

Pancreatic Cancer

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Updated Data Confirm Excellent Activity of Weekly “Metronomic Dosing” of Paclitaxel, Oxaliplatin, Leucovorin, and 5-Fluorouracil (POLF) in Metastatic Pancreatic Adenocarcinoma

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Background: Patients with metastatic pancreatic cancer (PC) have a dismal prognosis, with median survival of 3 to 6 months and a poor quality of life. A weekly “metronomic dosing” of chemotherapy allows for increased dose density and dose intensity, but with good tolerability, and can have antiangiogenic effects, especially with weekly dosing of paclitaxel. Work with the antiangiogenic agent bevacizumab has shown that blocking angiogenesis decreases interstitial tumor pressure, allowing for more chemotherapy to reach the tumor bed. Weekly paclitaxel may do the same, allowing for smaller amounts of chemotherapy which cause fewer systemic side effects to have better efficacy. We previously reported excellent results of weekly metronomic dosing of POLF for metastatic PC. We now report updated data of 26 patients who received at least 11 weeks of treatment with this POLF regimen.

Methods: Twenty-six (26) patients, 35 to 75 years old, with metastatic biopsy-proven PC were treated with weekly POLF (P: 60 mg/m², O: 50 mg/m², L: 20 mg/m², F: 425 mg/m²) for at least 11 weeks, with one patient (B.M.) switching to Abraxane (protein-bound paclitaxel) because of a reaction to paclitaxel. The majority of patients received at least one previous chemotherapy. One patient (A.B.) also received intermittent cetuximab, and two patients (M.C., J.S.) also received erlotinib. Glutathione, calcium, and magnesium were used to prevent oxaliplatin-related neuropathy. Glutamine was administered to prevent paclitaxel-related neuropathy.

Results: After at least 11 weeks of treatment, 15/26 patients had a greater than 50% reduction of CA 19-9 levels (see Table), improvement of cancer-related symptoms, and

shrinkage of tumor. Patient A.B. was severely debilitated, with Eastern Cooperative Oncology Group (ECOG) status of 4, following progression of disease after two previous lines of chemotherapy, but is alive and well 4 years since diagnosis, with ECOG of 0. Bilirubin level in patient D.P. was 27 and in patient L.C. was 9.6, both of which normalized with treatment without need for stent placement. G.B. had a small bowel obstruction, ECOG 4, but became unobstructed with treatment. H.N. also had a concurrent primary lung cancer, atrial fibrillation, and severe emphysema. The regimen was well tolerated with two cases each of grade 3 neurotoxicity (L.C., F.T.), grade 3 diarrhea (B.P., F.T.), and grade 3 nausea/vomiting (J.G-D., K.D.). Median survival is 14.0 months since diagnosis and 8.4 months since initiation of POLF. Survival at 12, 18, and 24 months is 16/26 patients (62%), 9/26 (35%), and 4/26 (15%), respectively.

Conclusions: A weekly metronomic combination of paclitaxel, oxaliplatin, leucovorin, and 5-fluorouracil has excellent activity against advanced PC, even in previously treated patients, with manageable side effects. A phase II study is opened to enrollment, and we welcome participation. We are also interested in conducting a phase III trial with this regimen.

Patient	Gender	Age	Tumor Sites	Previous Chemotherapy	CA 19-9		Survival (Months)		Clinical Response
					Before POLF	After 12 Weeks	Since Diagnosis	Since POLF Treatment	
A.B.	Male	35	Body of pancreas, liver	1)Gemcitabine+ Docetaxel 2)Gemcitabine+ Capecitabine	489	18	47.5+	42.4+	PR
D.P.	Male	55	Head of pancreas, liver	1)Gemcitabine+ Cisplatin	9,015	53	12.0	10.6	PR
L.C.	Female	43	Neck of pancreas, lungs, retroperitoneal and supraclavicular lymph nodes	None	8,893	326	31.9	30.6	MR/PR
J.G-D.	Female	59	Body, tail of pancreas, liver	1) Paclitaxel+ Gemcitabine	8105	11,182	9.1*/5.3**	4.9	PD
I.S.	Female	53	Body & tail of pancreas, liver	1)Gemcitabine 2)Capecitabine	124,692	23,131	22.5	10.4	MR/PR
R.R.	Male	66	Head of pancreas, liver	None	3,658	1,136	7.5	6.7	PR
B.P.	Male	65	Neck of pancreas, liver	1)Mitomycin C+ 5-FU+ Cisplatin 2)Gemcitabine	3,453	1,445	17.4	11.3	MR
G.L.	Female	75	Head of pancreas, liver,	1)Capecitabine	3,594	302	13.4*/7.9**	6.2	MR

			lung						
W.S.	Male	66	Head of pancreas, liver, periaortic LN.	None	112	66	15.0	12.3	Mixed
H.G.	Male	73	Head of pancreas, liver, lung	1)5-FU/LK 2)Gemcitabine+ Erlotinib 3)Capecitabine	5690	3978	22.4*/6.6**	6.2	MR
F.T.	Female	44	Head of pancreas, liver	1)Gemcitabine+ Docetaxel+ Erlotinib 2)Gemcitabine+ Capecitabine	3378	326	35+*/32.8+**	20.1+	PR
G.B.	Male	65	Body of pancreas, liver	1)Gemcitabine+ Docetaxel+ Capecitabine	6928	917	7.9	5.8	PR
C.O.	Female	65	Head of pancreas, liver	1)Gemcitabine+ Cisplatin+ Erlotinib 2)S1	1088	135	31.2+*/27.0+**	14.4+	PR
N.C.	Male	71	Head of pancreas, lungs	1)5-FU+XRT 2)Capecitabine 3)Gemcitabine+ Docetaxel+ Capecitabine	393	2066	85*/15**	6.9	PD
B.E.	Female	54	Head of pancreas, liver	1)Docetaxel+ Gemcitabine 2)5-FU+XRT	92	47	13.6	9.9	PR
M.C.	Male	53	Head of pancreas, colon, mesenteric LN, liver	1)Capecitabine+ Gemcitabine+ XRT 2)Paclitaxel+ Gemcitabine	8	6	18.3	14.8	PR
B.M.	Female	59	Head and tail of pancreas, stomach, mesocolon, and liver	1)Paclitaxel+ Gemcitabine 2)Docetaxel+ Gemcitabine	17	10	11.5	6.6	Mixed / SD
S.H.	Female	65	Head of pancreas, supraclavicular LN, lungs	1)Paclitaxel+ Gemcitabine 2)Erlotinib	10	10	22.0+	15.7+	PR
P.L.	Female	56	Tail of pancreas, liver, lung	1)Gemcitabine+ Oxaliplatin+ Erlotinib	47,446	69	10.7	7.4	PR
D.B.	Male	75	Head of pancreas, periaortic LN, hilar LN, bones	1)Paclitaxel+ Gemcitabine 2) Erlotinib	345,385	164,329	13.3	7.5	MR
J.S.	Female	69	Tail of pancreas, liver	1)Gemcitabine+ Docetaxel+ Capecitabine 2)Paclitaxel + Gemcitabine	8	-	15.7+	9.3+	PR
H.N.	Male	74	Tail of pancreas, liver	1)Paclitaxel+ Gemcitabine	5,320	11,734	19.3	6.3	PD
V.S.	Male	65	Head of pancreas, lungs, retroperitoneal LN	1)Gemcitabine+ Capecitabine	1,730	14	36.2+*/23.0+**	17.0+	SD
T.W.	Female	49	Tail of pancreas, liver	1)Paclitaxel+ Gemcitabine	1,760	691	11.9	5.5	SD
J.C.	Male	47	Tail of pancreas, liver	1)Paclitaxel+ Gemcitabine	154	1,237	10.0	6.0	SD
K.D.	Female	65	Head of pancreas, liver	1)Gemcitabine	2,027	4,569	10.2	5.8	PD

*Time since original diagnosis of pancreatic cancer. **Time since diagnosis of metastatic pancreatic cancer.

Abbreviations: 5-FU = 5-fluorouracil; LK = leucovorin; LN = lymph nodes; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; XRT = radiation therapy.