ORIGINAL ARTICLE

Is There any Survival Benefit of Maintenance Chemotherapy Following Adjuvant Chemotherapy in Patients with Resected Pancreatic Cancer Patients with Post-Surgery Elevated CA 19-9?

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ABSTRACT

Background Pancreatectomy offers only potential for cure but is only possible in a minority of patients. Even in those patients who receive adjuvant chemotherapy, majority of them succumb to death due to metastases. Radiation Therapy Oncology Group 9704 showed that post-surgery CA 19-9 levels are an important predictor of survival. European study group for pancreatic cancer-3 showed that completion of all 6 cycles of adjuvant chemotherapy was an independent prognostic factor. Any survival benefit of an intensified chemotherapy strategy has not been demonstrated in patients with persistently elevated CA 19-9 following surgery. The object of this study was to investigate any benefit of maintenance chemotherapy following adjuvant in these patients. **Methods** Twenty patients with R0 surgery of pancreatic cancer who received adjuvant chemotherapy with post-surgery elevated CA 19-9 but no radiographic evidence of cancer was identified from 2005-2017. Either biopsy or positron emission tomography scan determined recurrence of cancer. Efficacy endpoints including overall survival and disease-free survival were assessed. **Results** Maintenance and additional chemotherapeutic agents included 5-FU, capecitabine, platinum agents, irinotecan and nab-paclitaxel. CA 19-9 normalized in 3 patients while 22 persisted to be elevated or had further increase in the marker. Two patients underwent metastatectomy. Median disease-free survival was 14.5m (9-18), OS 29m (19-96) and OS rates were 80%, 50% at 1 and 2 years respectively. **Conclusions** We believe that the longer overall survival of our patients with elevated CA 19-9 post-surgery was due to maintenance and additional chemotherapy following planned 6-months of adjuvant therapy, close monitoring with monthly CA 19-9 and 3-monthly computed tomography scans. Our study also underlines importance of collecting pre-surgery CA 19-9 and complete staging including chest. Prospective study aiming to evaluate role of maintenance or intensified chemotherapy or targeted agents are indicated.

INTRODUCTION

Pancreatic cancer is one of the most lethal solid organ malignancies. Pancreatectomy offers the only potential for cure but is only possible in a minority of patients [1]. Even in those patients who receive adjuvant treatment, majority of them succumb to death due to metastatic disease [2, 3, 4, 5]. The optimal timing and duration of adjuvant therapy is not established. A focused guideline update on potentially curable pancreatic cancer from American Society of Clinical Oncology (ASCO) recommends adjuvant systemic chemotherapy for six months starting within eight weeks of surgery, assuming adequate recovery from surgery [1]. There are no randomized trials addressing the impact of delayed initiation of adjuvant therapy on outcomes or the effect of a longer duration of therapy [6, 7]. However, at least some data support the view that delaying treatment initiation to allow full recovery from surgery does not compromise the survival benefit, and modern adjuvant chemotherapy trials have permitted enrollment up to 12 weeks postoperatively as see in the European Study Group for Pancreatic Cancer-3 (ESPAC-3) trial [8, 9, 10, 11].

Postoperative surveillance studies have shown that serial determination of CA 19-9 can detect recurrence or metastasis of pancreatic cancer several months before finding clinical or radiologic evidence of disease [12, 13,

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Abbreviations RTOG Radiation Therapy Oncology Group; OS Overall Survival; DFS Disease-Free Survival; PET Positron Emission Tomography; ESPAC European Study Group for Pancreatic Cancer; GITSG Gastrointestinal Tumor Study Group; IRB Institutional Review Board; PDAC Pancreatic Ductal Adenocarcinoma; ASCO American Society of Clinical Oncology; ESMO European Society for Medical Oncology; NCCN National Comprehensive Cancer Network; MRI Magnetic resonance imaging; EUS Endoscopic Ultrasound; CT Computed Tomography
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14, 15, 16, 17]. Radiation Therapy Oncology Group (RTOG) 9704 study has shown that post-resection CA 19-9 levels are an important predictor of survival [6]. Moreover, another adjuvant study, ESPAC-3 study showed that completion of all 6 cycles of planned adjuvant chemotherapy was an independent prognostic factor after resection [8].

Any survival benefit of an intensified or maintenance strategy has not been demonstrated in patients with persistently elevated CA 19-9; despite the pivotal Gastrointestinal Tumor Study Group (GITSG) study suggested continuing bolus 5-FU weekly for 24 months from time of start of adjuvant therapy [2]. It is likely that pancreatic cancer cells remain locally and systemically present despite complete surgical resection. Studies in animal models demonstrate the potential for widely disseminated disease to occur before a visible primary tumor is first detected. It is possible that residual pancreatic cancer cells may lie dormant in G0 arrest and only infrequently enter the G1/S phase, so additional or maintenance chemotherapy may be necessary to maintain pressure on these cells. Limited data exists to support the idea of maintenance chemotherapy, though it is intriguing [18].

Prior to beginning adjuvant therapy, all patients should undergo formal restaging with CT scans and a serum level of the tumor marker CA 19-9 [19, 20, 21]. Persistent postoperative elevations of the serum tumor marker CA 19-9 are associated with poor long-term prognosis [22, 23, 24, 25, 26]. However, CA 19-9 levels are prognostic and not predictive of benefit from adjuvant therapy. While some suggest withholding adjuvant therapy from such patients or treating them as if they have advanced metastatic disease, and some adjuvant therapy protocols, such as Radiation Therapy Oncology Group (RTOG) 0848, only allow enrollment if the post-treatment CA 19-9 level is ≤ 180 units/mL [16].

As mentioned earlier that the GITSG study effectively used a maintenance approach by continuing bolus 5-FU for up to 2 years [2]. Additionally, several trials have evaluated maintenance chemotherapy in advanced pancreatic cancer, but no prospective studies have been done following adjuvant therapy for patients with resected pancreatic cancer, including those with elevated tumor makers [18]. The majority of recurrences after potentially curative treatment of pancreatic exocrine cancer occurs within two years, and they can be locoregional or to distant sites, most often the liver, lung, and peritoneal cavity. In one autopsy series of patients with known pancreatic cancer, approximately 30% died with locally destructive disease without evidence of metastases, while 70% died with widespread metastatic disease [27].

We performed a retrospective analysis of patients treated at our centers to investigate any benefit of maintenance and/or additional chemotherapy following planned 6 months of adjuvant therapy in these patients. As a secondary objective, we collected data to describe the toxicity associated with additional/maintenance chemotherapy.

PATIENTS AND METHODS

We conducted a retrospective chart review of patients who were treated for pancreatic cancer. Patients were selected who had pathology-proven pancreatic adenocarcinoma, had undergone surgical resection with curative intent from 2005-2017, and had received adjuvant chemotherapy with or without chemo-radiation. CA 19-9 was performed monthly and CT or MRI every 2-3 months.

Patients who had recurrence of disease while on adjuvant chemotherapy were excluded. Of the patients 25 met the inclusion criteria: R0 surgery, post-surgery elevated levels of CA 19-9, absence of radiographic including EUS evidence of cancer. Recurrent pancreatic cancer was confirmed either biopsy or PET scan after a multidisciplinary discussion. These patients received various chemotherapy regimens: schedule, dosage and duration were collected. In patients who showed toxicity, the dose was adjusted according to standard guidelines. Charts were reviewed to determine adverse events attributed to chemotherapy.

Primary end points for analysis were disease free survival (DFS) and overall-survival (OS). Descriptive statistics (e.g., mean, median, range, and proportion) were used to describe patients' demographic information. SAS software (version 9.3; SAS Institute Inc., Cary, NC) was used to perform the analyses. The study was approved by our institutional review board (IRB).

RESULTS

The demographics are summarized in **Table 1**. Seven patients did not have pre-operative CT scan of chest while nine patients did not have their pre-operative CA 19-9 measured.

Maintenance chemotherapy agents included 5-FU, capecitabine, palatinates [cisplatin, oxaliplatin], irinotecan and nab-paclitaxel. Capecitabine was the most commonly used agent (n=10), selected due to convenience of oral administration as well as relatively favorable toxicity, followed by FOLFOX/XELOX (n=5), gemcitabine-oxaliplatin (n=3), GTX (gemcitabine, docetaxel, capecitabine) (n=3) gemcitabine-cisplatin (n=1), gemcitabine-nab-paclitaxel (n=1) and FOLFIRI (n=1) **(Table 2)**. Overall the chemotherapy was well tolerated with expected toxicities.

Most common sites of metastases included liver (n=12), lungs (n=7), peritoneum (n=4), tumor bed (n=2) and lymph nodes (n= 2). One patient never showed any radiological evidence of cancer **(Table 2)**.

The average duration of therapy was 6.42 months (range, 3-12) till the recurrent or metastatic cancer was diagnosed. CA 19-9 normalized in 3 patients while 22 remained stable or further elevated. Two patients underwent metastatectomy. Median DFS was 14.5m (9-18), OS 29m (19-96) and OS rates were 80 %, 50 % at 1 and 2 years respectively.

Table 1. Summary of Demographics.

Characteristic	No. of patients
Sex	
Male	12
Female	13
Median age (year)	59 (range: 41-76)
Tumor location	
Head/Neck	18
Body/Tail	7
Pathology	
Adenocarcinoma	23
Mixed	2
Histologic (differentiation) grade	
Well-Moderately	14
Moderately	7
Poorly	4
Lymph Node Metastasis	
Present	14
Absent	11
LVI	
Present	9
Absent	16
PNI	
Present	7
Absent	18
CA19-9 pre-surgery (U/mL)	
Available	16
Missed	69
CT Chest (Complete staging)	
Performed	18
No	7
CA1-9 post-surgery (U/mL)	
<300	5
>300	20
Sites of Metastases	
Liver	12
Lungs	7
Peritoneum	4
Local (bed)	4
LN	3
Multiple sites	5

Table 2. Data on 25 patients who received additional chemotherapy post-adjuvant for rising CA19-9.

Patient	Age at Diagnosis	Gender	Location	Histology Grade	Pre-op CA19-9	Post-op CA19-9	CT CAP pre-op	Post-op CT CAP	Chemotherapy Given	Recurrent Site	DFS on Extra Chemo.	Survival	XRT	Surgery of Mets.
1	55	F	H	2	NA	448	CAP	Y	FOLFOX + Bev.	Bed	11.5	96	Y	-
2	75	M	H	1	181	340	AP	N	FOLFOX	Lung	6	15	-	-
3	63	F	H	1	NA	289	CAP	Y	XELOX	Liver	8	24.5	-	-
4	43	M	H	1	349	1000	CAP	Y	FOLFOX	Peritoneum, Liver	4	22	-	-
5	71	M	T	1	NA	684	CAP	N	Gem-Nab	Liver	9	18	-	-
6	58	M	B	1	NA	486	CAP	N	CAP	Lungs	12	30	-	-
7	61	F	H	2	206	561	CAP	Y	GTX	Liver	5	19	-	-
8	49	M	B	3	NA	605	AP	N	GTX	Liver, Lungs	6	15	-	-
9	53	F	H	1	161	302	AP	Y	GTX	Peritoneum	9	23	-	-
10	56	F	H	1	NA	501	AP	Y	FOLFOX	Liver	4	11	-	-
11	73	M	H	1	107	321	CAP	N	Gem-Cis	Lung	6	30	-	Y
12	65	F	H	1	76	128	CAP	N	CAP	Bed	12	24	Y	-
13	76	M	T	2	111	265	AP	N	CAP	Lung	6	29	-	-
14	48	F	B	3	89	211	CAP	Y	CAP	Peritoneum	9	23	-	Y

15	49	M	N	1	170	587	CAP	Y	CAP	Liver	6	15	Y	-
16	41	F	H	3	253	346	AP	Y	CAP	Liver	5	27	-	Y
17	59	F	H	3	102	398	CAP	N	CAP	None	12	SA	-	-
18	73	F	H	1	NA	703	AP	Y	CAP	Bed, Lung	3	9	Y	-
19	69	M	H	1	113	405	CAP	Y	CAP	Liver	3	11	-	-
20	68	F	H	2	NA	286	CAP	Y	CAP	Distant LN	6	23	-	-
21	57	F	H	2	57	311	CAP	N	Gem-Ox	Peritoneum	8	22	-	-
22	63	F	B	1	327	634	CAP	Y	FOLFOX	Liver, LN	4	14	-	-
23	68	M	H	3	NA	516	CAP	N	Gem-Ox	Liver	3	10.5	-	-
24	67	M	H	1	264	602	CAP	Y	Gem-Ox	Lung	6	SA	-	Y
25	71	M	H	2	216	420	CAP	N	FOLFIRI	Liver	6	13	-	-

CAP Capecitabine; FOLFOX Folinic acid, 5-FU, oxaliplatin; FOLFIRI folinic acid, 5-FU, irinotecan; CAP chest, abdomen, pelvis; Y yes; N no; NA not available; GTX gemcitabine, docetaxel, xeloda; Gem-Ox gemcitabine, oxaliplatin; Gem-Cis gemcitabine, cisplatin; XELOX xeloda, oxaliplatin; Bev bevacizumab; Nab-pacl nab-paclitaxel; LN lymph nodes; SA Still alive

Table 3. Summary of Continuing Chemotherapy Regimens and other treatments.

Immediate Additional Chemotherapy	
Yes	16
No (Upon further ↑ CA 19-9)	9
Commonly used Upfront agents	
Capecitabine/5-FU	10
Oxaliplatin-based	9
Irinotecan-based	1
Nab-paclitaxel	1
Docetaxel-based	3
Cisplatin-based	1
Number of Regimens	
1	8
>1	17
Oxaliplatin	2
Irinotecan	1
Nab-paclitaxel	1
5-FU/Capecitabine	3
Erlotinib	1
Mitomycin-C	4
Clinical Trial	7
Tamoxifen	1
Onivyde	3
Radiotherapy	
During Adjuvant	2
Post-Adjuvant (during Additional Chemo)	4
Surgery	
Lungs	2
Liver	1
HIPEC	1
Liver-directed Therapy	
Y90	3
RFA	1

DISCUSSION

It is evitable from our study that post-surgery CA 19-9 warns about the persistent cancer or a hidden microscopic locus [10]. In addition, absence of pre-op CA 19-9 can further complicate the decision for additional or adjuvant therapy course. Life expectancy of pancreatic ductal adenocarcinoma (PDAC) patients is usually short and selection of the most appropriate treatment is crucial.

Maintenance therapy has become quite a hot topic especially in metastatic setting for pancreatic cancer with BRCA mutation as well as in other tumors, such as colorectal in which oxaliplatin is administered for certain number of cycles and then omitted while continuing other agents, including targeted agents [28, 29, 30]. Given that we now have more management tools at our disposal, and as treatments given chronically have become more tolerable, we tested our strategies by offering a maintenance approach to patients with pancreatic cancer with an elevated tumor marker. We believe that the longer OS of our patients with elevated CA 19-9 post-surgery was due to additional/maintenance chemotherapy following the planned 6-months of adjuvant treatment. Ideally, we could find a biomarker of benefit for patients who should be managed this way, but thus far we have had no such luck.

We can speculate that survival benefit associated with the use of additional/maintenance chemotherapy, and not chemo-radiation as prolonged exposure to therapy, could potentially maintain pressure on dormant cancer cells that remain in G0 arrest, by attacking them as they infrequently enter G1/S. Though no evidence to support this hypothesis but many adjuvant studies support it. Completion of all six cycles of planned adjuvant chemotherapy was an independent prognostic factor after resection according to the ESPAC-3 study [9]. The study showed that median OS was 28 months for patients who completed the full six months of therapy versus 15 months for those who did not (hazard ratio (HR) for death 0.51, 95% CI 0.44-0.60). Any survival benefit of an intensified chemotherapy strategy has not been demonstrated in patients with persistently elevated CA 19-9. Our study tried to focus on all these important issues and set the platform for future prospective clinical trials.

Additionally, our study underlines the importance of collecting pre-surgery CA 19-9 and complete staging including chest as many had those tests missed. Prior to beginning adjuvant therapy, all patients should undergo formal restaging with CT scans and a serum level of the tumor marker CA 19-9. Persistent postoperative elevations of the serum tumor marker CA 19-9 are associated with poor long-term prognosis. CA 19-9 exists as an epitope of sialylated Lewis A blood group antigen and it is not expressed in subjects with Lewis α-β- genotype, which accounts for approximately 5-10% of the Caucasian population [31]. RTOG 9704 study has shown that post-resection CA 19-9 levels are an important predictor of survival [10]. Patients were grouped as having a post-resection CA 19-9 of >90 or <90. 385 patients had CA 19-9 levels tested and recorded, and of these, 132 were found to not express CA 19-9, leaving 253 patients for analysis. 200 (79%) had values <90, 53 (21%) were >90. The researchers found that these groups were significant predictors of survival. Median survival for the <90 group was 22.8 months, compared with 9.6 months for the >90 group. Three-year survival was 33% in the <90 group versus 2% in the >90 group. These results showed that post-resection CA 19-9 values >90 were associated with significantly worse survival in patients with pancreatic carcinoma according to RTOG 9704 study [10]. It implies that separating patients into these groups based on CA 19-9 levels may better clarify who benefits most from combination therapy in future trials, something we were able to further support in our study. Park JW et al recruited 1,446 patients with pancreatic cancer and excluded those with Lewis antigen negative or obstructive jaundice to eliminate the false effects on CA 19-9 level [32]. The clinic-pathologic factors were reviewed including initial and post-treatment CA 19-9, and statistical analysis was done to evaluate the association of clinic-pathologic factors with OS. They observed that patients with normalized post-operative CA 19-9 had significantly longer OS and DFS regardless of initial CA 19-9 level.

Previously, some investigators suggested withholding adjuvant therapy from such patients with elevated CA 19-9 and treating them as if they have advanced metastatic disease [16]. Postoperative CA 19-9 level was found higher in patients with microscopically positive surgical margin as well as with hepatic recurrence and peritoneal dissemination. Whether and how to use preoperative levels of the serum CA 19-9 to select the initial therapeutic strategy remains controversial.

Our experience and other reports also suggest that elevated levels of CA 19-9 can help to predict the presence of radiographically occult metastatic disease, the likelihood of a R0 resection, and long-term outcomes in patients with potentially resectable pancreatic cancer. We have practiced that high levels of CA 19-9 may guide surgeons to better identify the patients who may need staging laparoscopy. However, it is important to notify here that the ASCO recommended against the use of CA 19-9 alone as an indicator of operability [33] and we conclude that a multi-disciplinary approach must be taken in these cases. Both National Comprehensive Cancer Network (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines lack any recommendation for imaging during adjuvant therapy. Furthermore, experts do agree that a neoadjuvant approach can be used before surgery for patients who had potentially anatomically resectable but high-risk tumors, including elevated preoperative levels of CA 19-9. Our study further reassures that serum CA 19-9 levels should also be considered in planning with a multidisciplinary approach.

Patients who had a treatment-related decline in CA 19-9 levels generally exhibit prolonged median survival. In a multivariate analysis, a decrease of CA 19-9 during chemotherapy was found to be an independent prognostic factor regarding survival [34]. Data suggest that responders whose CA 19-9 levels were reduced by >50% of pre-treatment baseline levels have a longer median survival when compared to CA 19-9 non-responders. Okusaka et al showed that CA 19-9 responders in locally advanced pancreatic cancer had a longer median survival of 10.6 months compared to 4.1 months in non-responders [35]. Similarly, Ishii et al reported longer median survival times in CA 19-9 responders of 141 days versus 88 days in non-responders in advanced pancreatic cancer patients. The relative risk of cancer death in CA 19-9 responders versus non-responders was 0.47 (95% CI, 0.21-1.05) [35].

Based on our data, we believe that close monitoring with monthly CA 19-9 and 3-monthly CT scans also contributed to a better outcome by identifying any recurrent or metastatic cancer and by changing treatment. The median DFS following pancreatectomy and adjuvant gemcitabine was reported as 13.4 months vs. 6.9 months for untreated patients in the CONKO-001 trial [5]. Others have also reported that postoperative surveillance studies have shown that serial determination of CA 19-9 can detect recurrence or metastasis of pancreatic cancer several months before finding clinical or radiologic evidence of disease.

Identification of patients with early recurrence of pancreatic cancer is an extremely important issue, as regular staging of the tumor during chemotherapeutic treatment, e.g., using CT scans, allows the selection of an appropriate regimen and avoids unnecessary cytotoxic treatment if surgery is an option. It is important to remind here that CA 19-9 is increased in multiple gastrointestinal cancers, including benign diseases, such as peptic ulcers, chronic and acute pancreatitis, cirrhosis, cholangitis, and obstructive jaundice. Interestingly enough, poorly-differentiated pancreatic cancer is found to produce less CA 19-9 than moderately- or well-differentiated cancers. The clinical practice guidelines, such as ESMO, NCCN do not recommend regular imaging, though our study and the data discussed above clearly demands a recommendation for staging post-operatively with an initial postoperative CT scan, followed by regular staging every 3 months, especially in patients with elevated CA 19-9 [36]. In the near future there may be important molecular prognostic factors for the selection of appropriate chemotherapy regimens will hopefully lead to better identification of patients for treatment than CT follow-up screening.

CONCLUSION

In summary, the rising CA 19-9 levels in patients under observation or in those receiving active therapy could be an indicator of disease recurrence, progression, and ineffectiveness of the current regimen, and may be correlated with shorter survival time. However, the value of initiating therapy based on rising CA 19-9 levels remains to be demonstrated. We made these decisions to initiate or change chemotherapy based on multiple testing, multidisciplinary discussions and consent of patients. We therefore, would remind physicians to be mindful of the limitations when interpreting the significance of a rising CA 19-9 and decision to initiate or extend chemotherapy should be made based on universal guidelines and with help of expertise at your centre. Future prospective studies are needed to perform a future study to evaluate role of maintenance or intensified chemotherapy and explore patient stratification and selection based on biomarkers in patient selection for treatment.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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