



Chemotherapy-induced early transient increase and surge of CA 19–9 level in patients with pancreatic Adenocarcinoma[☆]

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ABSTRACT

This study aimed to characterize chemotherapy-induced transient increase and surge of CA 19–9 level to treatment response in patients with advanced pancreatic ductal adenocarcinoma (PDAC). A retrospective case series was performed of advanced PDAC patients treated with first-line chemotherapy at City of Hope Comprehensive Cancer Center from Jan 2017 to May 2020. CA 19–9 surge was defined as an increase of >20% from baseline followed by a >20% drop in one or more subsequent CA 19–9 levels compared to baseline. Out of 106 advanced PDAC patients, 38 were evaluable for CA 19–9 surge. Fourteen (51.9%) patients treated with FOLFIRINOX and 3 (27.3%) patients treated with nab-P + Gem chemotherapy demonstrated an early transient rise in CA 19–9 level. A CA 19–9 surge was documented in 9 (23.7%) patients, all with duration of surge lasting < 16 weeks. Five out of 9 (55.6%) patients (4: FOLFIRINOX, 1: nab-P + Gem) with CA 19–9 surge demonstrated partial objective response rate on surveillance cross-sectional imaging. One patient (FOLFIRINOX) had stable disease, and 2 patients (1: FOLFIRINOX, 1: nab-P + Gem) were found to have disease progression after treatment interruption. The initial early rise of CA 19–9 levels during chemotherapy in patients with advanced PDAC may not indicate tumor progression. Rather, it may represent a chemotherapy-induced transient increase or surge phenomenon of the tumor marker in patients responding to treatment.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains as one of the deadliest form of malignancy. Carbohydrate antigen 19–9 (CA 19–9) is a sialylated Lewis A blood group antigen with a half-life of approximately 14 h and commonly expressed and shed in hepatopancreatobiliary disease and other malignancies [1]. For Lewis antigen-positive patients, CA 19–9 is the best-validated tumor marker for surveillance of PDAC in various settings [2]. Pre-treatment baseline CA 19–9 level has been correlated to tumor burden and is an independent prognostic factor for survival [3–5]. Results from the PRODIGE and MPACT randomized trials led to 2 cytotoxic chemotherapy regimens, 5-fluorouracil (5-FU) and

gemcitabine-based combination, which were found to improve patients overall survival. The triplet chemotherapy regimen of 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX) and the doublet regimen of albumin-bound paclitaxel plus gemcitabine (nab-P + Gem) are considered as the standard first-line chemotherapy for patients with PDAC in advanced settings [6,7].

The trend of CA 19–9 level during chemotherapy treatment course is often used to correlate treatment effects for PDAC [8,9]. Rising CA 19–9 level during chemotherapy is usually indicative of treatment failure and tumor progression [10]. However, transient elevation and surge of tumor markers during chemotherapy has been described in different solid tumors. Carcinoembryonic antigen (CEA) surge, has been reported

[☆]**Simple Summary:** Rising serum tumor markers during chemotherapy treatment are generally indicative of solid tumor progression. Nonetheless, there are reports associating the transient increase or surge of serum tumor markers to improved efficacy of chemotherapy in patients with advanced gastrointestinal cancers. However, this phenomenon has not been described for CA 19–9 in patients with pancreatic ductal adenocarcinoma (PDAC). This retrospective review was performed to investigate the chemotherapy-induced transient increase and surge of CA 19–9 level in patients with advanced PDAC.

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in patients with metastatic colorectal cancer who benefited from palliative chemotherapy [11,12]. In addition, one report of early and transitory increase of CA 19-9 level in three patients with advanced PDAC was linked to high efficacy of FOLFIRINOX [13]. We have also observed this transient increase of CA 19-9 level amongst our patients undergoing these current chemotherapy regimens. Our observation found that CA 19-9 level tend to surge after 2 to 4 cycles of FOLFIRINOX or nab-P + Gem before decreasing to below baseline level. Therefore, we aim to characterize the trends of CA 19-9 level in PDAC patients who were treated with FOLFIRINOX or nab-P + Gem chemotherapy regimen and report on their treatment responses.

2. Materials and methods

Study population

After approval from our Data and Safety Monitoring Committee, a search of City of Hope cancer registry was done for patients with advanced (Stage III and IV), or unresectable PDAC who received first-line FOLFIRINOX or nab-P + Gem from January 2017 to May 2020. A retrospective review of these patient demographics, primary tumor sites, clinical staging, and chemotherapy regimen were collected. Patients with biliary obstruction or cholangitis were screened and excluded if pre-treatment CA 19-9 level was not available after 28 days of biliary decompression. Pre-treatment (baseline) and during treatment CA 19-9 levels were documented. Treatment response based on surveillance computed tomography (CT) scans obtained after 4-8 cycles of chemotherapy and interpreted by our internal radiologists. Best treatment response on therapy was measured and documented during the treatment course. Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [14].

CA 19-9 surge definition and measurement

CEA and CA 19-9 surge has been described in advanced gastrointestinal cancer patients as the criterion of 'a >20% increase from the baseline value followed by a >20% drop in subsequent levels compared to the baseline value.' [11,12,15] We are using the same criterion for CA 19-9 surge in this study. Early transient rise in CA 19-9 is defined as an increase of the tumor marker above baseline within 4 cycles of chemotherapy followed by a drop below peak level. The time to peak is the time from chemotherapy initiation to the peak CA 19-9 level. The duration of tumor marker surge is defined as the time period between the initiation of chemotherapy to a >20% drop of CA 19-9 below the baseline level.

Patient treatment course was divided into baseline and monthly interval during chemotherapy administration. The measurement of baseline CA 19-9 level was taken before the start of chemotherapy, and subsequent monthly during treatments. CA 19-9 levels were trended using ratio of CA 19-9 level after each subsequent 2 cycles of treatment compare to the previous month level. For the purpose of this study, the recording of CA 19-9 level was stopped after 8 cycles of chemotherapy. The recommended cut-off level of serum CA 19-9 was 37 U/ml. Difference in the means between the two groups of patients were calculated using Student's *t*-test for independent groups. Statistical analyses were completed using R Studio version 1.4. *P*-values < 0.05 were considered of statistical significance.

3. Results

During this time period, there were 106 patients found to have AJCC stage 3 and 4 PDAC. Of those, 40 patients received FOLFIRINOX and 11 patients received nab-P + Gem chemotherapy regimen. Of the 40

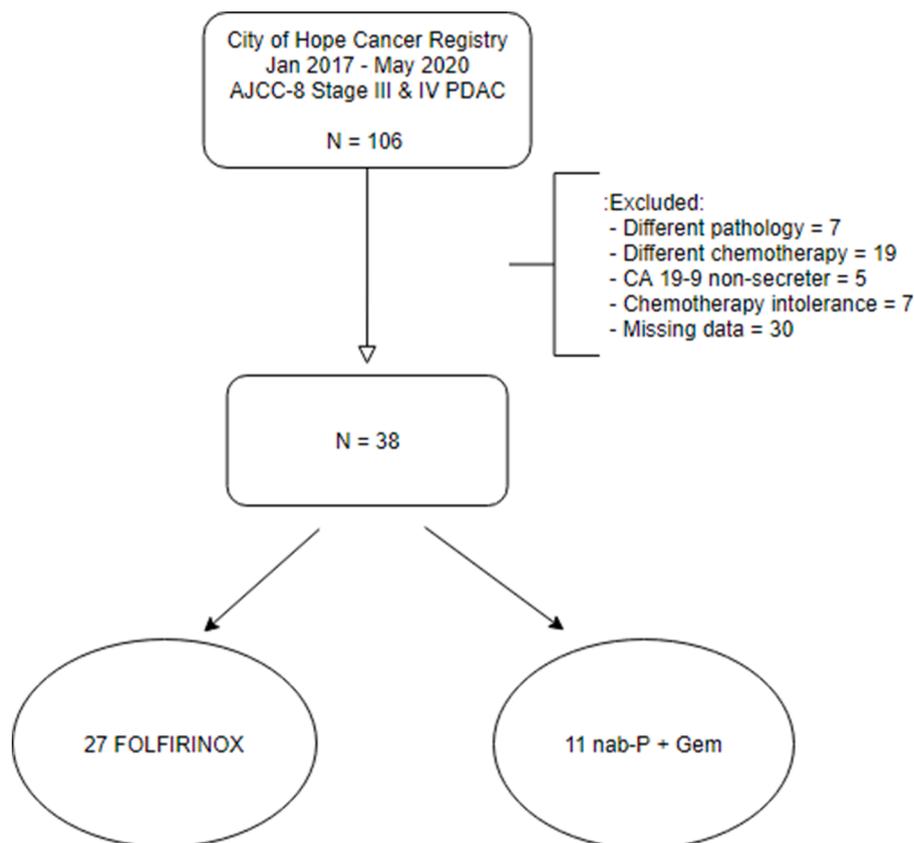


Fig. 1. Flow diagram of patient population with stage III and IV PDAC underwent FOLFIRINOX or nab-P + Gem first-line chemotherapy regimen. Abbreviations: PDAC = pancreatic ductal adenocarcinoma; FOLFIRINOX = 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; nab-P + Gem = albumin-bound paclitaxel plus gemcitabine.

patients treated with FOLFIRINOX, 13 patients did not have sufficient CA 19–9 data to trend and were excluded (Fig. 1). Of the 27 patients treated with FOLFIRINOX, 14 (51.9%) patients were found to have a rise in CA 19–9 level after 2 to 4 cycles of FOLFIRINOX chemotherapy from baseline. Of those, 7 (25.9%) patients exhibited CA 19–9 surge. For patients treated with nab-P + Gem, 3 patients had elevated CA 19–9 level from baseline and 2 patients (18.2%) exhibited CA 19–9 surge (Table 1).

Overall, patients treated with FOLFIRINOX were younger than those treated with nab-P + Gem (62.6 vs 74.9, p 0.002). There was no difference in the distribution of disease stage between the two patient groups (p 0.296). Furthermore, there was no difference in the distribution of the primary tumor location between the groups (p 0.097). Two patients in the FOLFIRINOX group were found to have disease recurrence after resection, compared to 1 patient in the nab-P + Gem group (Table 1).

Subgroup analysis of the 7 FOLFIRINOX patients with CA 19–9 surge demonstrated that 4 patients had partial objective response, 1 had stable disease, 1 had progressive disease, and 1 without evidence of recurrence in the adjuvant setting on surveillance CT scans. The time-to-peak of CA 19–9 level after FOLFIRINOX chemotherapy initiation ranged from 4 to 8 weeks. The durations of tumor marker surges, which is the time from chemotherapy initiation to nadir CA 19–9 level, were from 12 to 16 weeks. Three (42.9%) of the FOLFIRINOX patients had normalization of CA 19–9 after the surge. Of the two patients in the nab-P + Gem group with CA 19–9 surge, 1 had partial objective response and 1 had progressive disease on their surveillance CT scans. The time-to-peak of CA 19–9 levels seen with nab-P + Gem were 6 and 8 weeks. The durations of their tumor marker surges were 12 and 16 weeks (Table 2).

4. Discussion

Transient tumor marker elevation following initiation of a new chemotherapy regimen has been described in different types of solid tumors, [11,12,15–17] with many of those patients demonstrating clinical benefits. Tumor marker surges have been reported in metastatic gastrointestinal tumors. To our knowledge, there has been no report describing “CA 19–9 surge” phenomenon in PDAC. In our small series of patients with advanced, unresectable PDAC, we found that CA 19–9 surge is a relatively common phenomenon in patients following initiation of FOLFIRINOX and nab-P + Gem chemotherapy.

For patients undergoing FOLFIRINOX chemotherapy treatment, we found 51.2% of patients with transient elevation of CA 19–9, and 25.9% of those patients had CA 19–9 level surge. For the nab-P + Gem cohort,

Table 1
Characteristics of patient population.

	Patients treated with FOLFIRINOX	Patients treated with nab-P + Gem	p value
Overall	27	11	
Age (mean)	62.6	74.9	0.002
Gender			
Female (%)	12 (44.4%)	4 (36.4%)	
Stage			0.296
III (%)	8	4	
IV (%)	19	7	
Tumor Site			0.097
Head/			
Uncinate	11	5	
Neck	3	1	
Body	5	2	
Tail	6	2	
Recurrence after resection	2	1	
CA 19–9 surge (%)	7 (25.9%)	2 (18.2%)	

Table legend: CA 19–9 surge ($\alpha > 20\%$ increase from the baseline CA 19–9 value followed by $\alpha > 20\%$ drop in subsequent CA 19–9 levels compared to the baseline value.).

the transient elevation of CA 19–9 finding was more modest, occurred in 3 (27.3%) patients, with 2 (18.2%) of those patients had CA 19–9 surge phenomenon. Four out of 7 (57.1%) patients with CA 19–9 surge in the FOLFIRINOX group had partial objective response and 1 patient with stable disease on CT scans. One (50%) patient with CA 19–9 surge in the nab-P + Gem group had partial objective response on CT scan. There were 2 patients with CA 19–9 surge that had progressive disease. One patient in the FOLFIRINOX group with progressive disease had chemotherapy held for 6 weeks after the 12th cycle of treatment from thrombocytopenia. This patient already exhibited the CA 19–9 surge phenomenon before chemotherapy was held. Subsequent surveillance CT scan showed a new peritoneal nodule suggestive of peritoneal carcinomatosis. It is uncertain whether the hiatus of chemotherapy was the cause of disease progression or this was failure of therapy. One patient in the nab-P + Gem group with CA 19–9 surge and progressive disease had BRCA tumor mutation. This patient was subsequently switched to platinum-based chemotherapy after the 8th cycle of nab-P + Gem. Surveillance CT showed $\alpha > 20\%$ increase in the primary pancreatic tumor and liver metastases indicative of disease progression. The common factor in both patients with CA 19–9 surge and disease progression was chemotherapy interruption or adjustment during treatment course.

There are several hypotheses for the mechanism of tumor marker surge in gastrointestinal cancers. Cytotoxic chemotherapy has been shown to induce cancer cells to increase expression of tumor marker, supported by preclinical data in an up-regulation of CEA expression in tumor cell lines in response to 5-FU or platinum exposure [18,19]. This results in an initial surge in the tumor marker with subsequent decline associating with enhanced tumor cell death. Another plausible explanation is the increase in tumor cell lysis due to cytotoxic effect of chemotherapy leading to a tumor marker surge phenomenon [12], which is indicative of the treatment effect amongst patients responding to therapy.

Applying this study findings, we found the peak CA 19–9 level to occur between 2–4 cycles (4–8 weeks) of FOLFIRINOX or nab-P + Gem chemotherapy and the duration of CA 19–9 surges to last < 4 months. Within these parameters and in light of no other indicator of tumor progression, it is imperative for clinicians to continue the current line of chemotherapy treatment prior to consideration to switch line of therapy. Especially in the advanced, unresectable PDAC setting, patients have only limited treatment options, outside of clinical trials. Furthermore, in the setting of neoadjuvant or total neoadjuvant therapy for patients with resectable or borderline resectable tumors, continuation of chemotherapy despite CA 19–9 surge may lead to an objective response rate and could potentially improve R0 resection rate.

There are a few limitations to this study. This is a small retrospective case series with inherited limitations. During this time period, there was a relatively large number of patients referred for second opinion or clinical trial treatment options that did not have sufficient CA 19–9 data (30) and were excluded from the cohort. Additionally, the data in this study is mainly descriptive in nature and as such, no causal relationship could be derived. There is a need to study this phenomenon using a larger dataset to reach the needed power for a more confident assumption. Furthermore, we applied tumor markers surge definition and framework from other types of gastrointestinal cancer as the premise for our CA 19–9 surge analysis. This is done without knowing whether the optimal thresholds of the tumor marker are the same as the other disease sites. Nonetheless, it is within the exploratory nature of this study to investigate tumor marker surge phenomenon to CA 19–9 in PDAC patients. The finding in this study suggests that early transient increase and surge of CA 19–9 can occur in PDAC patients responding to chemotherapy.

In addition to response rate, future studies will need to evaluate other clinical outcomes. In the unresectable and metastatic settings, progression free survival is a meaningful outcome to explore in future studies. As systemic treatment paradigm for PDAC shifted toward

Table 2

Characteristics of patients with CA 19–9 surge and treatment response.

Patient	Chemotherapy	Baseline CA 19–9	Peak CA 19–9	Nadir CA 19–9	Time-to-peak (weeks)	Duration of surge (weeks)	Treatment response
1	FOLFIRINOX	417	1974	15	8	16	PR
2	FOLFIRINOX	54	134	21	4	16	PR
3	FOLFIRINOX	517	750	135	8	16	PR
4	FOLFIRINOX	1519	2632	198	4	12	PD ^a
5	FOLFIRINOX	234	359	133	4	16	PR
6	FOLFIRINOX	269	370	138	4	12	SD
7	FOLFIRINOX	96	223	28	4	12	NR ^b
8 ^c	nab-P + Gem	57	107	28	6	12	PR
9	nab-P + Gem	344	2349	220	8	16	PD ^d

Table legend: Time to peak, duration of tumor marker surges (the period between the initiation of chemotherapy and a >20% drop below the baseline level), and clinical outcome in patients with tumor marker surges; a = 6 weeks treatment interruption due to thrombocytopenia; b = NR (no recurrence) in adjuvant setting; c = 3 week chemotherapy cycle; d = BRCA mutation tumor; Abbreviations: PR = partial response, SD = stable disease, PD = progressive disease.

favoring neoadjuvant approach, we would like to study CA 19–9 early transient increase and surge in patients received neoadjuvant chemotherapy and measure surgical resection and disease-free survival outcomes. Furthermore, the prognostic utility of CA 19–9 surge will need to be evaluated with other clinical markers of response for PDAC patients receiving systemic therapy in various settings.

5. Conclusion

The initial early rise of CA 19–9 levels during chemotherapy in patients with advanced PDAC may not indicate tumor progression. Rather, it may represent a chemotherapy-induced transient increase or surge phenomenon of the tumor marker in patients responding to treatment. When using CA 19–9 as a surveillance tool for chemotherapy treatment response in PDAC patients, treatment decision on the initial rise or surge of CA 19–9 levels should be weighted in the context of other clinical variables for a more informed decision.

Disclosures

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Ethical approval statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the City of Hope Data and Safety Monitoring Committee (COH Protocol#/Ref#: 20,359/192,587 and date of approval: 6/24/2020). Ethics approval was not required for the study since the data considering for publication was retrospectively obtained and anonymized for this non-interventional study.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restriction.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the City of Hope Data and Safety Monitoring Committee (COH Protocol#/Ref#: 20,359/192,587 and date of approval: 6/24/2020).

Informed consent statement

Not applicable

CRediT authorship contribution statement

Viet H. Le: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Jan Franko:** Writing – review & editing. **Benjamin I. Paz:** Writing – review & editing. **Gagandeep Singh:** Writing – review & editing. **Marwan Fakh:** Conceptualization, Writing – review & editing. **Vincent Chung:** Conceptualization, Formal analysis, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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