

Samer TABCHI, Hampig R. KOURIE, Fadi FARHAT, Joseph KATTAN*

Tabchi S, Kourie HR, Farhat F, Kattan J. Early increase of CA 19-9 in advanced pancreatic cancer receiving FOLFIRINOX: Is it a sign of efficacy? J Med Liban 2016 ; 64 (2) : 97-99.

ABSTRACT • Introduction : Advanced pancreatic cancer (APC), one of the most aggressive tumors, was considered to be resistant to chemotherapy for decades. FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) regimen showed an improvement of quality of life and overall survival in APC patients with good performance status (ECOG < 2). **Material and methods :** Seven patients diagnosed with APC, during a six-month period, received FOLFIRINOX as first line treatment. Tumor measurement was assessed every two months and CA 19-9, the specific tumor marker of pancreatic cancer, was assessed every two weeks at every cycle. **Results :** Three patients out of seven receiving FOLFIRINOX experienced an early and transitory increase of CA 19-9 after the first two cycles resulting in a considerable response with a median survival of 15 months and suggesting a model of tumor release syndrome. **Conclusion :** This phenomenon of early and transitory increase of CA 19-9 in APC could reflect the high efficacy of FOLFIRINOX and could predict better outcome in these patients.

Keywords : pancreatic cancer, CA 19-9, FOLFIRINOX, early elevation, metastatic

INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies; this disease is the fourth most common cause of death among US men and women [1]. Its peak incidence occurs in the seventh or eighth decade, with roughly equal incidence amongst sexes [1]. The median overall survival (OS) is less than six months and less than five percent of the patients will survive more than five years [1].

Many regimens were approved for the treatment of advanced pancreatic cancer (APC). Neither 5-FU nor gemcitabine monotherapy were effective enough to achieve a median overall survival superior to seven months. However, given the significant improvement in clinical outcome, gemcitabine was initially approved as first line therapy for APC [2].

In 2011, a promising new combination regimen featuring short-term infusional 5-FU, bolus IV 5-FU, leucovorin, irinotecan, oxaliplatin (FOLFIRINOX) was a

Tabchi S, Kourie HR, Farhat F, Kattan J. L'élévation initiale de CA19-9 suite au traitement par FOLFIRINOX de tumeurs du pancréas métastatiques reflète-t-elle une efficacité? J Med Liban 2016 ; 64 (2) : 97-99.

RÉSUMÉ • Introduction : Le cancer du pancréas métastatique, l'une des tumeurs les plus agressives, était considérée pour longtemps comme résistante à la chimiothérapie. Le protocole FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) a montré une amélioration de la qualité de vie et de la survie globale chez les patients ayant un cancer du pancréas à un stade avancé avec un bon statut de performance (ECOG < 2). **Matériel et méthodes :** Sept patients diagnostiqués avec un cancer du pancréas à un stade avancé ont reçu, durant une période de six mois, le protocole FOLFIRINOX en première ligne. La mesure de la tumeur était prise chaque deux mois et le marqueur tumoral spécifique du FOLFIRINOX a été répété chaque deux semaines. **Résultats :** Trois des sept patients ayant reçu du FOLFIRINOX ont présenté une élévation rapide et transitoire du CA 19-9 après les deux premiers cycles avec une réponse considérable avec une survie globale de 15 mois, et suggérant un modèle de syndrome de lyse tumorale. **Conclusion :** Ce phénomène d'élévation précoce et transitoire du CA 19-9 dans le cancer du pancréas à un stade avancé reflète l'efficacité du FOLFIRINOX et pourrait prédire de meilleurs résultats chez ces patients.

major turning point in the treatment of APC patients with good performance status (ECOG < 2). Conroy *et al.* reported the superiority of FOLFIRINOX with an overall survival exceeding 11.1 months compared to 6.8 months in the group of patients receiving gemcitabine alone and a significantly higher objective response rate with FOLFIRINOX (32 versus 9 percent) [3]. After this study, FOLFIRINOX has emerged as the standard of care for patients having APC with a good performance status.

In patients undergoing chemotherapy for APC, follow-up and evaluation of response usually combine imaging techniques (high resolution CT) and cancer specific biomarkers.

Many biomarkers have been studied in the evaluation of pancreatic carcinoma, the most useful and clinically relevant is carbohydrate antigen CA 19-9. However, CA 19-9 requires the presence of the Lewis blood group antigen to be expressed and in patients with a Lewis-negative phenotype (5 to 10% of population) CA 19-9 levels are not a useful tumor marker [4].

CA 19-9 has potential uses in diagnosis with sensitivity of 80% and specificity of 85% in patients with suggestive symptoms but its low positive predictive value makes it a poor biomarker for screening [5,6]. The aim of our

*From the Department of Hematology-Oncology, Hôtel-Dieu de France University Hospital (HDF), Faculty of Medicine, Saint-Joseph University, Beirut, Lebanon.

Correspondence : Samer Tabchi, MD.
e-mail : tabchi@hotmail.com

manuscript is to shed some light on a potentially important phenomenon, in which an early increase in CA 19-9 could potentially reflect better response to combination chemotherapy.

MATERIAL AND METHODS

Seven patients diagnosed with APC, during a six-month period, received FOLFIRINOX as first line treatment. The combination regimen FOLFIRINOX consisted of:

- fluorouracil 400 mg/m² IV bolus
- leucovorin 400 mg/m² IV
- fluorouracil 2400 mg/m² infused over 46 hours
- irinotecan 180 mg/m²
- oxaliplatin 85 mg/m².

Tumor measurements were assessed every two months and CA 19-9 was assessed every two weeks at every cycle. The overall survival of these patients was calculated from the time of diagnosis until their death. All the results are summarized in a table and compared between patients presenting an early elevation of tumor marker and those who did not present such a phenomenon.

RESULTS

Three patients out of seven receiving FOLFIRINOX experienced an early and transient increase of CA 19-9 after the first two cycles by 36%, 29% and 100% respectively. CA 19-9 dropped steadily and continuously after the third cycle. Those three patients experienced a considerable clinical and radiological response. The median overall survival of these three patients was 15 months compared with 11 months in the four patients who did not present a tumor release.

Results are summarized in table I.

DISCUSSION

CA 19-9, the pancreatic cancer tumor marker, is commonly used in the follow-up of patients undergoing surgery with a curative intent and also in patients with advanced disease undergoing palliative chemotherapy. In both contexts, CA 19-9 has proven itself to be a valuable prognostic tool. Low postoperative values of the biomarker or a serial decrease after surgery seem to correlate

with a better long-term survival [5,7,8]. Also, patients with a CA 19-9 level < 90 U/ml had a longer disease free survival after gemcitabine based adjuvant chemotherapy [9].

In patients receiving chemotherapy for advanced disease, many studies have suggested a close correlation between the decrease of CA 19-9 levels and the duration of patient survival. However, the magnitude of serum biomarker decrease that best predicts optimal outcome remains unclear and whether the decrease in CA 19-9 levels can invariably predict improved survival in advanced disease has been called into question. Of note, some studies suggest that an increase of more than 5% of CA 19-9 levels after the first two gemcitabine-based chemotherapy cycles serves as a negative predictive marker [10].

We would suggest an alternative interpretation of the rising serum markers after the first two cycles of FOLFIRINOX-based chemotherapy. The relevance of this observation is certainly questionable but the phenomenon could probably be due to an increased release of tumor marker by dying tumor cells once exposed to more efficient chemotherapy. The possibility of a variant form of tumor lysis syndrome in solid tumors is certainly debatable. In fact, biochemical and clinical hallmarks of tumor lysis syndrome occur as a result of rapid tumor necrosis with release of intracellular ions and metabolic byproducts due to the initiation of effective chemotherapy [11]. Although tumor lysis syndrome mostly occurs in hematological malignancies upon the administration of highly efficient chemotherapy, a similar phenomenon could be triggered by the administration of efficient chemotherapy in solid tumors [12]; in this line of reasoning, an early and transient increase of CA 19-9 in APC could reflect the potency of FOLFIRINOX and could predict better outcome in these patients.

CONCLUSION

Despite many limitations to arrive at definite conclusions, we believe this early and transient increase in CA 19-9 could be a valuable asset for practicing clinicians and should be investigated in the context of a larger trial. Our results not only point out those patients who are most likely to respond to FOLFIRINOX treatment, but

TABLE I
LEVELS OF CA 19-9 AFTER 2, 4, 6 AND 8 CYCLES IN SEVEN PATIENTS WITH ADVANCED PANCREATIC CANCER RECEIVING FOLFIRINOX

Patients	Baseline CA 19-9 level	After 2 cycles (% of increase)	After 4 cycles	After 6 cycles	After 8 cycles
Patient 1	88000	120000 (36%)	46454	8230	7428
Patient 2	54429	70235 (29%)	4864	6550	3134
Patient 3	22319	44825 (100%)	1415	891	238
Patient 4	163	26.4	24.6	22.7	26.2
Patient 5	96.5	91.5	86.9	70.9	54.6
Patient 6	13823	10850	8432	5423	5355
Patient 7	1265	1132	845	732	599

they also highlight the importance of continuing this effective combination treatment instead of switching to less efficient treatments if the increase in CA 19-9 level is mistaken for tumor progression.

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