

A Phase II Trial of Full-Dose Gemcitabine with Concurrent Radiation Therapy in Patients with Resectable and Unresectable Non-Metastatic Pancreatic Cancer



W Small, Jr.¹, M Talamonti¹, D Normolle², G Freedman³, J Berlin⁴, T Kinsella⁵, P Philip⁶, M Zapulski², M Mulcahy¹, N Meropol³, A Chakraverthy⁴, J Brell⁵, T Lawrence², and C McGinn²

1. Northwestern University Medical School, Chicago, IL; 2. University of Michigan Medical School, Ann Arbor, MI; 3. Fox Chase Cancer Center, Philadelphia, PA; 4. Vanderbilt University Medical Center, Nashville, TN; 5. Case Western Reserve University, Cleveland, OH; 6. Karmanos Cancer Institute, Detroit, MI;

Updated Abstract

Purpose: To evaluate the toxicity, response rate, patterns of failure, and 1-year survival with the delivery of full-dose gemcitabine before, during, and after radiotherapy in a multi-institutional trial.

Material and Methods: Patients with resectable or unresectable pancreatic carcinoma and no evidence of metastatic disease were eligible. Three-dimensional treatment planning, based on a contrast-enhanced CT, was used for all patients. The planning target volume was the gross tumor volume with a 1-cm margin. Protocol therapy included 3 cycles of gemcitabine, with radiotherapy during the second cycle. Cycles 1 and 3 consisted of gemcitabine (1000mg/m² intravenously) on Days 1 and 8 of a 21-day cycle. Cycle 2 consisted of the same dose of gemcitabine on Days 1, 8, and 15 of a 28-day cycle concurrent with 2.4 Gy of radiotherapy Days 1-5, 8-12 and 15-19. Resectable patients underwent surgery 4-6 weeks following the last gemcitabine infusion. Toxicities were evaluated using version 2.0 of the NCI Common Toxicity Criteria.

Results: The study completed accrual with 39 patients enrolled at 6 institutions between 4/02 and 7/03. The median follow-up for this report was 10.5 months. The most common toxicities were neutropenia, nausea, vomiting, and thrombocytopenia. Grade 3/4 nonhematologic toxicities were experienced by 48.7% of all patients. There were no toxicity-related deaths and only one CTC Grade 4 toxicity (thrombocytopenia). The mean pre- and post-treatment CA 19-9 levels were 1068 ± 1961 and 226 ± 353, respectively (p<0.005). The radiographic response rate (CR+PR) was 5.1% and the disease control rate (CR+PR+SD) was 84.6%. A total of 17 patients underwent resection 4-6 weeks after the last dose of gemcitabine. There were no operative deaths. The overall 1-year survival of the entire patient group (N=39) was 73% (95% CI, 58,87). For patients judged to be nonresectable at trial entry (n=16) the 1-year survival rate was 57% (95% CI, 35,79). And, for patients initially judged to be resectable (n=23) the 1-year survival rate was 94% (95% CI, 82,100).

Conclusions: In a multi-institutional setting, full-dose gemcitabine and radiotherapy +/- resection was generally well tolerated. The regimen appeared active as measured by CA 19-9 response. Resectable patients had improved 1-year survival compared to nonresectable patients. Additional survival and pattern of failure data are under development. Full dose gemcitabine plus radiotherapy should be further evaluated in patients with early stage pancreatic cancer.

BACKGROUND

- Combined-modality therapy using 5-FU with concurrent radiotherapy in either the neoadjuvant or post-operative adjuvant setting has shown modest clinical benefit.
- Gemcitabine has proven effective in the treatment of advanced pancreatic cancer.
- Preclinical studies with gemcitabine have shown sensitization of pancreatic cancer cell lines to radiotherapy.
- Previous clinical trials with combination gemcitabine and radiotherapy have mainly focused on gemcitabine dose escalation with conventional radiotherapy.
- This study was focused on the use of full-dose gemcitabine before and after a three-week chemoradiation regimen of gemcitabine and concurrent radiation in patients with either resectable or nonresectable pancreatic cancer

OBJECTIVES

Primary

- Evaluate toxicity associated with full-dose gemcitabine and concurrent radiotherapy in a multi-institutional setting

Secondary

- Evaluate objective responses to treatment
- Evaluate patient survival

Methods

ELIGIBILITY CRITERIA

- Documented pancreatic carcinoma, excluding patients with either metastatic disease or neuroendocrine tumors
- Determination of resectability prior to entry
- Life expectancy of ≥12 weeks, Zubrod Performance Status ≤2, and adequate organ function
- No prior history of chemotherapy for pancreatic cancer or abdominal radiation therapy
- Patient informed consent

TREATMENT

WK	CHEMOTHERAPY*	RADIOTHERAPY**
1	GEM, Day 1	
2	GEM, Day 1	
4	GEM, Day 1	XRT, Days 1-5
5	GEM, Day 1	XRT, Days 1-5
6	GEM, Day 1	XRT, Days 1-5
8	GEM, Day 1	
9	GEM, Day 1	

* Gemcitabine administered by IV infusion at 1000 mg/m² over 30 minutes

** Radiotherapy administered in 2.4 Gy fractions to a total of 36 Gy over 19 days during weeks 4-6

Results

PATIENT CHARACTERISTICS

Parameter	(N=39)
Median age (range)	59.5 (41-81)
Gender	
Male	23 (59.0%)
Female	16 (41.0%)
Ethnic Origin	
Caucasian, White	37 (94.9%)
Black	2 (5.1%)
ECOG performance status	
0	15 (38.5%)
1	20 (51.3%)
2	4 (10.3%)
Stage of Tumor	
Ia: T1 N0 M0	3 (7.7%)
Ib: T2 N0 M0	6 (15.4%)
II: T3 N0 M0	13 (33.3%)
III: Ant T N1 M0	17 (43.6%)
Prior Chemotherapy	
Yes	1 (2.6%)
No	38 (97.4%)
Prior Surgery	
Yes	3 (7.7%)
No	35 (89.7%)
Prior Radiotherapy	
No	39 (100.0%)
Patient Complete Study	
Yes	33 (84.6%)
No	6 (15.4%)
Reason for Discontinuation	
Death	1 (2.6%)
Toxicity	1 (2.6%)
Other*	4 (10.3%)

* Two patients withdrew from the study and 2 patients discontinued after dose reductions

TOXICITIES (Patient Based)

Hematologic	Grade 3	Grade 4
Neutropenia	5 (12.8%)	0 (0.0%)
Thrombocytopenia	2 (5.1%)	1 (2.6%)
Leukopenia	2 (5.1%)	0 (0.0%)
Anemia	1 (2.6%)	0 (0.0%)

Nonhematologic*	Grade 3	Grade 4
Nausea	4 (10.3%)	0 (0.0%)
Vomiting	4 (10.3%)	0 (0.0%)
Fatigue	2 (5.1%)	0 (0.0%)
Anorexia	2 (5.1%)	0 (0.0%)

* 48.7% of patients experienced grade 3/4 non-hematologic toxicities.

CA 19-9 RESPONSE

	CA 19-9 Mean (U/ml)
Baseline	1068 ± 1961
Post-chemoradiotherapy	226 ± 353
p < 0.005	

SURVIVAL RATES

Cohort	6 Month (95% CI)	12 Month (95% CI)	18 Month (95% CI)
All Patients (N=39)	92% (84-100%)	73% (58-87%)	NA
Unresectable (n=23)	87% (73-100%)	57% (35-79%)	15% (0-41%)
Resectable (n=16)	100% (100-100%)	94% (82-100%)	42% (0.5-83%)

TUMOR RESPONSE

Parameter (N=39)	N (%) (90% CI)
Complete Response (CR)	1 (2.6%) (0-12%)
Partial Response (PR)	1 (2.6%) (0-12%)
Stable Disease (SD)	31 (79.5%) (66-89%)
Progressive Disease (PD)	2 (5.1%) (1-15%)
Overall Response Rate (CR+PR)	2 (5.1%) (1-15%)
Disease Control Rate (CR+PR+SD)	33 (84.6%) (72-93%)

Conclusion

- In a multi-institutional setting, full-dose gemcitabine with radiotherapy was well tolerated.
- The chemoradiotherapy treatment regimen was active as measured by the CA 19-9 response.
- While the overall tumor response rate (CR+PR) was low (5.1%), the disease control rate (CR+PR+SD) was notable (84.6%).
- Patients initially judged as resectable at study entry had improved 1-year survival compared to patients entered as unresectable.
- Full-dose gemcitabine plus radiotherapy should be further evaluated in patients with early stage pancreatic cancer.