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Qualification en hépato-gastro-entérologie.

Correlation between O^6-methylguanin-DNA methyltransferase (MGMT) and p53 in clinical response in metastatic pancreatic adenocarcinoma treated by FOLFIRINOX regimen

Corrélation entre O6-méthylguanine-ADN méthyltransférase (MGMT) et p53 à la réponse clinique dans l'adénocarcinome pancréatique métastatique traité par FOLFIRINOX

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Sous la direction de M. CAROLI-BOSC François Xavier

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Liste des abréviations

PDA	Pancreatic ductal cancer
MGMT	O^6-methylguanin-DNA-methyltransferase
P53	Protein 53
OS	Overall survival
PFS	Progression-free survival
DNA	Desoxyribonucleic acid
C6	6th cycle
C12	12th cycle
CpG	Cystein-phosphate-guanine
CT	Computed tomodensitometric
CPTs	Camptothecin-derived topoisomerase I inhibitors
MMR	Mismatch repair
PARP	PolyADP-ribose polymerase
RECIST	Response Evaluation criteria in solid tumor
EUS-FNA	Endoscopic Ultrasound and Fine Needle Aspiration

Plan

ABSTRACT

Background: No predictive biomarker for FOLFIRINOX efficacy in metastatic pancreatic adenocarcinoma has so far been demonstrated. The deficiency in O6-methylguanine-DNA methyltransferase (MGMT) has been associated with therapeutic response in endocrine tumors of the pancreas and the lack of expression of protein 53 (p53) could interfere with the action of MGMT. The aim of our study was to investigate in these patients treated by FOLFIRINOX in first line the prevalence of MGMT status and if any relation exists between the tumor expression of p53 and MGMT and the therapeutic response and survival.

Patients and methods: The immunohistochemical expression of MGMT was recorded as present or absent and the expression of p53 was semi-quantitatively scored in 30 patients with metastatic pancreatic adenocarcinoma at Angers hospital, France, between September 2011 and June 2015. Clinical and radiologic data were collected retrospectively.

Results: There was no significant difference depending on the presence or absence of MGMT expression in response rate, progression free survival (PFS) and overall survival (OS). No significant relationship for response rate and PFS was observed in relation with p53 expression. By cons, patients with strong tumor expression of p53 had a significantly lower OS comparing to patients with no or weak expression of the protein ($p= 0.027$). There was a positive relation between the expression of the p53 and MGMT but no significant($p= 0.08$).

Conclusions: Our study suggests that for patient treated with first-line FOLFIRINOX in metastatic pancreatic adenocarcinoma the immunohistochemical evaluation of MGMT does not predict the clinical evolution while a strong tumor expression of p53 is correlated with a poor prognosis in terms of overall survival.

INTRODUCTION

Pancreatic ductal cancer (PDA) was the fourth leading cause of death from cancer in the United States in 2010 with a poor prognosis: the 5-year survival rate is 6% in Europe and the United States. FOLFIRINOX an association of fluorouracil, leucovorin, irinotecan and oxaliplatin has become a standard therapeutic in metastatic pancreatic adenocarcinoma for selected patients with good performance status below 70 years old by increasing median overall survival at 11,1 months (1). Currently, the studies seek to enhance therapeutic efficacity by studying molecular targets. Unfortunately, there is little information regarding biomarkers for FOLFIRINOX regimen at the current time (2).

Mutations in genes encoding proteins involved in DNA damage repair promote to genetic instability and cancer. And the identification of impaired DNA repair in different cancers has allowed the development of treatments that use DNA repair defects in certain patient populations with for example, the PolyADP-ribose polymerase (PARP) inhibitors, that inhibit the activity of PARP proteins which are involved in a variety of DNA damage repair pathways. Clinical studies have shown that BRCA 1/2-deficient tumours are sensitive to PARP inhibitors and platinium agents by synthetic lethality (3). One of the most supported mechanisms of tumor resistance to DNA-damaging agents is the overexpression of the repair protein MGMT. MGMT protects cells against mutagenic and cytotoxic alkylation DNA damage and represents a significant barrier to the successful treatment of patients with cancer (4-5). MGMT levels have been reported previously to be elevated in advanced adenocarcinoma of the pancreas contrasted to normal pancreatic tissue (6). The MGMT gene, located on chromosome 10, encodes a repair enzyme excising the alkyl groups of the o6 position of guanine. During the process, the alkyl group is transferred to the enzyme, which becomes irreversibly inactive and comes to be degraded. This protein rapidly reverses formation of adducts at the o6 position of guanine and averts the formation of lethal DNA cross-links induced by alkylating

agents. Recently, it has been reported that cytotoxic activity of temozolomide, an alkylating agent, is correlated with a loss of MGMT expression measured by immunohistochemistry both in pancreatic endocrine tumors and glioblastoma (7-8). The loss of MGMT expression results from the hypermethylation of the MGMT promoter cysteine-phosphate-guanine (CpG) island (4). The efficacy of camptothecins is explained only in part by their ability to damage DNA. It has been shown that MGMT may act to modulate cytotoxicity of camptothecin-derived topoisomerase I inhibitors (CPTs) (9). Interestingly; loss of MGMT expression could render cells more sensitive to CPTs through the modulation of protein-linked DNA breaks (9). Platinums are cytotoxic by virtue of the formation of DNA cross-links preferentially at the N7 position of guanine and adenine. Their activity is not affected by the presence of the DNA-repair protein o6-alkylguanine DNA alkyltransferase (10). However, it has been suggested that platinum compounds caused substantial and prolonged MGMT depletion and play a role in the down regulation of MGMT expression and this may increase the sensitivity to CPTs (11-12). Furthermore, Murakami et al (13) have observed an enhancement of the anti-tumor effect of 5-Fluorouracil in response to MGMT depletion in colon and oral cancer cells lines. So, a key role of the MGMT as a mechanism of resistance to chemotherapy could be involved in pancreatic adenocarcinoma.

P53 is one of the most important tumor suppressor proteins identified (14). It is mutated in most of human tumors and represents an important step in pancreatic tumor progression. The lack of expression of p53 is possibly associated with a post-MGMT mechanism of tumor resistance because p53 is involved in regulation of cell cycle checkpoint in response to DNA damage (15). It has been reported that decreased MGMT expression is correlated with p53 activation, and this could reduce pancreatic tumor growth. Nonetheless, the specific roles of MGMT and p53 in the therapeutic response of human pancreatic cancer are unknown. At our knowledge, MGMT and p53 expression has never been studied in patients treated by

FOLFIRINOX combination. In a preliminary study, we want investigate the prevalence of MGMT status in metastatic adenocarcinoma pancreatic and search if a any relationship exists between the tumor expression of MGMT and p53 and therapeutic response and survival in patients treated with FOLFIRINOX regimen.

PATIENTS AND METHOD

Patients were eligible to be included in the study if they were 18 years old of age or older and had histologically confirmed, measurable metastatic pancreatic adenocarcinoma treated by first-line treatment FOLFIRINOX in the University hospital of Angers (France). Other inclusion criteria were a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The data were retrospectively collected.

Clinical Data

At the inclusion of patients, number parameters were collected: the age at diagnosis, the sex of patients, the location of the cancer in pancreas and metastatic sites, the date of beginning and end date of FOLFIRINOX, the number of cycles of chemotherapy, the received dose of chemotherapy, the computed tomodensitometric scans (CT scans) evaluations at 6 (C6) and 12 cycles (C12), the date of progression disease, the date of death. An inform consent was collected in alive patients.

Evaluation of MGMT and p53 status

The immunohistochemical analyses were realized at Department of anatomopathology in Angers hospital. Immunohistochemical studies were performed on 5-µm-thick whole tissue sections of formalin-fixed, paraffin-embedded tissue in a Bond 3 automated immunostainer (Leica Microsystems) with the MGMT mouse monoclonal antibody (MAB16200, clone MT3.1; Chemicon International, Temecula, CA, USA; dilution: 1/100) and the p53 protein mouse

monoclonal antibody (Leica, clone: D07; dilution: 1/100). All slides were evaluated in a blind fashion without knowledge of the clinical outcome of the patients.

P53 was scored by evaluating the percentage of cancer cell nuclei as follows: 0, negative (0% to 30%); 1, weak (30% to 60%); 2, moderate (60 to 90%); 3, diffuse (>90%). p53 was considered as overexpressed for a score ≥ 2.

For MGMT status, as previously reported by Kulke MH and al (7), we used a simplified binary classification scheme in our study in order to minimize potential subjectivity in the analysis. MGMT positivity was defined by a percentage of stained cancer cell nuclei > 35%. Nuclear expression in normal cells or lymphocytes provided positive internal controls.

Assessment of response and survival

All patients could be evaluable for response rate and survival. Tumors were measured every 3 months.

For all patients included in this analysis, radiologic response will be measure according to revised RECIST Criteria (version1.1).

The progressions free survival (PFS) will be define as the time from initiation chemotherapy to the date of documented progression or death.

Overall survival (OS) will be defined as the time from initiation of chemotherapy until death from any cause.

PFS and OS will be calculated using the Kaplan-Meier method.

Statistical analysis

Statistical analyses were performed using SAS software version 9.3 (SAS Institute INC., USA). Characteristics of patients were expressed as frequency (%) or median (min-max). Comparison between groups were performed using the non-parametric Wilcoxon-Mann-

Whitney test for continuous variables and the non-parametric Fisher's exact test for qualitative variables.

Overall survival and progression-free survival were calculated using the Kaplan-Meier method. Comparisons of survival between groups were performed using the traditionnal logrank test and a permutation logrank test, which is more appropriated approach in case of small sample size and/or number of deaths.

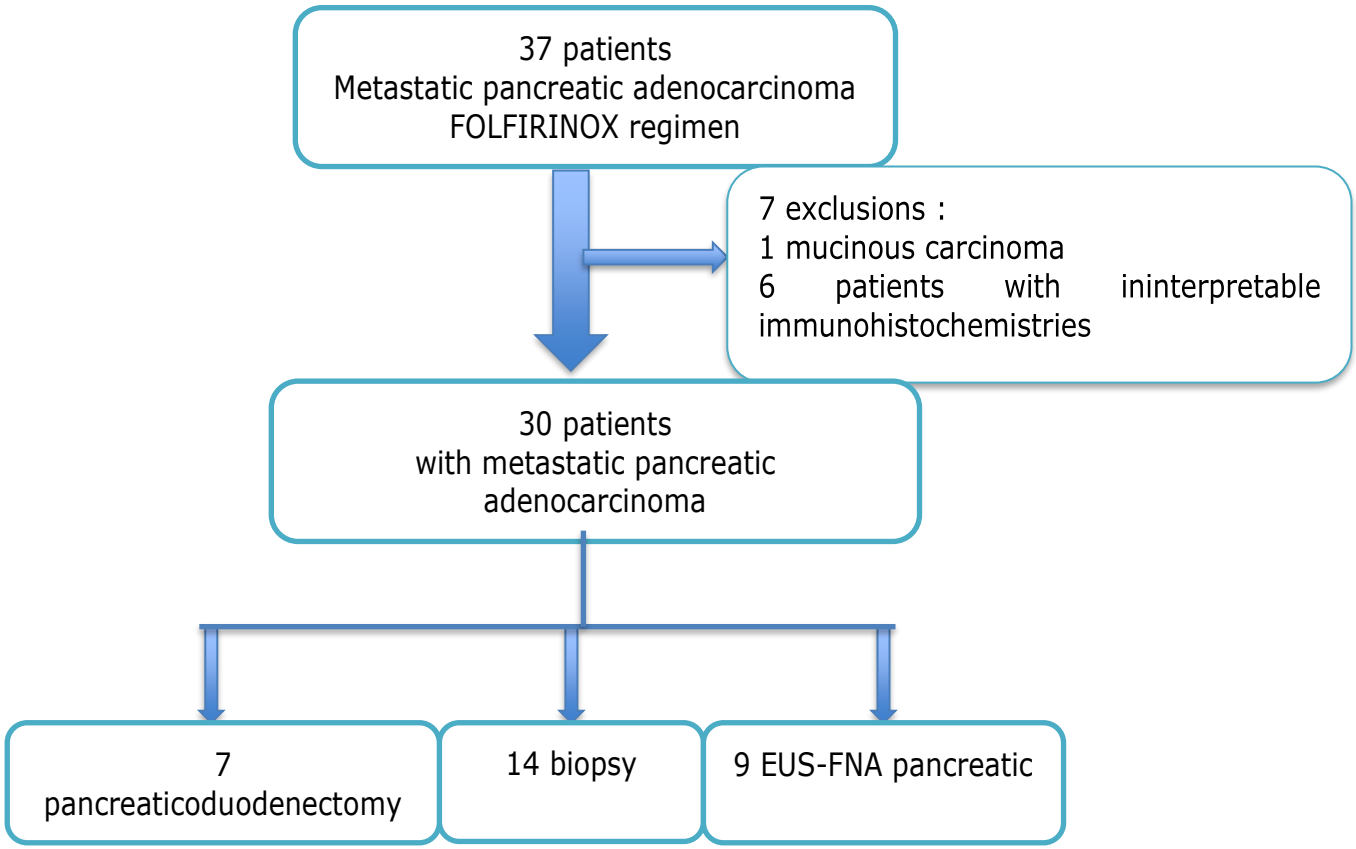
All tests were two-sided; with a P value of less than 0.05 considered to indicate statistical significance.

RESULTS

1. Clinical data

Between September 2011 and June 2015, 30 patients with metastatic pancreatic adenocarcinoma were recruited in the study (Figure 1).

Figure 1 Flow Chart of the study



The average age of patients was 65.3 years (range 45.6 to76). The location of the pancreatic tumors was mainly the head of the pancreas (80.0%) and the most frequent metastatic site was the liver (76.6%). The median number of treatment cycles administered was 12 (range 3 to 16). The median relative dose intensity of fluorouracil, irinotecan and oxaliplatin were 85%, 80% and 76% respectively. 9 patients were treated in second line (Table I).

Table I : Patients characteristics

Characteristics	
Age at diagnosis (years)	65.3 (45.6-76)
Gender	
Male	n=19 (63.3%)
Female	n=11 (36.7%)
Pancreatic tumor location	
Head	n=24 (80.0%)
Body	n=3 (10.0%)
Tail	n=1 (3.3%)
Number of metastatic sites involved	
Median	n=1
range	1-4
Number of measurable metastatic sites	
Liver	n=23 (76.6%)
Lung	n=8 (26.7%)
Lymph nodes	n=5 (16.7%)
Peritoneal	n=3 (10.0%)
Other	
Median number of treatment cycles	12 (3-16)
Median relative dose intensity	
Fluorouracil	85.0%
Irinotecan	80.0%
Oxaliplatin	76.0%
Diagnosis	
EUS-FNA	n=9 (30.0%)
Biopsy	n=14 (46.7%)
Surgery (pancreatectomy)	n=7 (23.3%)
Chemotherapy before	
Yes	n=7 (23.3%)
No	n=23 (76.7%)
Chemotherapy after FOLFIRINOX	
Yes	n=9 (30.0%)
No	n=21 (70.0%)

After 6 cycles: 16.7% patients had a progressive disease, 56.7% had stable disease, 23.3% had a partial response and 3.3% a complete response.

After 12 cycles: 8 patients were not evaluated, 13.3% had a progressive disease, 40.0% had stable disease, 16.7% had a partial response and 3.3% a complete response.

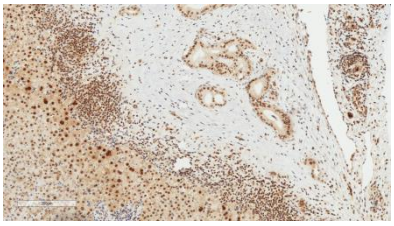
At the end of the study, 56.7% patients died.

Table II : Objective responses in the overall population

Variable	n
After 6 cycles	
Complete response	1(3.3%)
Partial response	7 (23.3%)
Stable disease	17 (56.7%)
Progressive disease	5 (16.7%)
After 12 cycles	
Complete response	1(3.2%)
Partial response	5 (16.7%)
Stable disease	12 (40.0%)
Progressive disease	4 (13.3%)
Could not be evaluated	8 (26.6%)

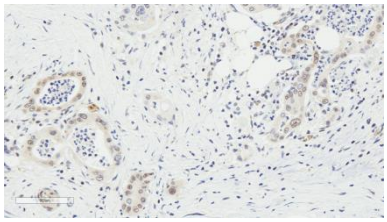
2. MGMT and p53 status

Tissue collections were collected from 9 EUS-FNA pancreatic, 14 liver biopsy and 7 pancreaticoduodenectomy. 76.7% tumors were MGMT positive (figure 2). Concerning to the expression of p53: 23.3% tumors had negative expression, 26.7% had a weak expression, 13.3% had moderate expression and 36.7% had a diffuse expression (figure 3).



Metastatic liver

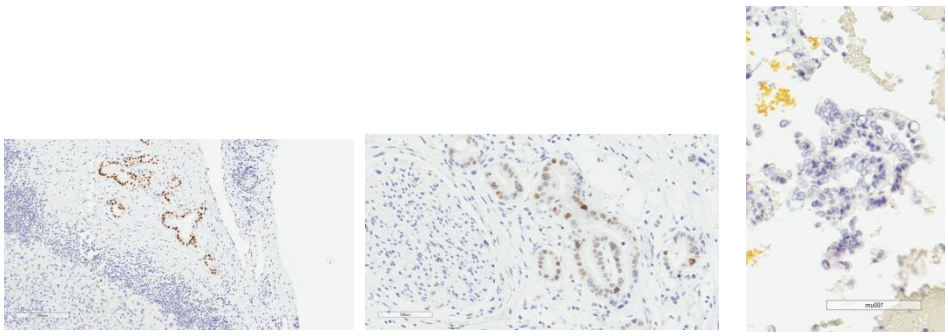
diffuse cancer nuclei



Pancreaticoduodenectomy

Lack of cancer nuclei

Figure 2. MGMT immunochemistry



1. EUS-FNA pancreatic *2.Pancreaticoduodenectomy* *3. EUS-FNA pancreatic*

diffuse cancer nuclei | focal et weak cancer | lack of cancer

Figure 3. p53 immunochemistry

3. Objective response

Table III shows the objective response rate in the population correlated with MGMT and p53 status.

Table IIII : Objective responses in the overall population correlated with immunohistochemical MGMT and P53 status

Variable	MGMT -	MGMT +	p	P53 0/1	P53 2/3	p
After 6 cycles			0.836			0.781
n	7 (23.3%)	23 (76.7%)		15	15	
Complete or partial response	1 (14.3%)	7 (30.4%)		3 (20.0%)	5 (33.3%)	
Stable disease	5 (71.4%)	12 (52.2%)		9 (60.0%)	8 (53.3%)	
Progressive disease	1 (14.3%)	4 (17.4%)		3 (20.0%)	2 (13.3%)	
After 12 cycles			0.435			0.949
n	7	21		15	13	
Complete or partial response	1 (14.3%)	5 (23.8%)		3 (20.0%)	3 (23.1%)	
Stable disease	5 (71.4%)	7 (33.3%)		6 (40.0%)	6 (46.2%)	
Progressive disease	0 (0.0%)	4 (19.1%)		2 (13.3%)	2 (15.4%)	
Could not be evaluated	1 (14.3%)	5 (23.8%)		4 (26.7%)	2 (15.4%)	

3.1. After 6 cycles:

Among patients who have tumors MGMT positive: 30.4% have a complete or partial response, 52.2% have a stable disease and 17.4% have a progressive disease.

Among patients who have tumors MGMT negative: 14.3% have a complete or partial response, 71.4% have a stable disease and 14.3% have a progressive disease. There was no significant difference in response rate at 6 cycles (p=0.836).

Among patients who have tumors that expressed negative or weak p53: 20.0% have a complete or partial response, 60.0% have a stable disease and 20.0% have a progressive disease.

Among patients who have tumors that expressed moderate or strong p53: 33.3% have a complete or partial response, 53.3% have a stable disease and 13.3% have a progressive disease. There was no significant difference in response rate at 6 cycles (p=0.78).

3.2. After 12 cycles:

Among patients who have tumors MGMT positive: 23.8% have a complete or partial response, 33.3% have a stable disease and 19.1% have a progressive disease.

Among patients who have tumors MGMT negative: 14.3% have a complete or partial response, 71.4% have a stable disease and 0.0% has a progressive disease. There was no significant difference in response rate at 12 cycles (p=0.435) depending on the positive or negative expression of MGMT.

Among patients who have tumors that expressed negative or weak p53: 20.0% have a complete or partial response, 40.0% have a stable disease and 13.3% have a progressive disease.

Among patients who have tumors that expressed moderate or strong p53: 23.1% have a complete or partial response, 46.2% have a stable disease and 15.4% have a progressive disease. There was no significant difference in response rate at 12 cycles (p=0,949).

3.3. PFS and OS

The progression-free survival and the overall survival were not significantly different on depending MGMT status (Figure 4).

At the end of the study, 60.8% patients with tumors MGMT positive died and 42.9% with tumors MGMT negative. The average OS in patients with tumors MGMT positive was 522.3 +/- 68.9 days and in patients with tumors MGMT negative 618.0 +/-146.4 days. There was no significant difference in OS depending on the positive or negative expression of MGMT (p=0.39).

The average PFS in patients with tumors MGMT positive was 257.0 +/- 38.2 days and in patients with tumors MGMT negative 325.7 days +/-19.1 days. There was no significant difference in PFS depending on the positive or negative expression of MGMT (p=0.112).

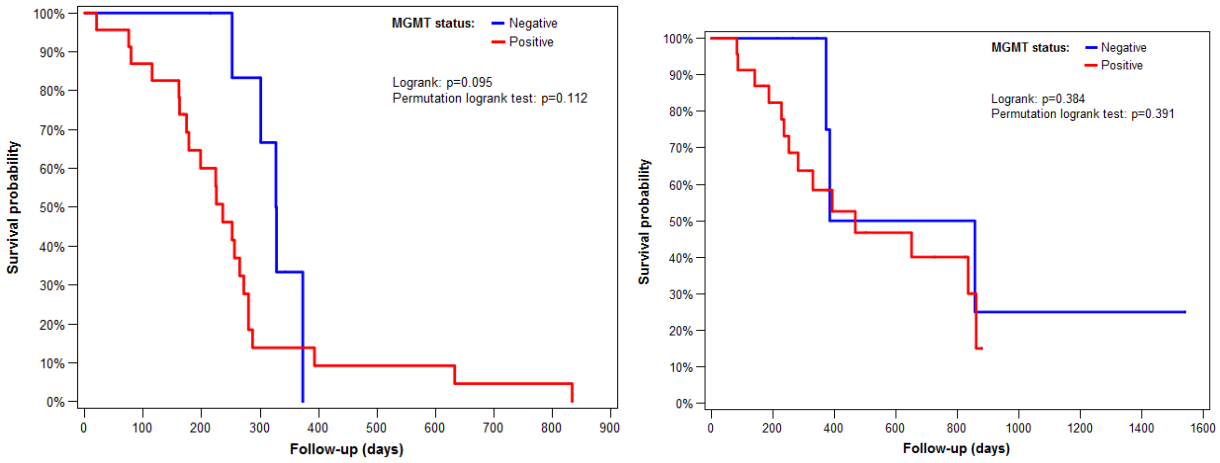


Figure 4: Progression free survival and overall survival correlated with MGMT status

Concerning p53, the results on PFS and OS depending on p53 expression were shown in Figure 5.

40.0% patients with tumors expressed negative or weak p53 died and 73.3% with tumors expressed moderate or strong p53 died. The average OS in patients with tumors expressed a moderate or strong expression of p53 was 444.0 +/- 75.9 days whereas in patients with a negative or weak expression of p53, the average OS was 677.5 +/- 85.3 days. Patients with tumors expressed a negative or weak expression of p53 had an OS significantly longer comparing to those with strong expression (p=0.027).

The average PFS in patients with tumors expressed a moderate or strong expression of p53 was 288.7 +/- 52.8 days whereas in patients with a negative or weak expression of p53, the average PFS was 253.6 +/- 24.6 days. There was no significant difference on progression free survival in accordance with the strong or weak expression (p=0.896).

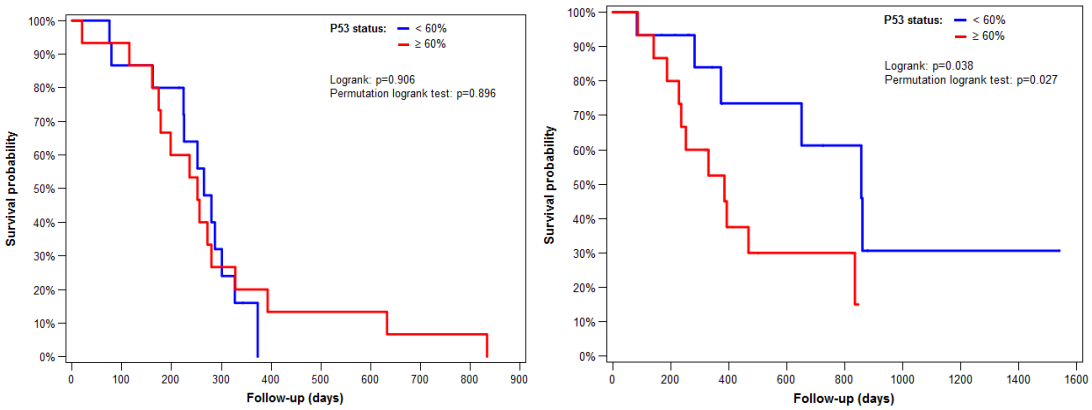


Figure 5: Progression free survival and overall survival correlated with P53 status

4. Relationship between MGMT and p53

Furthermore, 85.7% tumors MGMT negative expressed negative or weak p53 and 60.9% tumors MGMT positive expressed moderate or strong p53. There was no significant difference (p=0.08).

DISCUSSION AND CONCLUSION

PDA is one of the major causes of cancer death worldwide and the treatment of metastatic disease remains challenging as only certain patients benefit from advances made with the intensified chemotherapy regimen FOLFIRINOX (1). Up to date, no established approach for prediction of treatment response exists (2,15). Recently, the methylation status of the MGMT gene promoter was an important biomarker highlighted in pancreatic endocrine tumors (7) increasing progression-free survival and overall survival in alkylant use (17-18). Moreover the blockade of MGMT expression could lead to reduce pancreatic tumor growth in mice model (19). Correlations between promoter methylation and response to chemotherapy with alkylating agents are explained by the assumption that DNA methylation of a cysteine-phosphate-guanine (CpG) island within the MGMT promoter directly leads to a repression of MGMT transcriptional activity and MGMT protein expression (6). In addition, platinium salts may modulate the activity of MGMT (12). However, MGMT methylation does not confer sensitivity to the killing action of alkylating agents if the tumor is also MMR deficient (20). It has been previously reported association between MMR genes variants and overall survival (21) supporting a role for DNA MMR deficiency in pancreatic cancer progression and defective MMR has been reported in up to 13% of sporadic pancreatic cancer (10). Genetic variations in MGMT were correlated with overall survival in patients with localized disease (21). So, it was interesting to check the frequency of MGMT deficiency in pancreatic adenocarcinoma and to study a possible correlation with therapeutic efficacy.

MGMT deficiency is rare in metastatic pancreatic adenocarcinoma (23.3% in our study) (6). MGMT status assessed by immunohistochemistry failed to modulate response rate, progression free survival and overall survival in patients treated by FOLFIRINOX. Notably, MGMT deficiency was not correlated with a poor prognosis in contrast with previous observation in other tumors (22). This could be explained by a better activity of irinotecan in

MGMT negative patients. Another hypothesis to explain the effectiveness of FOLFIRINOX in pancreatic adenocarcinoma is that oxaliplatin as cisplatin could perform a downregulation on MGMT expression (23) and sensitize tumor cells to CPTs. MGMT antibodies does not necessarily indicates a MGMT deficient phenotype because the presence of connective tissue and normal-appearing pancreatic components have markedly lesser MGMT (6). The true methylation status of MGMT by molecular techniques should however be investigated before definitive conclusions of this subject. An analysis of MMR genes would be interesting.

P53 tumor suppressor gene protein is a regulator transcriptional controlling cell cycle arrest; apoptosis, senescence and DNA damage response. The potential role of p53 as a prognostic biomarker in oncology has long been recognized and p53 is mutated in 50% of cancers. In pancreatic adenocarcinoma, resulting in the accumulation of mutated protein and playing a role in genomic instability, hyperproliferation and chemoresistance (24). Studies have shown that non-functional p53 affect sensitivity of cancer cells to gemcitabine. P53 could interact with the EGFR/KRAS signaling pathway and would be a potential contraindication of responsiveness to EGFR inhibition (25). Our study demonstrates that a longer overall survival in pancreatic adenocarcinoma is associated with a weak p53 tumoral expression in patients treated by FOLFIRINOX regimen. Findings from 50 patients treated using an erlotinib-based first-line regimen within AIO-PK0104 showed that overall survival was independent of p53 expression (26). However, progression free survival was significantly reduced in patients with p53 loss (1.8 months) or overexpression of p53. According to our study, these findings may provide that overexpression of p53 could be an important step in carcinogenesis and might be correlated to poor prognosis as also suggested by others studies. But we have not studied the functionality of the protein p53 and if a mutation exists.

The relationship between p53 and MGMT status are not clear. It has been suggested that MGMT inhibition modulates p53 function leading cell cycle arrest and apoptosis (20). Recent

studies have showed MGMT inactivation by hypermethylation increased the occurrence of p53 mutation (26), especially in lung adenocarcinomas (27). But an inverse correlation between MGMT and p53 has been also described in other cancers like breast, nasopharyngeal, gastric and biliary tract cancers (22,28,29) and MGMT immunonegativity and p53 immunopositivity may be strong predictors of breast cancers survival (30). Others studies have demonstrated that wild type p53 was accompanied by lower MGMT protein expression (31) whereas Rolhion et al. (32) reported that MGMT gene expression was significantly lower in p53 mutated tumors. Effectively mutations of p53 in human cancer are common and occur in all malignant cell types, the relationship observed between MGMT expression and p53 is highly relevant (32). In our study, we found a positive relation between the expression of p53 and MGMT: tumors MGMT positive have a stronger expression of p53 but these results were no significant.

Our study presents few limits. It is a preliminary study and only 30 patients were included responsible for a weak power. Moreover it's a retrospective study. Our histological sample is heterogeneous because the analysis come from EUS-FNA, duodenopancreatectomy and radiological or surgical biopsy and we studied analysis from primitive tumor and metastatic lesions. Moreover the fiability of immunohistochemistry come from EUS-FNA can be discussed because the analysis is made from a sample low in cells.

In conclusion, our study suggests that in patients with a metastastic pancreatic adenocarcinoma treated in first-line by FOLFIRINOX, the immunohistochemical evaluation of MGMT does not predict the clinical evolution while a strong tumor expression of p53 is correlated with a poor prognosis in terms of overall survival.

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Corrélation entre O6-méthylguanine-ADN méthyltransférase (MGMT) et p53 à la réponse clinique dans l'adénocarcinome pancréatique métastatique traité par FOLFIRINOX

RÉSUMÉ

Introduction: Il n'existe pas à l'heure actuelle de biomarqueur prédictif de l'efficacité du traitement par FOLFIRINOX dans l'adénocarcinome pancréatique métastatique. Des études ont montré que la perte d'expression en O6-methylguanine-DNA méthyltransférase (MGMT) était associée à une réponse thérapeutique dans les tumeurs endocrines du pancréas et la perte d'expression de la protéine p53 (p53) pourrait interférer avec l'action de la protéine MGMT. Le but de notre étude était de déterminer rétrospectivement la prévalence du statut MGMT et d'étudier si ce statut et celui de la p53 étaient corrélés à la réponse thérapeutique et au pronostic des patients ayant un adénocarcinome pancréatique métastatique traité en première ligne par du FOLFIRINOX.

Sujets et Méthodes: Les statuts MGMT et p53 ont été évalués par immunohistochimie sur les tissus tumoraux primitifs (cytoponction sous écho-endoscopie ou chirurgie) ou secondaires (métastases) chez 30 patients ayant un adénocarcinome pancréatique au CHU d'Angers entre septembre 2011 et juin 2015. L'expression de MGMT était évaluée comme présente ou absente et l'expression de p53 était semi-quantitativement gradée. Des données clinico-biologiques et radiologiques ont été recueillies rétrospectivement.

Résultats: Selon la présence ou l'absence de MGMT, il n'y avait pas de différence significative en terme de taux de réponse, de survie globale ou sans progression. Il n'existait pas de relation significative entre l'expression de p53 et les taux de réponse ou la survie sans progression. Par contre, les patients avec une expression tumorale forte de p53 avaient une survie globale significativement inférieure aux patients sans et avec une faible expression de la protéine (p=0,027). Il y avait une corrélation positive entre l'expression de MGMT et celle de p53 (p=0,08).

Conclusion: Notre étude suggère que pour les patients ayant un adénocarcinome pancréatique métastatique traités en première ligne par du FOLFIRINOX, l'évaluation immunohistochimique du statut MGMT ne prédit pas l'évolution clinique alors qu'une expression tumorale forte de la p53 est corrélée avec un faible pronostic en terme de survie globale.

Mots-clés : adénocarcinome pancréatique métastatique, FOLFIRINOX, MGMT, p53

Correlation between O6-methylguanin-DNA methyltransferase (MGMT) and p53 in clinical response in metastatic pancreatic adenocarcinoma treated by FOLFIRINOX regimen

ABSTRACT

Background: No predictive biomarker for FOLFIRINOX efficacy in metastatic pancreatic adenocarcinoma has so far been demonstrated. The deficiency in O6-methylguanine-DNA methyltransferase (MGMT) has been associated with therapeutic response in endocrine tumors of the pancreas and the lack of expression of protein 53 (p53) could interfere with the action of MGMT. The aim of our study was to investigate in these patients treated by FOLFIRINOX in first line the prevalence of MGMT status and if any correlation exists between the tumor expression of p53 and MGMT and the therapeutic response and survival.

Patients and methods: The immunohistochemical expression of MGMT was recorded as present or absent and the expression of p53 was semi-quantitatively scored in 30 patients with metastatic pancreatic adenocarcinoma at Angers hospital, France, between September 2011 and June 2015. Clinical and radiologic data were collected retrospectively.

Results: There was no significant difference depending on the presence or absence of MGMT expression in response rate, progression free survival (PFS) and overall survival (OS). No significant relationship for response rate and PFS was observed in relation with p53 expression. By cons, patients with strong tumor expression of p53 had a significantly lower OS comparing to patients with no or weak expression of the protein (p= 0.027). There was a positive correlation between the expression of the p53 and MGMT but no significant (p= 0.08).

Conclusions: Our study suggests that for patient treated with first-line FOLFIRINOX in metastatic pancreatic adenocarcinoma the immunohistochemical evaluation of MGMT does not predict the clinical evolution while a strong tumor expression of p53 is correlated with a poor prognosis in terms of overall survival.

Keywords : metastatic adenocarcinoma pancreatic, FOLFIRINOX, MGMT, p53

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