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Comparison of Intra-Arterial and Systemic Chemotherapy as Second-Line Treatment an Patients with Advanced Pancreatic Cancer: A Retrospective Study

(Running title: Second-line chemotherapy in pancreatic cancer)

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Abstract

***Background:** Pancreatic cancer is a poor prognosis disease. Although recent advances have improved outcomes in first-line therapy, recurrence occurs within 6 months. Today, there is no a standard of care of second-line therapy.*
***Methods:** We analysed data about 114 advanced pancreatic cancer patients underwent to FOLFIRINOX first-line chemotherapy. All patients underwent to second-line treatment: 50 received EC-GEMCAP loco-regional/systemic chemotherapy (group A) and 64 received gemcitabine alone or gemcitabine-based chemotherapy (group B).*
***Results:** Group A: epirubicin 35mg/mq and cisplatin 42mg/mq into celiac axis by bolus injection (on day 1). Capecitabine orally at the dose of 650mg/mq twice a day, on days 2-15. Gemcitabine 1,000mg/mq iv on day 2 of each cycle. Treatment was repeated every 28 days. Group B: 64 patients received gemcitabine alone or in combination. The disease control rate was 66% in group A and 26,6% in group B. From the start of second-line chemotherapy, overall survival was 9,8 months and 5,4 months for patients in group A and group B, respectively (p=0,0001). Progression-free survival was 4,6 months for group A and 2,5 months for group B (p=0,00005).*
***Conclusions:** Second-line EC-GEMCAP treatment showed important activity and effectiveness in terms of OS, PFS and disease control rate towards standard chemotherapy.*

Introduction

Pancreatic cancer is still a poor prognosis disease, mainly due to biological cancer aggressiveness and the low sensitivity to medical treatments. Although new standard schedules of chemotherapy have improved outcomes in first-line therapy, recurrence or progression disease occurs within 6 months and fewer than 10% of patients reaches 5 years after the initial diagnosis [1-3]. Today, there is not a standard of care for this setting of patients and a second-line therapy should be considered in terms of risk-benefit considering that clinical condition can be deteriorated, chemotherapy is often burdened by significant side effects and the outcome with second-line chemotherapy remains unsatisfactory, with a low response rate [4-5]. In both first and second-line approach it has been demonstrated that intra-arterial chemotherapy is well tolerated. In a phase III study an intra-arterial four-drug regimen improved overall survival compared with use of systemic gemcitabine, in a

first-line setting [6]. Recently, we have presented a retrospective study that investigated the role of intra-arterial epirubicin-cisplatin injected into celiac axis plus systemic gemcitabine-capecitabine (EC-GEMCAP regimen) after FOLFIRINOX first line chemotherapy, proving to be a viable treatment in terms of toxicity and activity [7]. Later, we retrospectively compared EC-GEMCAP regimen with gemcitabine or gemcitabine-based schedule, in patients progressed after FOLFIRINOX first-line therapy.

Patients and Methods

Patients diagnosed with histologically or cytologically surgical unresectable, locally advanced or metastatic pancreatic adenocarcinoma treated with FOLFIRINOX first-line chemotherapy, from 2011 to 2018 where eligible for analysis.

Inclusion criteria: age between 18 to 75 years, ECOG performance status ≤2 and adequate organ function (leukocyte count >3500/µL, haemoglobin ≥10.0 g/dL, serum creatinine <1.25 times upper limit of normal (ULN), transaminases and alkaline phosphatase <2.5 times ULN, bilirubin <1.5 times ULN). The interval from the end of adjuvant gemcitabine and disease relapse had to be at least 6 months. Staging included abdominal sonography, total abdomen and chest CT scan. Weight, performance status, CA 19-9 levels, and side effects were evaluated at study entry, after each cycle of regional therapy and every two months of systemic chemotherapy. An abdomen and chest CT scan was repeated every 3 treatment cycles. Evaluation was performed according to RECIST criteria version 1.1. All patients gave their informed consent according to our institutional guidelines. Adverse events were recorded according to the National Cancer Institute of Canada common toxicity criteria (NCIC-CTC).

Treatment plan

Group A: patients treated with EC-GEMCAP

On day 1, epirubicin 35 mg/mq and cisplatin 42 mg/mq were administered into celiac axis by bolus injection through a catether inserted in the femoral artery with the Seldinger method. Capecitabine was given orally at the dose of 650 mg/mq twice a day, on days 2-15. Gemcitabine was administered on day 2 of each cycle at a dose of 1,000 mg/mq (intravenously, over 30 minutes). Treatment was repeated every 28 days, until evidence of progression disease or in event of unacceptable toxicity, or in case of patient request. In addition, an antiemetic (granisetron 8 mg) and an H2-receptor antagonist (famotidine 40 mg) were given intravenously. The epirubicin and/or cisplatin and/or capecitabine dosage was adjusted, delayed or omitted for toxic effects ≥ grade 2, based on protocol guidelines.

Group B: patients treated with systemic therapy

Patients were treated with gemcitabine alone (gemcitabine at a dose of 1000 mg/mq weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks) or with gemcitabine plus capecitabine (oral capecitabine 650 mg/mq twice daily on days 1 to 14 plus gemcitabine 1000 mg/mq by 30-minute infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks) or plus nab-paclitaxel (nab-paclitaxel 125 mg/mq and gemcitabine 1000 mg/mq on days 1, 8 and 15, every four weeks) or plus oxaliplatin (gemcitabine 1000 mg/mq as a 100-minute infusion on day 1 and oxaliplatin 100 mg/mq as a 2-hour infusion on day 2, every two weeks) or plus carboplatin (gemcitabine 1000 mg/mq on days 1, 8 and 15 and carboplatin, area under the serum concentration-time curve of 5, on day 1, every four weeks).

Statistics

Demographic and clinical characteristics were retrospectively recorded in database and summarized by medians and frequencies, as appropriate. The primary end-point was progression free survival (PFS), defined as the time interval between second-line therapy beginning and time of disease progression based on imaging studies or death, whichever occurred first. Overall survival (OS) was defined as the time interval between second-line therapy beginning and time of death or last follow-up. PFS and OS were estimated by Kaplan-Meier method. A clinical response was defined as an improvement in symptoms present at the beginning of treatment and was based on the investigators' evaluation. The objective response rate was calculated as the sum of complete and partial responses. The disease control rate (DCR) was defined as the sum of complete and partial responses and stable disease. SPSS for Windows version 13 was used for data analysis.

Results

We collected data on 114 patients with locally advanced or metastatic pancreatic cancer treated with FOLFIRINOX first line chemotherapy. A total of 611 cycles of FOLFIRINOX was administered, a median of 9 cycles for each patient (range 3-15). Eleven patients also received a loco-regional treatment: surgery (2 patients), radiotherapy alone (2), radiotherapy associated to gemcitabine (5) and radiofrequency ablation (2). Fourty-seven patients (41,2%) progressed during or after first-line treatment, while 46 patients (40,3%) had a stable disease and 17 patients (14,9) had a partial response. In 4 patients the response was not evaluable. The DCR with FOLFIRINOX was 55,2%. At the beginning of second-line treatment, 23 patients presented a stage III and 91 a stage IV disease. Median age was 59 years (range 41-75) and ECOG PS was 0/1/2 in 69, 34 and 11 patients (Table 1).

Table 1. Characteristics of the patients and tumours (at the beginning II line-therapy)

	Group A (50)	Group B (64)	
		Gemcitabine (30)	Gemcitabine based (34)
Sex			
Male	30	13	17
Female	20	17	17
Age (years, median (range))	58 (42-75)	61 (38-75)	59 (41-71)
ECOG PS			
0	32	8	28
1	11	14	6
2	7	3	0
Not avaible	0	5	0
Stage			
III	18	4	1
IV	32	25	33
Not avaible	0	1	0
Metastatic sites			
Liver	25	21	26
Peritoneum	8	13	13
Lung	0	9	7

Abbreviation: ECOG PS= Eastern Cooperative Oncology Group performance status.

Group A

We administered a total of 245 cycles of EC-GEMCAP therapy in 50 patients, with a median of 4 cycles per patient (range 1-15).

Toxicities

Globally, treatment was well tolerated, without dose reductions or delays. All grade haematological toxicity was observed in 58% of patients, grade 3-4 in 34% (leucocytopenia 20%, thrombocytopenia 14%). Twenty-eight per cent of patients had non-haematological toxicity, grade 3-4 in 10% (fatigue 2%, vomiting 6%, diarrhoea 2%).

Response and survival

Response to treatment by RECIST criteria was evaluated in 44 of 50 patients (6 patients had clinical deterioration before the third cycle). Stable disease was observed in 22 patients (50%), partial response in 7 patients (16%), with a DCR in 29 patients (66%). Fifteen patients (34%) had a progression of disease (Table 2).

Table 2. Efficacy of loco-regional-systemic chemotherapy vs gemcitabine/gemcitabine-based chemotherapy, as second-line therapy after FOLFIRINOX progression.

	Group A (44)	Group B (64)
Complete response	0	0
Partial Response	7 (16%)	4 (6,2%)
Stable disease	22 (50%)	13 (20,3%)
Progressive disease	15 (34%)	47 (73,4%)
Disease control rate	29 (66%)	17 (26,5%)

Group A: patients treated with EC-GEMCAP
Group B: patients treated with gemcitabine/gemcitabine-based chemotherapy
Responses evaluated using RECIST v 1.1 criteria

Considering both clinical and radiological progression of disease, the DCR however remains meaning (58%). One patient with locally advanced disease had a partial response and underwent to radical surgery after 6 cycles of EC-GEMCAP therapy. All 50 patients were considered for survival analysis. Median PFS was 4,6 months (95% CI: 2.1-7.1) (Fig.1) with PFS rates at 6, 12 and 24 months of 46%, 22% and 10%, respectively. Median OS from diagnosis was 17,5 months (95% CI: 14.1-20,9) with OS rates at 6, 12 and 24 months of 96%, 82% and 36%, respectively (Fig.2). Median OS from the start of second-line therapy was 9,8 months (95% CI: 7.7-11.8) (Fig.3) with OS rates at 6, 12 and 24 months of 68%, 32% and 19%, respectively.

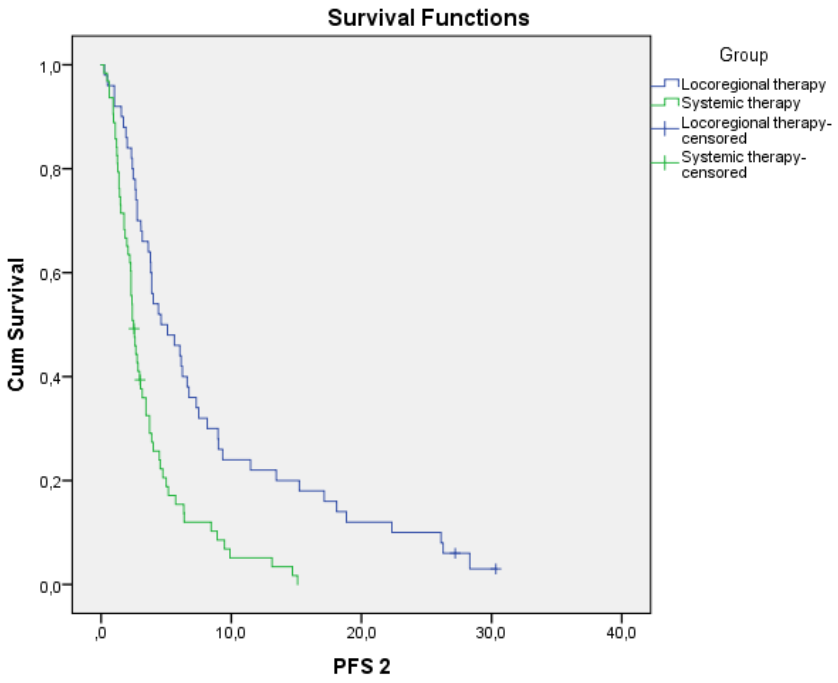

Figure 1: Progression free survival from second line (group A and B).

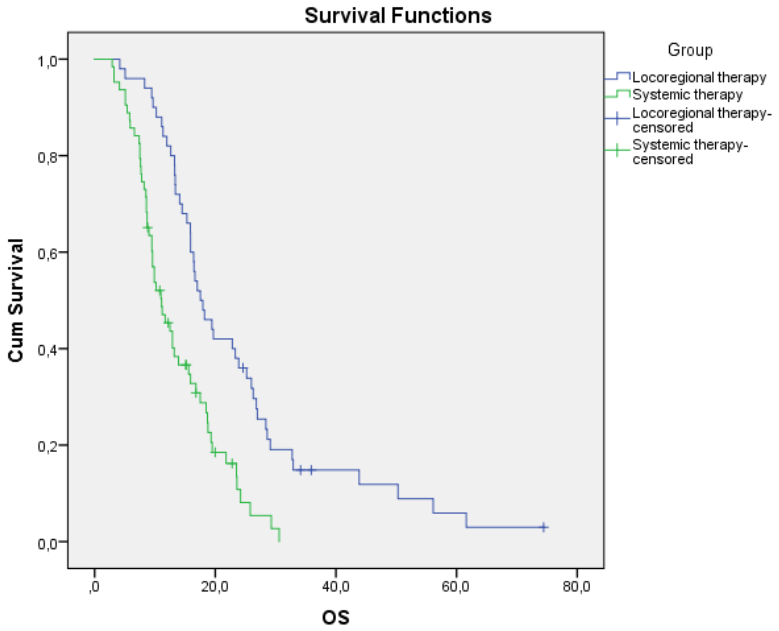

Figure 2: Overall Survival since diagnosis (group A and B).

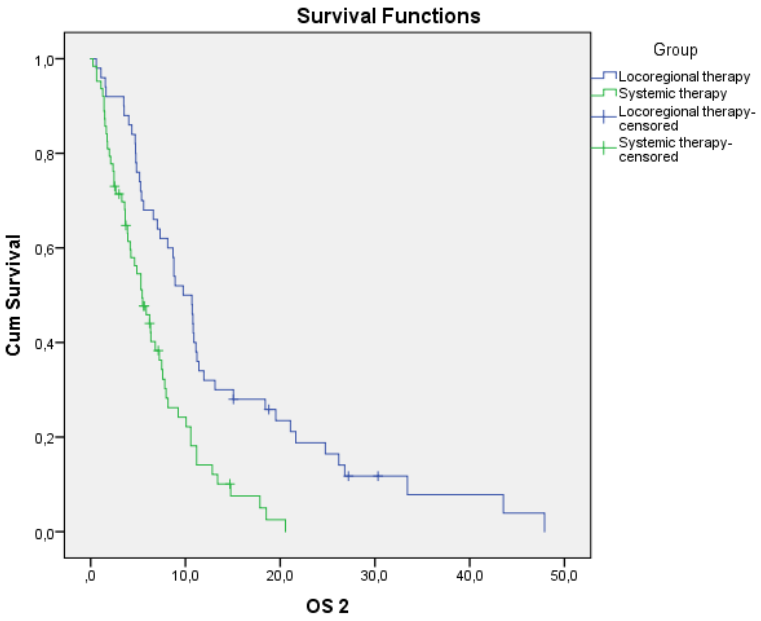

Figure 3: Overall Survival from second-line (group A and B).

Group B

Thirty patients (46,9%) received gemcitabine alone and 34 (53,1%) received a combination of gemcitabine plus nabpaclitaxel (21 patients, 32,8%), or plus capecitabine (9 patients, 14,1%), or plus platinum (oxaliplatin in 3 patients, 4,7%, and carboplatin in 1 patient, 1,5%).

Toxicities

All grade haematological toxicity was observed in 18,5% of patients, grade 3-4 in 7,7% (leucocytopenia 6,2%, anemia 1,5%). Fifty per cent of patients had non-haematological toxicity, grade 3-4 in 3,1% (fatigue 1,5%, neurotoxicity 1,5%).

Response and survival

Response to treatment by RECIST criteria was evaluated in all 64 patients. Stable disease was observed in 13 patients (20,3%), partial response in 4 patients (6,2%), with a disease control rate in 17 patients (26,6%) (Table 2). We have seen a better DCR for patients treated with gemcitabine-doublet chemotherapy, but the difference is not statistically significant (16,7% in gemcitabine alone versus 35,3% in gemcitabine-doublet, p = 0,07). Median PFS from the start of second-line treatment was 2,5 months (95% CI: 2,1-2,9) (Fig.1) with PFS rates at 6 and 12 months of 15% and 5%, respectively. Regarding OS from diagnosis, it was of 11,1 months (95% CI: 8,4-13,8) with OS rates at 6, 12 and 24 months of 86%, 45% and 11%, respectively (Fig.2). Median OS from the start of second-line chemotherapy was 5,4 months (95% CI: 3,8-7,1) (Fig.3), with OS rates at 6 and 12 months of 46% and 13%, respectively. Considering second-line gemcitabine or doublet, no major difference was detected in term of survival, with a median OS of 3,9 months (95% CI: 2,2-5,6) in gemcitabine group versus 6,8 months (95% CI: 4,6-9,0) in doublet group, respectively (p = 0,215).

Discussion

Recent studies confirmed the role of FOLFIRINOX and nab-paclitaxel plus gemcitabine regimens as standard first-line chemotherapy for metastatic pancreatic cancer patients, with a good performance status and not important comorbidity. Unfortunately, although the improvements in term of median overall survival (11,1 months for FOLFIRINOX and 8,5 months for nab-paclitaxel plus gemcitabine), most relapse or progression disease occurs within 6 months from chemotherapy end [8,9].

As reported by most important guidelines, a second-line chemotherapy can be an option for patients with good clinical conditions, considering previous treatments and any residual toxicity. Today, the dilemma of which is the best second-line treatment has not yet an answer [4, 5].

Many phase II or III studies have tested several drugs on second-line chemotherapy after gemcitabine-based treatment, such as 5-fluorouracil, oxaliplatin, irinotecan, docetaxel, cisplatin, liposomal irinotecan, capecitabine, gemcitabine, alone or in combination. They showed median PFS ranging from 1,5 to 5,1 months, and median OS from 3,3 to 9,9 months [10-16].

A recent meta-analysis considered 8 randomized studies of second-line chemotherapy after failure of gemcitabine, alone or in combination, for a total of 1587 patient. The second-line chemotherapy studied drugs were irinotecan, fluoropyrimidine, folinic acid and oxaliplatin, in various combinations. The results suggest that the use of irinotecan-fluoropyrimidine-folinic acid may offer a benefit in terms of both OS and PFS in patients naïve for these drugs [17)]

Similarly, Sonbol et al. performed a meta-analysis showing that the combination of various irinotecan formulations with fluoropyrimidine may be an appropriate second-line

chemotherapy, after gemcitabine-based treatment progression [4)]

Regarding second-line chemotherapy after FOLFIRINOX, in the Conroy and Coll. study 80 patients received gemcitabine (82,5%) or a gemcitabine-based chemotherapy (12,5%), while 85 patients in gemcitabine first line chemotherapy group received a second-line with FOLFOX (49,4%), or gemcitabine plus cisplatin (17,6%), or a regimen of fluorouracil and leucovorin plus cisplatin (16,5%), or FOLFIRINOX (4,7%). Interesting, no difference in median OS was noted between the groups (4,4 months in each arm) from the introduction of second-line therapy [8].

In 2015, Portal and Coll. reported results on 57 patients prospectively treated with nab-paclitaxel and gemcitabine after FOLFIRINOX failure. Treatment was stopped in 42 patients (74%) due to disease progression (40 patients) or unacceptable toxicity (2 patients). Grade 3-4 toxicities occurred in 21 patients (37%) and consisted mainly of haematological adverse effects or neurotoxicity. Thirty-eight patients (67%) had a transient or permanent dose reduction because of asthenia, haematological toxicities or peripheral neurotoxicity. Seven patients (12,5%) had to stop nab-paclitaxel permanently because of peripheral neurotoxicity, haematological toxicity or asthenia. As regard efficacy, a clinical response was observed in 19 patients (33%), clinical stability in 21 patients (37%) and clinical progression in 17 patients (30%). Nab-paclitaxel plus gemcitabine resulted in an improvement in pain and asthenia in 63% of patients. Median OS was 8,8 months and the OS rates at 6 and 12 months were, respectively, 69% and 15%. Median PFS was 5,1 months and the PFS rates at 6 and 12 months were, respectively, 39% and 6% [18].

In the same year, Zhang and Coll. have published data of a retrospective trial on 28 patients with metastatic or locally advanced unresectable pancreatic cancer, treated with nab-paclitaxel and gemcitabine schedule after FOLFIRINOX first-line failure. All patients started at a reduced dose of nab-paclitaxel and 13 patients started gemcitabine at a reduced dose as well, due to clinical condition or residual toxicity after FOLFIRINOX. Grade 3-4 haematological toxicities included neutropenia (17,9%), anemia (25%) and thrombocytopenia (25%). The median time to treatment failure was 2,8 months and the median OS was 5,5 months [19].

A french retrospective study in which 96 patients were treated with gemcitabine after failure of FOLFIRINOX, has demonstrated that gemcitabine is not beneficial in this setting, producing a median PFS of 2,1 months and a median OS of 3,7 months [20].

Caparello and Coll. conducted a prospective evaluation of a series of patients who underwent second-line chemotherapy after modified FOLFIRINOX. Only 71 patients (66%) were able to start a second-line treatment, with a combination regimen in 52% of the cases. Second-line chemotherapy did not provide such encouraging results, achieving a median PFS of only 2,5 months, a median OS of 6,2 months and even a low DCR of 34% [21].

Regarding our study, we retrospectively analysed data about a homogeneous group of 114 patients treated with FOLFIRINOX first-line chemotherapy. Of these patients, 11 also received loco-regional treatment (surgery, or radiotherapy alone, or radiotherapy associated to gemcitabine or radiofrequency ablation). At the progression disease, all patients underwent to second-line treatment, in particular: 50 patients were submitted to local-regional/systemic chemotherapy EC-GEMCAP regimen (group A) and 64 patients received gemcitabine alone or gemcitabine-based chemotherapy (group B).
The combined four-drug EC-GEMCAP regimen was firstly evaluated in a phase I study in which it resulted feasible and well tolerated. At the suggested doses, no grade 3-4 haematological and non-haematological toxicities were reported [22].

The same regimen was administered to 26 patients progressed to gemcitabine first-line treatment, in a phase II study. This four-drug approach obtained a DCR of 73% and a median overall survival of 11,6 months, with a six-months and one-year survival rate of 84% and 43%, respectively [23].

In 2016 we evaluated the combined EC-GEMCAP regimen in a group of patients who have failed first-line FOLFIRINOX chemotherapy. The 41 patients tolerated very well the treatment and had a DCR of 63% with a median PFS of 4,1 months and a median OS of 8,9 months, from the start of second-line treatment [7].

In our retrospective study, we have evaluated a group of 114 patients progressed to FOLFIRINOX fist-line therapy in order to compare EC-GEMCAP regimen with systemic chemotherapy in second-line treatment. Fifty patients underwent to EC-GEMCAP (group A) and 64 patients were submitted to systemic gemcitabine or gemcitabine-based treatment (group B).

For group A patients, we administered a total of 245 EC-GEMCAP cycles (with a median of 4 cycles per patient, range 1-15), with a fairly good tolerance (all grade haematological and non-haematological toxicities were 58% and 28%, grade 3-4 were 34%) and without dose reductions or delays. A DCR was obtained in 29 patients (66%) (table 2). One patient with locally advanced disease obtained a partial response to treatment and underwent to radical surgery after 6 cycles of EC-GEMCAP therapy. She died after 43,6 months from the star of second-line chemotherapy and 50,3 months from the diagnosis.
EC-GEMCAP is resulted to be superior to systemic chemotherapy in terms of both OS (9,8 months vs 5,4 months, p = 0,0001, Fig.3) and PFS (4,6 months vs 2,5 months, p = 0,0000478, Fig.1), with a rate of patients alive at 6, 12 and 24 months of 68%, 32% and 19% in group A, and of 46%, 14% and 0% in the group B; the rate of patients progression-free at 6, 12 and 24 months was 46%, 22% and 10% in the group A and of 15%, 5%, and 0% in the group B, respectively.

Considering all 114 patients, median OS from diagnosis were 15,3 months (range 2,9-74,4 months); patients alive at 6, 12 and 24 months were 90%, 61% and 22%. Comparing group, A versus group B, median OS from diagnosis were 17,5 months vs 11 months (p = 0,000061) (Fig.2), with a survival rate at 6, 12 and 24 months of 96% versus 86%, 82% versus 45% and 36% versus 11%, respectively. The significant benefit in term of survival was confirmed even in stage IV patients, with a median OS from diagnosis of 15,8 months versus 11 months (p = 0,00476).

We consider very interesting also the difference in survival seen in stage III patients: 11,4 months for group A and 5,3 months for group B (p = 0,001).

In conclusion, although our study has the limitation of being a retrospective analysis, second-line EC-GEMCAP treatment demonstrated its important activity and effectiveness in terms of OS, PFS and disease control rate towards standard chemotherapy, regardless of the stage (III vs IV).

Loco-regional/systemic chemotherapy was well tolerated, with toxicities easily managed, which has definitely helped to maintain a discreet ECOG PS during all treatment, avoiding the deterioration of general conditions that often lead to early discontinuation of therapy and bad prognosis.

Furthermore, the manageable toxicity profile means that it can be a viable second-line therapeutic alternative after FOLFIRINOX, also in patients without optimal general conditions.

On the basis of these results, considering the most effective therapeutic potential of new drugs, we have planned a prospective trial of chemotherapy with nab-paclitaxel plus gemcitabine or FOLFIRINOX as first-line chemotherapy, followed by second-line loco-regional/systemic EC-GEMCAP chemotherapy versus systemic chemotherapy, in metastatic pancreatic cancer patients.

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