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Yanis Dahel, Brice Chanez, Christophe Zemmour, Gilles Piana, Emmanuel Mitry, et al.. Assessment of biological effect of nab-paclitaxel combined with gemcitabine, using contrast enhanced ultrasonography and elastography, in advanced pancreatic ductal carcinoma: A single-center pilot study. *Endoscopic Ultrasound*, 2023, 12 (2), pp.273-276. 10.4103/eus-d-22-00040 . inserm-04546987

HAL Id: inserm-04546987

<https://inserm.hal.science/inserm-04546987>

Submitted on 15 Apr 2024

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Assessment of biological effect of nab-paclitaxel combined with gemcitabine, using contrast enhanced ultrasonography and elastography, in advanced pancreatic ductal carcinoma: A single-center pilot study

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ABSTRACT

EUS associated with contrast-enhanced harmonic EUS (CH-EUS) and EUS elastography (EUS-E) are used in clinical practice to assess pancreatic tumor at the diagnosis. In case of pancreatic ductal adenocarcinoma (PDAC) with liver metastasis, nab-paclitaxel combined with gemcitabine is a first-line treatment option. We aimed to assess the modification of PDAC microenvironment induced by the combination of nab-paclitaxel with gemcitabine, by endoscopic ultrasonography techniques. This single center phase III study conducted between February 2015 and June 2016 included patients with pancreatic adenocarcinoma with measurable liver metastasis and no prior cancer treatment fit for two cycles of nab-paclitaxel combined with gemcitabine. We aimed to perform EUS with CH-EUS and EUS-E of the pancreatic tumor, CT scan and contrast enhanced ultrasonogram (CE-US) of a reference liver metastasis, before and after the two cycles of chemotherapy. Primary end point was modification of vascularization of primary tumor and a reference liver metastasis. Secondary end points were modification of stromal content, safety profile of drug combination and tumor response rate. Sixteen patients were analyzed, but only 13 received two cycles of chemotherapy (CT) (toxicity [$n = 1$] or death [$n = 2$]). There was no statistical modification induced by CT concerning vascularity of primary tumor (time to maximum intensity $P = 0.24$, value of maximum intensity $P = 0.71$, hypoechoic aspect generated by injection of contrast enhancing agent), vascularity of a reference liver metastasis (time to maximum intensity $P = 0.99$, value of maximum intensity $P = 0.71$) and tumor elasticity ($P = 0.22$). Eleven patients had tumor response assessment, 6/11 (54%) had measurable disease response 4/11 (36%) with partial responses and 2/11 (18%) with stable disease. All other patients showed disease progression. No serious side effects occurred, 6/11 patients had a dose adjustment. We did not show significant modification of vascularity and elasticity but these results should be taken with caution because of important limitations.

Key words: Chemotherapy, contrast enhanced ultrasonography, elastography, pancreatic adenocarcinoma

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How to cite this article: Dahel Y, Chanez B, Zemmour C, Piana G, Mitry E, Giovannini M. Assessment of biological effect of nab-paclitaxel combined with gemcitabine, using contrast enhanced ultrasonography and elastography, in advanced pancreatic ductal carcinoma: A single-center pilot study. *Endosc Ultrasound* 2023;12:273-6.

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10.4103/EUS-D-22-00040

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Received: 2022-02-19; **Accepted:** 2023-01-18; **Published online:** 2023-04-28

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most fatal malignancy among gastrointestinal cancer, with increasing incidence over years and with a 5-year overall survival rate of 5%–7%.^[1,2]

New therapeutics and new technics to analyze early tumor response are highly needed.

When metastases are detected, which the most frequent being liver metastases, only palliative chemotherapy computed tomography (CT) are validated;^[3] however, first-line regimen, mainly poly-CT based, depend on the country and health system.^[4] Nab-paclitaxel, an albumin bound paclitaxel nanoparticle, is combined with gemcitabine as first-line treatment option for advanced PDAC.^[5] The combination of the taxane drug with the albumin bound compound has shown in a preclinical study improvement of intratumoral concentration of gemcitabine in mice treated with the combination and this could be related to the modification of the desmoplastic micro environment of the pancreatic tumor.

In a phase III trial, the combination demonstrated superior overall survival, progression-free survival and response rate compared with gemcitabine alone in metastatic untreated PDAC;^[6] however, reimbursement of nab paclitaxel through public health policies is not equal across European countries. In France, the French Agency for the Safety of Health product has classified nab-paclitaxel as an important therapy in advanced PDAC and its use is approved by French authorities. However, the medical service improvement has been evaluated as “low” and the molecule is not reimbursed by social security.^[7]

EUS is a key procedure allowing fine-needle aspiration biopsies of the tumor and precise staging. Recently, contrast-enhanced harmonic EUS (CH-EUS)^[8,9] and EUS elastography (EUS-E)^[10,11] became available. These modalities, done at the same time with conventional EUS, allow an excellent evaluation of the stromal tissue. CH-EUS allows visualization of micro vasculature and assessment of parenchymal perfusion, useful for characterizing pancreatic lesions and detecting PDAC with a sensitivity of 94% and specificity of 89% as a result of the hypo-enhancement of these lesions. PDAC is usually not enhanced after injection of ultrasound contrast agent (SonoVue®, Bracco, Italy) and 5–10 times stiffer than normal tissue.

EUS-E is an ultrasound-based method for the visualisation of relative strain distribution. By calculating the elasticity of tissue we're able to differentiate benign (soft) tissue from malignant (hard) tissue. Comparison should be made between the pancreatic mass and the duodenal or the gastric wall elasticity; using this technique a ratio > 17 is always correlated with a malignant pancreatic mass, a ratio of < 7.8 is associated in 93% of cases with an inflammatory mass.

In 2013, a mechanism of action trial in 16 resectable patients has been published.^[12] Conclusions are that the combination of nab-paclitaxel + gemcitabine decreased tumor stiffness (assessed by EUS-E), and tumor stromal content (when compared with patients resected without preoperative CT or another CT).

It seems then of peculiar interest to try to confirm these and to check if these tumor modifications are limited to the PDAC itself or will be also noticed in liver metastases. It is obvious that a decrease in stromal content associated with an increase in tumor vascularity allows for an increase in drug delivery to the tumor cells. This is of major interest and can lead to test combinations of nab-paclitaxel with other efficient treatments.

The main objective were to assess if, compared to baseline, the combination of nab-paclitaxel with gemcitabine induces modification of the PDAC microenvironment particularly in vascularization of the primary tumor as well liver metastasis after two cycles of treatment and second to assess the modification of tissue's elasticity. We also evaluated overall response rate and toxicity profile.

METHODS

In this single-center pilot study, we included patients with pancreatic adenocarcinoma with measurable liver metastasis, no prior pancreatic or liver surgery, no radiotherapy and/or CT, with life expectancy longer than 2 months and a performance status (PS) 0–2. Tumors other than ductal adenocarcinoma were excluded. Patients were treated with two cycles of nab-paclitaxel (Abraxane®) 125 mg/m² intravenous (IV) and gemcitabine 1 g/m² IV on days 1, 8, and 15 every 4 weeks.

The treatment was continued after the two cycles until progression or unacceptable toxicity occurred (Common

Toxicity Criteria for Adverse Events version 4.03, National Institutes of Health, 2010, USA) or discontinued per patient's request.

Before and 2 months after initial CT we performed CH-EUS and EUS-E of the primary tumor during general anesthesia. We also conducted a contrast-enhanced ultrasonogram (CE-US) of a reference liver metastasis and CT scan tumor measurement according to RECIST v1.1 as well as density measurement according to Choi criteria.

Based on empirical considerations, a total of 16 patients are planned to be evaluated.

The primary end point was to evaluate if two cycles of nab-paclitaxel combined with gemcitabine-induced modifications in vascularization of pancreatic adenocarcinoma measured by CH-EUS. We also assessed these modifications by C-US in a reference liver metastasis.

Secondary end points were to evaluate if this combination induces a modification in stromal content of the pancreatic primary tumor by assessing stiffness with E-EUS and density of liver metastases by CTs. The safety profile of the drug combination and the tumor response rate were also evaluated.

RESULTS

Between February 2015 and June 2016 19 patients were evaluated with a mean age of 69 year (range, 49–78), 10 were women (52%). Three patients were excluded, one neuroendocrine tumor, one because of PS 3 and another patient at the discretion of the principal investigator. Finally, 16 patients were analyzed in the study.

Thirteen patients (81.25%) received two cycles of CT. Two patients died before the beginning of the second cycle and one patient did not start the second cycle because of toxicity. Eleven patients had tumor response assessment before and after CT.

Vascularity and elasticity of primary tumor

Assessment of vascularity of the primary tumor was performed by CH-EUS in 13 patients before CT and in 12 patients after CT. There was no statistically significant difference of time to maximum intensity ($P = 0.24$, paired t -test), value of maximum intensity ($P = 0.71$) and hypoechogenic aspect generated by injection of contrast enhancing agent (12/13 before and 12/12 after).

Assessment of vascularity of a reference liver metastatic lesion was performed by CE-US on 8 patients before and after CT. There was no statistically significant difference of time to maximum intensity ($P = 0.99$) or value of maximum intensity ($P = 0.71$).

Pancreatic tumor elasticity assessment done by E-EUS in 11 patients before CT and 12 patients after CT showed no statistical significant difference ($P = 0.22$).

Tumor response assessment

Eleven patients evaluated by Choi and Recist: 6/11 (54%) had measurable disease response with 4/11 (36%) partial responses and 2/11 (18%) had stable disease. All other patients showed disease progression.

Toxicity profile

No serious side effects occurred and 6/11 patients had a dose adjustment because of hematologic toxicity (5/6) or asthenia (1/6).

CONCLUSION

Our pilot study is the first to evaluate the effect of gemcitabine in combination with nab-paclitaxel in advanced PDAC utilizing EUS techniques (CH-EUS and E-EUS). We aimed to assess if CT increased tumor vascularity to improve drug diffusion but we did not see any increase of vascularity of PDAC or liver metastasis after two cycles of CT in patient without prior treatment.

Our results should be taken with caution and reasons for the absence of variation in elasticity or vasculature can be multiple. First of all, the small sample of patients associated with known heterogeneity of pancreatic adenocarcinoma had probably led to heterogeneous measurements. Second, endoscopic ultrasound techniques are innovative techniques but operator dependent that could lead to variation of values. Moreover, we had technical difficulty with endoscopic ultrasound. The data extracted from contrast-enhanced imaging and elastography showed missing data.

A recent study described the decrease of tumor vascularity, assessed by CH-EUS and chemotherapies in 23 patients treated by gemcitabine alone. They showed modification of the pancreatic tumor with appearance of avascular areas in 11/23 patients.^[13]

Our global response rate is 54% and is slightly better than those observed in the literature in particular in the pivotal study,^[6] but our patient sample was small and selective.

In conclusion, we did not show significant modification of vascularity and elasticity of pancreatic tumor and liver metastasis after combination treatment with nab-paclitaxel and gemcitabine, but these results should be taken with caution because of important limitations.

Financial support and sponsorship

Nil.

Conflicts of interest

Marc Giovannini is a Founding Editor-in-Chief of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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