsen, D. P.: Phase II trial of edatrexate in patients with advanced pancreatic cancer. *Invest New Drugs* 10, 313-6 (1992)

37. Moore, Jr. D. F. Pazdur, R. Abbruzzese, J. L. Ajani, J. A. Dubovsky, D. W. Wade, 3rd, J.L. Belt, R. J. Mangold, C. Bready, B. Winn, R. J.: Phase II trial of edatrexate in patients with advanced pancreatic adenocarcinoma. *Ann Oncol* 5, 286-7 (1994)

38. Carlson, R. W. Doroshow, J. H. Odujinrin, O. O., Flam, M. S. Malec, M. Lamborn, K. R.:Trimetrexate in locally advanced or metastatic adenocarcinoma of the pancreas, a phase II study of the Northern California Oncology Group. *Invest New Drugs* 8, 387-9 (1990)

39. Whitehead, R. P. Jacobson, J. Brown, T. D. Taylor, S . A. Weiss, G. R. MacDonald, J. S.: Phase II trial of Paclitaxel and granulocyte colony stimulating factor in patients with pancreatic carcinoma, a Southwest Oncology Group study. *J Clin Oncol* 15, 2414-9 (1997)

40. Safran, H. King, T. P. Choy, H. Hesketh, P. J. Wolf, B. Altenhein, E. Sikov, W. Rosmarin, A. Akerley, W. Radie-Keane, K. Cichetti, G. Lopez, F. Bland, K. Wanebo, H.J.: Paclitaxel and concurrent radiation for locally advanced pancreatic and gastric cancer, a phase I study. *J Clin Oncol* 15, 901-7 (1997)

41. Rougier, P. Adenis, A. Ducreux M.: Phase II study of docetaxel in pancreatic adenocarcinoma: finalresults after extra-mural review. *Second International Conference on biology, prevention and treatment of gastrointestinal malignancies*, 126 (1995)

42. Okada, S. Taguchi, T.: Phase III trial of docetaxel as first-line chemotherapy in patients with metastatic pancreatic cancer, a Japanese Cooperative study. *Proc Am Soc Clin Oncol* 17, (1998)

43. Kouroussis, C. Kakolyris, S. Samelis, G. Aravantinos, G. Dimopoulos, A. M.Papadimitriou, CGenatas, K. Tsavaris, N. Karabekios, S. Stathopoulos, G. Kotsakis, T.Souglakos, J. Samonis, G. Georgoulias, V.: Treatment of advanced Pancreatic Cancer with docetaxel, a multicenter phase II study. *Proc Am Soc Clin Oncol* 17, (1998)

44. Johnson, P. J. Corbishley, T. P.: Sex steroid receptors and antisteroid agents in the treatment of pancreatic adenocarcinoma. *Monograph series European OrganizationResearch Treatment of Cancer* 8, 99 (1987)

45. Wong, A. Chan, A. Arthur, K.: Tamoxifen therapy in unresectable adenocarcinoma of the pancreas. *Cancer Treat Rep 71*, 7-8 (1987)

46. Taylor, O. M. Benson, I. A. McMahon, M. J.: Clinical trial of tamoxifen in patients with irresectable pancreatic adenocarcinoma, the Yorkshire Gastrointestinal Tumor Group. *Br J Surg* 80, 384-6 (1993)

47. Bakkevold, K. E. Pattersen, A, Arnesjo, B. Espehaug, B.: Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and papilla of Vater. *Br J Surg* 77, 725-30 (1990)

48. Phillip, P. A. Carmichael, J. Tonkin, K. Buamah, P. K. Britton, J. Dowsett, M. Harris, A.L.: Hormonal treatment of pancreatic carcinoma, a phase II study of LHRH agonist goserelin plus hydrocortisone. *Br J Cancer* 67, 379-82 (1993)

49. Allegretti, A. Lionetto, R. Saccomanno, S. Paganuzzi, M. Onetto, M. Martinoli, C.Rollandi, G. Marugo, M. Fazzuoli, L. Pugliese, V. :LH-RH analogue treatment in adenocarcinoma of the pancreas, a phase II study. *Oncology* 50, 77-80 (1993)

50. Weckbecker, G. Raulf, F. Tolcsvai, L. Bruns, C.: Potentiation of the anti-proliferative effects ofanti-cancer drugs by octreotide *in vitro* and *in vivo*. *Digestion* 57, 22-8 (1996)

51. Upp, Jr. J. R. Olson, D. Poston, G. J. Alexander, R. W. Townsend, Jr. C. M. Thompson,J. C.: Inhibition of growth of two human pancreatic adenocarcinomas *in vivo* by somatostatin analog SMS 201-995. *Am J Surg* 155, 29-35 (1988)

52. Klijn, J. G. Hoff, A. M. Planting, A. S. Verweij, J. Lamberts, S. W. Portengen, H.Foekens, J. A.: Treatment of patients with metastatic pancreatic and gastrointestinal tumours with the somatostatin analogue sandostatin, a phase II study including endocrine effects. *Br J Cancer* 62, 623-30 (1990)

53. Friess, H. Buchler, M. Beglinger, C. Weber, A. Kunz, J. Fritsch, K. Dennler, H. J. Beger,H. G.:Low-dose octreotide treatment is not effective in patients with advanced pancreatic cancer. *Pancreas* 8, 540-5 (1993)

54. Fazeny, B. Baur, M. Prohaska, M. Hudec, M. Kremnitzer, M. Meryn, S. Huber, H. Grunt, T. Tuchmann, A. Dittrich, C.: Octreotide combined with goserelin in the therapy of advanced pancreatic cancer-results of a pilot study and review of the literature. *J Cancer Res & Clin Oncol* 123, 45-52 (1997)

55. Pederzoli, P. Maurer, U. Vollmer, K. Buechler, M. Kjaeve, J. van Cutsem, E. DiCarlo, V.Stauder, H. Bergan, A. Ebert, M. Kiese, B. Raymond, M. C. Kay, A.: Phase 3 trial of SMS 201-995 pa LAR vs. placebo in unresectable stage II, III and IV pancreatic cancer. *Proc Am Soc Clin Oncol* 17, (1998)

56. Roy, A. Jacobs, A. Bukowski, R. Cunningham, D. Hamm, J. Schlag, P. M. Rosen, P.Francois, E. Finley, G. Lipton, A. Bruckner, H. Haller, D. Conroy, T. Goel, R. Price, P. Smith,G. Mietlowski, W. Linnartz, R. Russo, D. Kay, A.: Phase 3 trial of SMS 201-995 pa LAR and continuous infusion 5-FU in unresectable stage II, III, and IV pancreatic cancer. *Proc Am Soc Clin Oncol* 17, (1998)

57. Abbruzzese, J. L. Gholson, C. F. Daugherty, K. Larson, E. DuBrow, R. Berlin, R. Levin,B.: A pilot trialof the cholecystokinin receptor antagonist MK 329 in patients with advanced pancreatic cancer. *Pancreas* 7, 165-71 (1992)

58. Militello, C. Sperti, C. DiPrima F. Pedrazzoli, S.: Clinical evaluation and safety of loxiglumide in nonresectable pancreatic cancer patients. Italian Pancreatic Study Group. *Pancreas* 14, 222-8 (1997)

59. MacDonald, J. S. Woolley, P. V. Smythe, T. Veno W., Hoth, D. Schein, P. S.: 5- Fluorouracil, adriamycin, and mitomycin-C (FAM) combination chemotherapy in the treatment of advanced gastric cancer. *Cancer* 44, 42-7 (1979)

60. Smith, F. P. Hoth, D. F. Levin, B. Karlin, D. A. MacDonald, J. S. Woolley, P. V. Schein,P. S.: 5-Fluorouracil, adriamycin, and mitomycin-C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. *Cancer* 46, 2014-8 (1980)

61. Bitran, J. D. Desser, R. R. Kozloff, M. F. Billings, A. A. Shapiro, C. M.: Treatment of metastatic pancreatic and gastric adenocarcinoma with 5-FU, adriamycin, and mitomycin-C (FAM). *Cancer Treat Rep* 63, 2049-51 (1979)

62. Cullinan, S. A. Moertel, C. G. Fleming, T. R. Rubin, J. R. Kruok, J. E. Everson, L. K.Windschitel, H. E. Twito, D. I. Marschke, R. F. Foley, J. F.: A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. *JAMA* 253, 2061-7 (1985)

63. Takada, T. Kato, H. Matsushiro, T. Nimura, Y. Nagakawa, T. Nakayama, T.: Comparison of 5-fluorouracil, doxorubicin and mitomycin-C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinoma. *Oncology* 51, 396-40 (1994)

64. Frey, C. Twomey, P. Keehn, R. Elliott, D. Higgins, G.: Randomized study of 5-FU and CCNU in pancreatic cancer, report of the veterans administration surgical adjuvant cancer chemotherapy study group. *Cancer* 47, 27-31 (1981)

65. Buroker, T. Kim, P. N. Groppe, C. McCracken, J. O'Bryan, R. Panettiere, f. Costanzi, J.Bottomley, R. King, G. W. Bonuet, J. Thigpen, T., Whitecar, J. Haas, C. Vaitkevkius, V. K. Hoogstraten, B. Heilbron, L.: 5-FU infusion with mitomycin-C vs 5-FU infusion with methyl-CCNU in the treatment of advanced upper gastrointestinal cancer. *Cancer* 44, 1215-21 (1979)

66. Abderhalden, R. T. Bukowski, R. M. Groppe, C. W., Hewlett, J. S., Weick, J. K.: Streptozotocin and 5-fluorouracil with and without mitomycin-C in the treatment ofpancreatic adenocarcinoma. *Proc Am Soc Clin Oncol* 18, 301 (1977)

67. Wiggans, R. G. Woolley, P. V. MacDonald, J. S. Smythe, T. Veno, W. Schein, P. S.: Phase II trial of streptozotocin mitomycin-C, and 5-fluorouracil in the treatment of advanced pancreatic cancer. *Cancer* 41, 387-391 (1978)

68. Bukowski, R. M. Balcerzak, S. P. O'Bryan, R. M. Bonnet, D. A. Chen, T. T.: Randomized trial of 5-FUand mitomycin-C with or without streptozotocin for advanced pancreatic cancer. *Cancer* 52, 1577-82 (1983)

69. Bukowski, R. M. Schacter, L. P. Groppe, C. W., Hewlett, J. S. Weick, J. K. Livingston, R.B.: Phase II trial of 5-fluorouracil, adriamycin, mitomycin-C, and streptozotocin in pancreatic carcinoma. *Cancer* 50, 197-200 (1982)

70. The Gastrointestinal 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* 4, 1794-8 (1986)

71. Douglass, Jr. H. O. Nava, H. R. Smith, J. L. Meropol, N. J. Raghavan, D.: Phase II trial of streptozotocin, mitomycin-C and 5-fluorouracil/leucovorin in metastatic pancreatic cancer. *Proc Am Soc Clin Oncol* 17, (1988)

72. Oster, M. W. Gray, R. Panasci, L. Perry, M. C.: Chemotherapy for advanced pancreatic cancer. *Cancer* 57, 29-33 (1986)

73. Mallinson, C. N. Rake M. O., Cocking, J. B., Fox, C. A. Cwynarski, M. T. Diffey, B. L. Jackson, G. A. Hanley, J. Wass, V. J.: Chemotherapy in pancreas cancer. *Br Med J* 281, 1589-91 (1980)

74. Cullinan, S. Moertel, C. G. Wieand, H. S. Schutt, A. J. Krook, J. E. Foley, J. F. Norris, B.D. Kardinal, C. G. Tschetter, L. K. Barlow, J. F.: A phase III trial on the therapy of advanced pancreatic carcinoma. *Cancer* 65, 2207-12 (1990)

75. Wils, J. A. Kok, T. Wagener, D. J. Selleslags, J. Duez, N.: Activity of cisplatin in adenocarcinoma of the pancreas. *Eur J Cancer* 29!, 203-4 (1993)

76. Rougier, P. Zarba, J. J. Ducreux, M. Basile, M. Pignon, J.P. Mahjoubi, M. Benahmed, M.Droz, J. P. Cvitkowic E. Armand, J. P.: Phase II study of cisplatin and 120 hour continuous infusion 5-fluorouracil in patients with advanced pancreatic adenocarcinoma. *Ann Oncol* 4, 333-6 (1993)

77. Rothman, H. Cantrell, Jr. J. E. Lokich, J. Difino, S. Harvey, J. Ahlgren, J. Fryer, J.: Continuous infusion 5-fluorouracil plus weekly cisplatin for pancreatic carcinoma. *Cancer* 68, 264-8 (1991)

78. Nicolson, M. Webb, A. Cunningham, D. Norman, A. O'Brien, M. Hill, A. Hickish, T.: Cisplatin and protracted venous infusion 5-fluorouracil - good symptom relief with low toxicity in advanced pancreatic carcinoma. *Ann Oncol* 6, 801-4 (1995)

79. Andre, T. Lotz, J. P. Bouleuc, C. Azzouzi, K. Houry, S. Hannoun, L. See, J. Esteso, Avenin, D. Izrael, V.: Phase II trial of 5-fluorouracil, leucovorin and cisplatin for treatment of advanced pancreatic adenocarcinoma. *Ann Oncol* 7, 173-8 (1996)

80. Evans, T. R. Lofts, F. J. Mansi, J. L Glees, J. P. Dalgleish, A. G., Knights, M. J.: A phase II study of continuous infusion 5-fluorouracil with cisplatin and epirubicin in inoperable pancreatic cancer. *Br J Cancer* 73, 1260-4 (1996)

81. Moertel, C. G. Rubin, J. O'Connell, M. J. Schutt, A. J. Wieand, H. S.: A phase II study of combined 5-fluorouracil, doxorubicin, and cisplatin in the treatment of advanced upper gastrointestinal adenocarcinomas: *J Clin Oncol* 4, 1053-7 (1996)

82. Dougherty, J. B. Kelsen, D. Kemeny, N. Magill, G. Botet, J Niedzwiecki, D.: Advanced pancreatic cancer- a phase I-II trial of cisplatin, high-dose cytarabine, and caffeine. *J Natl Cancer Inst* 81, 1735-8 (1989)

83. Kelsen, D. Hudis, C. Niedzwiecki, D. Doughert, J. Casper, E. Botet, J. Vinciguerra, V. Rosenbluth, R.: A phase III comparison trial of streptozotocin, mitomycin, and 5-fluorouracil with cisplatin, cytosine arabinoside,and caffeine in patients with advanced pancreatic carcinoma. *Cancer* 68, 965-9 (1991)

84. Auerbach, M. Wampler, G. L. Lokich, J. J. Fryer, D. Fryer, J. G., Ahlgren, J. D.: Treatment of advanced pancreatic carcinoma with a combination of protracted infusional 5-fluorouracil and weekly carboplatin: a Mid-Atlantic Oncology Program study. *Ann Oncol* 8, 439-44 (1997)

85. Sporn, J. R. Buzaid, A. C. Slater, D. Cohen, N. Greenberg, B. R.: Treatment of advanced pancreatic adenocarcinoma with 5-FU, leucovorin, interferon-alpha-2b, and cisplatin. *Am J Clin Oncol* 20, 81-3 (1997)

86. Cascinu, S. Silva, R. R. Bami, S. Labianca, R. Frontini, L. Pancera, G. Zaniboni, A.Ferretti, B. Giordani, P. Pessi, M. A. Fusco, V. Luporini, G. Catalano, G. Cellerino, R.: Gemcitabine and 5- fluorouracil in advanced pancreatic cancer, a GISCAD phase II study. *Proc Am Soc Clin Oncol* 17, (1998)

87. Cortes-Funes, H. Castellano, D. Paz-Ares, L. Gravalos, C. Alonso, S. Hitt, R. Hidalgo, M.: A phase I-II study of gemcitabine plus continuous infusion 5-fluorouracil in patients with advanced pancreatic cancer. *Proc Am Soc Clin Oncol* 17, (1998)

88. Oettle, H. Hochmuth, K. Schmidt, C. A. Vogl, T. J. Keck, H. Schmidt-Wolf, I. Neuhaus,P. Riess, H. Huhn, D.: Phase I trial of Gemzar and 24 hour infusion of 5-fluorouracil, folinic acid, in patients withinoperable pancreatic cancer. *Proc Am Soc Clin Oncol* 17, (1998)

89. Scheithauer, W. Funovics, J. Mueller, C. Ludwig, H.: Sequential high-dose methotrexate, 5-fluorouracil, and doxorubicin for treatment of advanced pancreatic cancer. *J Cancer Res & Clin Oncol* 117, S135-8 (1991)

90. Wils, J. Bleiberg, H. Dalesio, O. Duez, N. Blijham, G. Planting, A. Splinter, T. Weber, W.: An EORTC Gastrointestinal Group phase II evaluation of epirubicin combined with 5-fluorouracil in advanced adenocarcinoma of the pancreas. *Eur J Cancer Clin Oncol* 23, 1017-8 (1987)

91. Weiner, L. M. Harvey, E. Padavic-Shaller, K. Willson, J. K. Walsh, C. LaCreta, F. Khazaeli, M. B. Kirkwood, J. M. Haller, D. G.: Phase II multicenter evaluation of prolonged murine monoclonal antibody 17-1A therapy in pancreatic carcinoma. *J Immunother* 13, 110-6 (1993)

92. Tempero, M. A. Sivinski, C. Steplewski, Z. Harvey, E. Klassen, L. Kay, H. D.: Phase II trial of interferon gamma and monoclonal antibody 17-1A in pancreatic cancer, biologic and clinical effects. *J Clin Oncol* 8, 2019-26 (1990)

93. Moore, Jr. D. F. Pazdur, R, Sugarman, S. Jones 3rd D., Lippman, S. M. Bready, B.Abbruzzese, J. L: Pilot phase II trial of 13-cis retinoic acid and interferon-alpha combination therapy for advanced pancreatic adenocarcinoma. *Am J Clin Oncol* 18, 525-7 (1995)

94. Giantonio, B. J. Alpaugh, R. K. Schultz, J. McAleer, C. Newton, D. W. Shannon, B. Guedez, Y. Koto, M. Vitek, L. Persson, R. Gunnarsson, P. O. Kalland, T. Dohlsten, M.Persson, B. Weiner, L. M.: Superantigen-based immunotherapy, a phase I trial of PNU- 214565, a monoclonal antibody-staphylococcal enterotoxin A recombinant fusion protein, in advanced pancreatic and colorectal cancer. *J Clin Oncol* 15, 1994-2007 (1997)

95. Gjertsen, M. K. Bakka, A. Breivik, J. Saeterdal, I. Gedde-Dahl, T. Stokke, K. T. Solheim, B. G. Egge, T. S. Soreide, O. Thorsby, E. Gaudernack, G.: Ex vivo ras peptide vaccination in patients with advanced pancreatic cancer, results of a phase I/II study. *Int J Cancer* 65, 450-3 (1996)

96. Rosenfeld, M. E. Vickers, S. M. Raben, D. Wang, M. Sampson, L. Feng, M. Jaffee, E. Curiel, D. T.: Pancreatic carcinoma cell killing via adenoviral mediated delivery of the

herpes simplex virus thymidine kinase gene. *Ann Surg* 225, 609-18 (1997)

97. Aoki, K. Yoshida, T. Matsumoto, N. Ide, H. Hosokawa, K. Sugimura, T. Terada, M.: Gene therapy for peritoneal dissemination of pancreatic cancer by liposome-mediated transfer of herpes simplex virus thymidine kinase gene. *Human Gene* 8, 1105-13 (1997)

98. Block, A. Chen, S. H. Kosai, K. Finegold, M. Woo, S. L.: Adenoviral-mediated herpes simplex virus thymidine kinase gene transfer, regression of hepatic metastasis of pancreatic tumors. *Pancreas* 15, 25-34 (1997)

99. Yang, L. Hwang, R. Pandit, L. Gordon, E. M. Anderson, W. F. Parekh, D.: Gene therapy of metastatic pancreas cancer with intraperitoneal injections of concentrated retroviral herpes simplex thymidine kinase vector supernatent and ganciclovir. *Ann Surg* 224, 405-14 (1996)

100. Pazdur, R. Meropol, N. J. Casper, E. Fuchs, C. douglass, H. O. Vincent, M. Abbruzzese,J. L.: Phase II trial of ZD 1694 in patients with advanced pancreatic cancer. *Invest New Drugs* 13, 355-8 (1996)

101. Loh, K. Stuart, K. Cohn, A. White, C. Hines, J. Miller, W. Green, M.R., Chew, T.Johnston, A. Clendeninn, N.: A phase II trial of Thymitaq in patients with adenocarcinoma of the pancreas. *Proc Am Soc Clin Oncol* 16, (1997)

102. Hubbard, K. P. Pazdur, R. Ajani, J. A. Broud, E. Blaustein, A. King, M. Llenado-Lee, M.Winn, R. Levin, B. Abbruzzese, J. L.: Phase II evaluation of iproplatin in patients with advanced gastric and pancreatic cancer. *Am J Clin Oncol* 15, 524-7 (1992)

103. Mahjoubi, M. Rougier, P. Oliviera, J. Herait, P. Tigaud, J. M. Droz, J. P.: Phase II trial of pirarubicin in the treatment of advanced pancreatic cancer. *Cancer Invest* 12, 403-5 (1994)

104. Friess, H. Beger, H. G. Kunz, J. Funk, N. Schilling, M. Buchler, M. W.: Treatment of advanced pancreatic cancer with mistletoe, results of a pilot trial. *Anticancer Res* 16, 915-20 (1996)

105. Jenkins, T. R. Tangen, C. MacDonald, J. S. Weiss, G. Chapman, R. Hantel, A.: A phase I trial of piroxantrone in adenocarcinoma ofthe pancreas. A Southwest Oncology Group study. *Invest New Drugs* 11, 329-31 (1993)

106. Leichman, C. G. Tangen, C. MacDonald, J. S. Leimert, T. Fleming, T. R.: Phase II trial of amonafide in advanced pancreas cancer. A Southwest Oncology Group study. *Invest New Drugs* 11, 219-21 (1993)

107. Bukowski, R. M. Fleming, T. R. MacDonald, J. S. Oishi, N. Taylor, S. A. Baker, L. H.: Evaluation of combination chemotherapy and phase II agents in pancreatic adenocarcinoma. A Southwest Oncology Group study. *Cancer* 71, 322-5 (1993)

108. Wils, J. Bleiberg H. Blijham, G. Dalesio, O. Duez, N. Lacave, A. Splinter, T.: Phase II study of epirubicinin advanced adenocarcinoma of the pancreas. *Eur J Cancer & Clin Oncol* 21, 191-4 (1985)

109. Schwartz, G. K. Casper, E. S.: A phase II trial of doxorubicin HCL liposome injection in patients with advanced pancreatic adenocarcinoma. *Invest New Drugs* 13, 77-82 (1995)

110. Moore, M. Maroun, J. Robert, F. Natale, R. Neidhart, J. Dallaire, B. Sisk, R. Gyves, J.: Multicenter phase II study of brequinar sodium in patients with advanced gastrointestinal cancer. *Invest New Drugs* 11, 61-5 (1993)

111. Kraut, E. H. Fleming, T. MacDonald, J. S. Spiridonidis, C. H. Bradof, J. E. Baker, L. H.: Phase II trial of merbarone in pancreatic carcinoma. A Southwest Oncology Group study. *Am J Clin Oncol* 16, 327-8 (1993)

112. Sternberg, C. N. Magill, G. B. Cheng, E. W. Applewhite, A. Sordillo, P. P.: Etoposide in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol* 11, 172-3 (1988)

113. Casper, E. S. Schwartz, G. K. Kelsen, D. P.: Phase II trial of fazarabine (aribinofuranosyl-5-azacytidine) in patients with advanced pancreatic adenocarcinoma. *Invest New Drugs* 10m 205-9 (1992)

114. Kilton, L. J. Benson, 3rd. A. B., Greenberg, A. Johnson, P. Shapiro, C. Blough, R.French, R. Weidner, L.: Phase II trial of fludarabine phosphate for adenocarcinoma of the pancreas. An Illinois Cancer Center study. *Invest New Drugs* 10, 201-4 (1992)

115. Rosvold, E. Schilder, R. Walczak, J. DiFino, S. M. Flynn, P. J. Banerjee, T. K. Heim, W.J. Engstrom, P. F. Ozols, R. F. O'Dwyer, P. J.: Phase II trial of PALA in combination with 5-fluorouracil in advanced pancreatic cancer. *Cancer Chem & Pharm* 29, 305-8 (1992)

116. Kajanti, M. J. Pyrhonen, S. O: Phase II trial of oral carmofur in advanced pancreatic carcinoma. *Ann Oncol* 2, 765-6 (1991)

117. Ajano, J. A. Pazdur, R. Winn, R. J. Abbruzzese, J. L. Levin, B. Belt, R. Young, J. Patt, Y. Z. Krakoff, I. H.: Phase II study of intravenous 6-thioguanine in patients with advanced carcinoma of the pancreas. *Invest New Drugs* 9, 369-71 (1991)

118. Morrell, L. M. Bach, A. Richman, S. P. Goodman, P. Fleming, T. R. MacDonald, J. S.: A phase II multi-institutional trial of low-dose N-(phosphonacetyl)-L-aspartate and high- dose 5-fluorouracil as a short-term infusion in the treatment of adenocarcinoma of the pancreas. *Cancer* 67, 363-6 (1991)

119. Kraut, E. H. Fleming, T. Segal, M. Neidhart, J. A. Behrens, B. C. MacDonald, J. S.: Phase II study of pibenzimol in pancreatic cancer. A Southwest Oncology Group study. *Invest New Drugs* 9, 95-6 (1991)

120. Brown, T. Goodman, P. J. Fleming, T. R. Baker, L. H. MacDonald, J. S.: Phase II trial of menogaril in adenocarcinoma of the pancreas. A Southwest Oncology Group study. *Invest New Drugs* 9, 77-8 (1991)

121. Cerny, T. Martinelli, G. Goldhirsch, A. Terrier, F. Joss, R. Fey, M. F. Brunner, Kupfer, A.: Continuous 5-day infusion of ifosfamide with mesna in inoperable pancreatic cancer patients, a phase II study. *J Cancer Research Clin Oncol* 117, S135-8 (1991)

122. Scher, R. M. Kosierowski, R. Lusch, C. Alexander, R. Fox, S. Redei, I. Green, F. Raskay, B. Amfoh, K. Engstrom, P. F. O'Dwyer, P. J.: Phase II trial of topotecan in advanced or metastatic adenocarcinoma of the pancreas. *Invest New Drugs* 13, 347-54 (1996)

123. Hansen, R. Quebbeman, E. Ritch, P. Chitambar, C. Andersen, T.: Continuous 5-fluorouracil infusion in carcinoma ofthe pancreas, a phase II study. *Am J Med Sci* 295, 91-3 (1988)

Key words: Pancreatic cancer, Treatment, Chemotherapy

Send correspondence to: Dr Lawrence Blaszkowsky, New , England Medical Center, Division of Hematology/ Oncology, 750 Washington Street, Box 542, Boston, MA 02111, Tel: (617) 636-5627, Fax: (617) 636-0342, E-mail: lawrence.blaszkowsky@es.nemc.org