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Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma

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Abstract

Introduction: Recently, novel chemotherapeutic agents like nab-paclitaxel and gemcitabine demonstrated a survival benefit over gemcitabine alone in metastatic pancreatic cancer. However, there are limited clinical results using this chemotherapy in potentially resectable pancreatic adenocarcinoma. Our aim is to report the oncological results of patients affected by potentially resectable pancreatic adenocarcinoma that underwent surgery after a combination of gemcitabine and nab-paclitaxel.

Methods: A total of 25 patients have been included. We evaluated: (1) Drug toxicity; (2) tumoral response (tumoral size at CT scan, SUV of FDG PET-CT scan and CA 19.9; (3) resection rate; (4) R0 resection rate and histopathological response and (5) survival and disease free survival.

Results: Overall treatment was well tolerated. Treatment resulted in a statistical decrease of CA19-9 ($p = 0.019$) tumoral size ($p = 0.04$) and SUV ($p = 0.004$). The resection rate was 68% (17/25 patients). All specimens were R0 and 13 of 17 specimens had major pathological regressions (complete and important response). Median survival and medial disease free survival of patients that underwent surgery was 21 months and 19 months, respectively at a mean follow up of 38.5 months.

Conclusions: This data suggests that nab-paclitaxel and gemcitabine is a safe and effective neoadjuvant treatment for potentially resectable pancreatic adenocarcinoma. This promising data should be confirmed in larger, randomized studies.

Keywords: Pancreatic cancer; Pancreatectomy; Neoadjuvant treatment

Introduction

Pancreatic adenocarcinoma (PA) is a highly lethal disease with an extremely poor prognosis.[1] Surgical resection followed by systemic treatment remains the best potential treatment to improve survival. However, even after oncological resection, overall survival (OS) rate as well as overall disease free (DFS) rate remains poor.[2] Neoadjuvant treatment aims to minimize local recurrence, increase R0 resection rate and, therefore, to maximize survival. Traditional neoadjuvant treatments, with or without radiotherapy, have not demonstrated any real benefit after surgery. Therefore, nowadays, most of PA underwent surgery without any preoperative treatment.[3]

However, recently, the better understanding of the molecular biology of PA, allowed the development of novel chemotherapeutic agents and combination such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) or nab-paclitaxel (an albumin-coated formulation of paclitaxel).[3,4] In combination with gemcitabine, nab-paclitaxel drug is claimed to disrupt the PA stroma increasing the intratumor concentration of gemcitabine by approximately three-fold in xenograft models.[5,6]

Up to now, only few phase I, II and III studies are in progress with this combination chemotherapy regimen, showing promising results in advanced, unresectable

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PA.[5,7,8] To the best of our knowledge, in the current literature there are only 4 clinical results using this chemotherapy in potentially resectable PA.[9–12] However, in these studies there are still not available data on survival as they are very recent except for one of them which includes only 10 cases.[12]

The aim of this study is to report the oncological results of a treatment protocol including patients affected by potentially resectable PA that underwent surgery at our center after a combination of gemcitabine and nab-paclitaxel.

Materials and methods

We prospectively recruited patients with potentially resectable pancreatic cancer with histological or cytological confirmed PA from August 2011 to December 2012 at Sanchinarro University Hospital. Inclusion criteria were age >18 years old; no prior treatment for pancreatic cancer; Eastern Cooperative Group (ECOG) performance status ≤1; adequate hematologic, renal and liver function; potentially resectable PA. We define as localized and resectable PA (R-PA) or borderline resectable (BR-PA) according to the NCCN guidelines[13] and assessed by preoperative study (CT scan, MRI and endoscopic ultrasound).

Preoperative work up

It included tumoral markers CA 19.9, thoraco-abdominal CT scan, FDG-PET scan measuring max standardized uptake value (SUV), pancreato-biliary MRI and endoscopic ultrasound with fine needle biopsy. Jaundice was treated before neoadjuvancy by metallic full covered biliary stent.

Treatment protocol

The protocol was adopted from the previous MPACT study for metastatic PA[7] in which our group has contributed.

This protocol consisted of Gemcitabine 1000 mg/m^2 and Nab-paclitaxel 125 mg/m^2 administered on days 1, 8 and 15 every 28 days for at least 2 cycle. Adjuvant treatment consisted in four cycles of standard dose of gemcitabine.

Restaging after neoadjuvant treatment

After completing the neoadjuvant regimen, patients underwent to CA 19.9 serum level, abdominal CT scan and FDG-PET scan. Furthermore, patients were restaged and considered for surgical resection if their disease had not progressed by emergence of metastatic disease. Radiological post treatment evaluation was performed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).[14]

Surgery is performed between 4 and 6 weeks after the last cycle of treatment.

Patients found to be unresectable underwent to treatment based on different drugs from gemcitabine and nab-paclitaxel.

Chemotherapy related toxicity

Treatment related toxicities were evaluated by National Cancer Institute Common Terminology Criteria of Adverse Events version.[15] In case of prolonged toxicity of more than 1 week, chemotherapy was terminated, and surgery was performed after restaging had excluded distant metastases. Severe adverse events are defined as grade 3 and grade 4.

Patients underwent surgery 6–8 weeks once the treatment was finished. Those patients with cancer progression were not scheduled for surgical resection and excluded from the study.

Pathological data

Two pathologists using a standardized technique have independently reviewed all pathological data. If they weren't in agreement, a third pathologist was asked to revise the specimen.

Tumoral stage was assessed according to the sixth edition of the TNM staging system.[16]

The tumor regression grade (TRG) in the surgical specimen was determined adapting the rectal cancer Ryan classification (TRG = 0: complete response; TRG = 1: important response; TRG = 2: partial response; TRG = 3: low or no response).[17] Major pathological regression is defined as TRG 0–1.

R1 resection was considered if there were tumor cells present <1 mm of resection margin.

Post operative complication

Complications were graded according to the Clavien–Dindo scoring system and defined as severe from grade III.[18] Pancreatic fistula was classified according to the International Study Group of Pancreatic Fistula (degrees A, B and C).[19]

Surveillance

After operation, patients were seen in clinic 2 weeks after hospital discharge and then once monthly during the first year after surgery and then every 3–4 months with a focus on surveillance for recurrences.

Endpoints

The primary outcome measure was overall survival (OS) and disease free survival (DFS). Secondary outcome measures included radiological, tumoral markers, R0 resection rate and histological tumoral response, overall toxicity of