Original Article

Prognostic factors in advanced pancreatic cancer patients receiving second-line chemotherapy: a single institution experience

Alessandro Bittoni, Chiara Pellei, Andrea Lanese, Riccardo Giampieri, Andrea D'Angelo, Enrica Giglio, Luca Cantini, Tania Meletani, Maria Giuditta Baleani, Rossana Berardi

Clinica Oncologica, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona, Ancona, Italy

Contributions: (I) Conception and design: A Bittoni, R Giampieri; (II) Administrative support: R Berardi; (III) Provision of study materials or patients: R Giampieri, L Cantini, E Giglio, A Lanese; (IV) Collection and assembly of data: C Pellei, A D'Angelo, MG Baleani, T Meletani; (V) Data analysis and interpretation: A Bittoni, R Berardi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rossana Berardi. Clinica Oncologica, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona, Via Conca 61, 60126 Ancona, Italy. Email: r.berardi@univpm.it.

Background: First-line chemotherapy in pancreatic ductal cancer has been shown to improve the survival and quality of life, while there is still no consensus concerning the role and the optimal regimen for second-line chemotherapy. The aim of our study was to identify prognostic factors that could predict which patients may receive benefit from second-line treatment.

Methods: Data regarding 144 patients, with progressive disease after first-line chemotherapy and measurable or evaluable disease, who received second-line chemotherapy were collected. The regimens included capecitabine, 5-fluorouracil (5-FU) or 5-FU based combinations, gemcitabine or gemcitabine-based combinations, nab-paclitaxel or taxanes. Prognostic variables examined were gender, ECOG PS, stage of disease, metastatic localization, presence or absence of peritoneal involvement, surgery on the primary tumor, age, hemoglobin levels (Hb), neutrophil-lymphocyte ratio (NLR), carbohydrate antigen 19-9 (Ca 19-9), lactate dehydrogenase (LDH), sodium (Na+) levels, mono-chemotherapy *vs.* combination therapy and PFS after first line chemotherapy.

Results: The median OS was 5.26 months (95% CI, 4.01–6.84 months) while median PFS was 2.76 months (95% CI, 2.50–3.22 months). At multivariate analysis, three clinical-laboratoristic features (ECOG PS, CA 19-9 value and LDH value) resulted significant independent prognostic factors for OS, with a hazard ratio (HR) respectively of 1.94 (95% CI, 1.18–3.19), 2.99 (95% CI, 1.37–6.54; P=0.006) and 2.10 (95% CI, 1.08–4.04; P=0.029). No significant impact on prognosis was observed for the other variables.

Conclusions: This study confirms the role of CA 19-9 in second line setting and highlights the potential role of LDH, as a prognostic relevant factor in this disease. Main limitation of the study is the small percentage of patients treated in first line with intensified regimens such as FOLFIRINOX or gemcitabine and nab-paclitaxel.

Keywords: Carbohydrate antigen 19-9 (CA 19-9); lactate dehydrogenase (LDH); pancreatic cancer; second-line chemotherapy; prognostic factor

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth highest cause of cancer-related death among men and women in the US and continues to have the worst prognosis of all the gastrointestinal malignancies. Because of its aggressive growth and early metastatic dissemination, the overall 5-year survival rate for patients with pancreatic cancer remains around 3–5%; in fact, death rates from 2010 to 2014 increased in particular for men (1). The use of palliative first-line chemotherapy has been shown to improve the survival and quality of life compared with best supportive care (BSC) in patients with good performance status, although the survival gain was modest (2). The FOLFIRINOX regimen, including 5-fluorouracil (5-FU), oxaliplatin and irinotecan (3), and the combination of nab-paclitaxel with gemcitabine (4) in first-line setting provide more effective treatment options, in particular for the patients with a good performance status but there is currently no consensus concerning the role and the optimal regimen for second-line chemotherapy after first-line chemotherapy treatment failure. In the light of such bleak statistics, it is important to select subgroups of patients with metastatic or recurrent pancreatic adenocarcinoma that could benefit from second-line chemotherapy in order to maximize benefit and avoid over-treatment in frail patients. The aim of our study was to identify prognostic factors that could predict which patients may receive the maximum benefit of second-line treatment.

Methods

The study included patients with a cytological or histological diagnosis of ductal pancreatic adenocarcinoma who received second-line chemotherapy at the Department of Oncology of AOU Ospedali Riuniti–Università Politecnica delle Marche from January 2002 to December 2016 and who were then followed on a regular basis in a specific follow-up program, based on the evaluation of routine blood tests, CEA and carbohydrate antigen 19-9 (CA 19-9) biomarkers for each chemotherapy cycle and 3-month-cyclic instrumental re-evaluation (by TC Chest/Abdomen with contrast or TC Chest without contrast + RMN abdomen with contrast). The inclusion criteria for the study included progressive disease after first-line chemotherapy and presence of measurable or evaluable disease. Recorded patient characteristics and clinical features included: gender, age, sex, weight, risk factors (smoking status), symptoms (pain, jaundice), Eastern Cooperative Oncology Group Performance Status (ECOG PS), type of surgery (when performed), histological type, grading, pathological stage of disease (T, N, M), presence or absence of peritoneal involvement, value of tumor markers CA19-9 (NL <5 ng/mL) and CEA (NL <37 U/mL), dates of chemotherapy and radiotherapy, response to first line chemotherapy and clinical benefit, and time to progression, hemoglobin levels (Hb), neutrophil-lymphocyte ratio (NLR), CA 19-9, lactate dehydrogenase (LDH), sodium (Na+) levels, mono-chemotherapy *vs.* combination therapy and PFS after first line chemotherapy (more *vs.* less than 4 months). The upper limit of normal (ULN) was 250 UI/L for LDH and 35 UI/mL for CA 19-9. The cut-off chosen to determine high NLR was 5, as already tested in similar studies on advanced pancreatic cancer (5). Data were retrieved from institutional database and patients' clinical records. The study was approved by local ethics committee (AOU Ospedali Riuniti, No. 214341).

Statistical analysis

Primary endpoint of this study was to evaluate the prognostic role of clinical and biological factors in patients with advanced pancreatic cancer who received second-line chemotherapy. Overall survival (OS) was defined as the time between the start of second-line chemotherapy and the date of death; progression-free survival (PFS) was defined as the time from the date of second-line chemotherapy to the date of disease progression or death from any cause. The association between categorical variables was estimated by χ^2 test. Survival distribution was estimated by the Kaplan-Meier method. Significant differences in probability of surviving between strata were evaluated by log-rank test. Variables that achieved statistical significance ($P<0.05$) for univariate analysis were used for multivariate analysis by Cox's multiple regression to identify independent prognostic factors. The hazard ratio (HR) was also calculated. The statistical analysis was conducted using the MedCalc version 14.10.2 for Windows software.

Results

Three hundred and thirty-three advanced PDAC patients were treated with first-line chemotherapy from January 2002 to December 2016. One hundred and forty-four patients (43.2%) received second-line chemotherapy and were included in this retrospective study. Median age of the

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Table 1 Baseline tumor and patients' characteristics

Patients' characteristics	No. of patients (%), (total=144)
Age, median [range] (years)	62 [31–81]
Sex	
Male	90 [63]
Female	54 [37]
ECOG PS	
0	63 [44]
1	57 [40]
2	24 [16]
Site of metastases	
Loco-regional	23 [16]
Distant metastases	121 [84]
Previous treatment	
Surgery on primitive	62 [43]
Radiotherapy	38 [26]
Chemotherapy	144 [100]
G	25 [17]
G + P/O	62 [43]
G + P + X	8 [6]
FOLFIRINOX	15 [10]
G + nab-PC	4 [3]
G + P	26 [18]
Others	4 [3]
Smoking status	
Current smokers	37 [25.7]
Never smokers or former smokers	107 [74.3]
Pain	
No	81 [56.2]
Yes	63 [43.8]
CA 19-9 (UI)	
Normal/> ULN/unknown	23 [16]/108 [75]/13 [9]
Median	950

ECOG PS, Eastern Cooperative Oncology Group Performance Status; G, gemcitabine; P/O, cisplatin/oxaliplatin; G+P+X, gemcitabine + paclitaxel + capecitabine; FOLFIRINOX, 5-fluorouracil, Irinotecan, Oxaliplatin; nab-PC, nab-Paclitaxel; PFS, progression free survival; CA 19-9, carbohydrate antigen 19-9; ULN, upper limit of normal.

patients was 62 years (range, 31–81 years). Ninety patients (63%) were male and 54 (37%) female. ECOG performance status was 0 in 63 patients (44%) and 1 or 2 in the remaining 81 patients. *Table 1* summarize patients' clinical and pathological characteristics. Most of the patients received first-line treatment with gemcitabine-based regimens (70%) while 10% received FOLFIRINOX chemotherapy. Second line chemotherapy regimens included capecitabine, 5-FU or 5-FU based combinations, as FOLFOX (5-FU, leucovorin and oxaliplatin) or FOLFIRI (5-FU, leucovorin and irinotecan) regimens. A significant proportion of patients, in particular those treated with FOLFIRINOX or with a long PFS to first-line gemcitabine-based treatment, received gemcitabine or gemcitabine-based combinations. A small percentage of patients were treated with nab-paclitaxel or taxanes. Median PFS for second line treatment was 2.76 months while median OS was 5.26 months. *Table 2* summarizes second line regimens used and patients' outcome. The median OS was 5.26 months (95% CI, 4.01–6.84) (*Figure 1*) while median PFS was 2.76 (95% CI, 2.50–3.22) (*Figure 2*).

Prognostic variables were selected based on those identified in previous studies on the same setting (6-8) and their prognostic role was analyzed. The variables examined were gender, ECOG PS, stage of disease, metastatic localization, presence or absence of peritoneal involvement, surgery on the primary tumor, age, smoking status, pain, hemoglobin levels (Hb), NLR, CA 19-9, LDH, sodium (Na+) levels, mono-chemotherapy *vs.* combination therapy and PFS after first line chemotherapy (more *vs.* less than 4 months). The ULN was 250 UI/L for LDH and 35 UI/mL for CA 19-9. The optimal cut-off value for NLR was determined using time-dependent receiver operating curve (ROC) analysis. The NLR value was categorized in two groups, NLR ≤2.5 and NLR >2.5. At univariate analysis, 6 out of these 16 clinical-laboratory features showed a significant correlation with OS. In particular ECOG PS was found to be a significant prognostic factor (ECOG 0 *vs.* 1–2; median OS =8.55 *vs.* 3.42 months, respectively; HR 0.47; 95% CI, 0.28–0.64; P<0.0001). Also, PFS to first line chemotherapy was significantly related to OS (median OS of 6.84 *vs.* 4.14 months in patients with first-line PFS more than 4 months *vs.* less than 4 months respectively, HR 1.48; 95% CI, 1.02–2.16; P=0.035). Furthermore, patients with a single metastatic site had median OS of 6.77 *vs.* 3.91 months for multiple site of metastases (HR 0.65; 95% CI, 0.39–0.96; P=0.032). Again, NL ratio showed a correlation with OS (NL ≤2.5 ratio *vs.* NL >2.5; median OS =7.33 *vs.*

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Table 2 Correlation between second-line regimens and patients' outcomes

Regime	No. of patients	CR/PR (%)	SD (%)	mOS (months)	1-year OS (percentage)
Capecitabine	22	0	4 [18]	3.1	46
de Gramont	3	0	0	2.8	0
FOLFIRI	26	1 [4]	7 [27]	5.6	23
FOLFOX	2	0	0	6.8	0
Gemcitabine	26	0	6 [23]	5.9	27
G + F	4	0	0	4.9	25
G + nab-PC	6	1 [17]	1 [17]	5.5	40
G + P/O	16	1 [6]	2 [13]	6.4	20
GTX	6	0	0	5.9	16
nab-PC	2	0	0	7.2	33
XELIRI	4	0	1 [25]	5.7	0
XELOX	2	0	0	2.1	0
Others	24	0	1 [4]	3.7	25

CR/PR, complete response/partial response; SD, stable disease; mOS, median overall survival; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; G+F, gemcitabine + 5-fluorouracil; G + nab-PC, gemcitabine + nab-paclitaxel; G+P/O; gemcitabine + cisplatin/oxaliplatin; GTX, gemcitabine + docetaxel + capecitabine; XELIRI, capecitabine, irinotecan; XELOX, capecitabine, oxaliplatin.

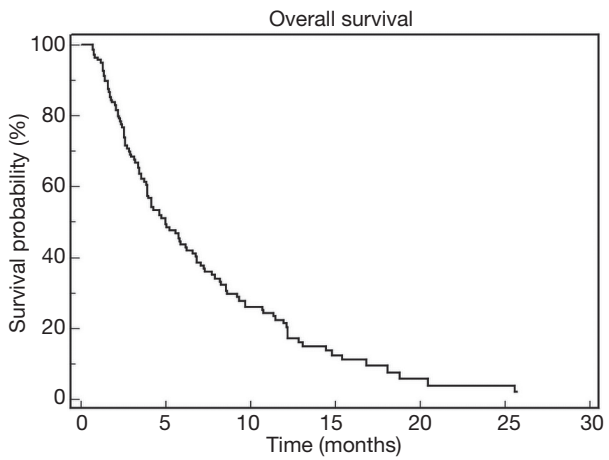

Figure 1 Kaplan-Meier curve for overall survival.

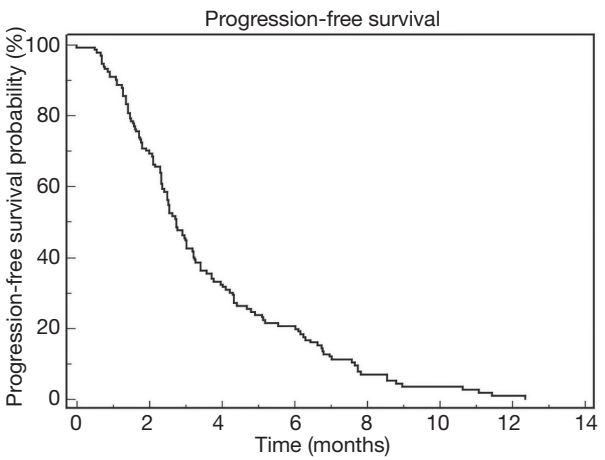

Figure 2 Kaplan-Meier curve for progression-free survival.

4.14 months, respectively; HR 0.55; 95% CI, 0.34–0.81; P=0.003), as well as CA 19-9 (CA 19-9 <10 *vs.* >10 ULN; median OS =10.72 *vs.* 3.91 months, respectively; HR 0.39; 95% CI, 0.24–0.55; P<0.0001). LDH level also was significantly associated with prognosis (LDH < ULN *vs.* LDH > ULN, 10.72 *vs.* 4.77 months; HR 0.49; 95% CI, 0.33–0.87; P=0.011). Conversely, no significant impact on prognosis was observed for age, serum levels of Na+ and Hb. Patients who underwent surgical resection of primary tumor did not have a better survival than patients with non-resectable disease at diagnosis. At multivariate analysis, three clinical-laboratoristic features, in particular ECOG PS (HR =1.94; 95% CI, 1.18–3.19; P=0.009), CA 19-9 value (HR =2.99; 95% CI, 1.37–6.54; P=0.006) and LDH

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value (HR =2.10; 95% CI, 1.08–4.04; P=0.029), resulted significant independent prognostic factors for OS (*Table 3*).

Discussion

In therapeutic guidelines for the treatment of advanced PDAC, the administration of second line chemotherapy after disease progression under first line treatment is currently recommended (9). However, the real benefit of second line chemotherapy in the palliative treatment of PDAC remains controversial and the choice of second line treatment is still a matter of debate (10). According to literature data, the benefit of second line chemotherapy in terms of OS seems to be marginal and there is no consensus on an optimal regimen to be administered (11-13). A phase III study from CONKO group, published in 2011, was the first to demonstrate a benefit for second line treatment with a regimen based on 5-FU, oxaliplatin and leucovorin (OFF regimen) *vs.* BSC with a median OS of 4.8 months for chemotherapy *vs.* 2.3 months for BSC (12). Recently the phase III NAPOLI-1 trial evaluating a combination of 5-FU and nanoliposomal irinotecan (nal-IRI) in second line showed interesting results, demonstrating a median OS of 6.1 months, introducing a new treatment option in this setting (14). Overall, these results indicate that second-line treatment may provide a clinical benefit in patients with advanced pancreatic cancer as confirmed in a systemic analysis of 34 second-line studies, including over 1,500 patients who had progressed on gemcitabine, reporting a median OS of 2.8 months for patients who received BSC and 6 months for patients who received second-line treatment (13). The choice of second-line regimen in clinical practice depends upon the first-line regimen used, the patients' ECOG PS, residual toxicities and comorbidities. Moreover, in this very palliative setting it must be remembered that toxicities and quality of life are of paramount importance. In this scenario, prognostic factors able to help in selection of patients who are more likely to receive a benefit from second line chemotherapy is really important in daily practice. This retrospective analysis aims to identify prognostic factors related to the patient and the disease for the choice of second line chemotherapy of advanced PDAC. Indeed, as mentioned above, identification of prognostic variables can be an important aid to the clinician in the choice of patients to treat after progression to first-line chemotherapy. At the same time, validated prognostic factors to stratify patients in clinical trials in the setting of second line chemotherapy may be particularly useful. In our study ECOG PS, CA 19-9 and LDH value were demonstrated to be

Table 3 Multivariate analysis of prognostic factors associated with OS

Characteristics	N pts	UVA		mOS (months)	MVA	
		HR	P		HR	P
Gender						
Male	89	1.14 (0.78–1.66)	0.49	–	–	–
Female	53			–		
ECOG						
0	60	0.47 (0.28–0.64)	<0.0001	8.55	1.94 (1.18–3.19)	0.009
1–2	71			3.42		
PFS (first line CT)						
≥4 months	66	1.48 (1.02–2.16)	0.035	6.84	0.72 (0.38–1.37)	0.32
<4 months	75			4.14		
Stage						
Loco-regional relapse	23			–	–	–
Distant metastases	121	1.08 (0.67–1.76)	0.74	–		
N° sites of metastases						
1	70	0.65 (0.39–0.96)	0.032	6.77	0.88 (0.47–1.65)	0.69
>1	51			3.91		

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristics	N pts	UVA		mOS (months)	MVA	
		HR	P		HR	P
Peritoneal carcinosis						
Present	9	0.66 (0.26–1.38)	0.23	–	–	–
Absent	106			–		
Surgery on primary tumor						
Yes	61	0.84 (0.57–1.21)	0.34	–	–	–
No	80			–		
Age						
>75 years	9	0.99 (0.36–2.74)	0.99	–	–	–
<75 years	133			–		
Hemoglobin						
>12 g/dL	28	0.62 (0.35–1.13)	0.11	–	–	–
<12 g/dL	45			–		
Neutrophil/lymphocyte ratio						
>2.5	46	0.55 (0.34–0.81)	0.003	4.14	1.41 (0.76–2.62)	0.27
≤2.5	71			7.33		
CA 19-9						
>10 ULN	81	0.39 (0.24–0.55)	<0.0001	3.91	2.99 (1.37–6.54)	0.006
<10 ULN	45			10.72		
LDH						
>ULN	67	0.49 (0.33–0.87)	0.011	4.77	2.10 (1.08–4.04)	0.029
<ULN	36			10.72		
Na^+						
>ULN	102	0.61 (0.26–1.14)	0.10	5.00	–	–
<ULN	14			2.60		
Monotherapy *vs.* combination therapy						
Mono therapy	51	0.84 (0.57–1.23)	0.84	–	–	–
Combination therapy	91			–		
Pain						
Yes	63	1.68 (0.81–1.94)	0.13	–	–	–
No	81			–		
Smoking status						
Current smokers	37	0.88 (0.45–1.76)	0.47	–	–	–
Never or former smokers	107			–		

HR, hazard ratio; UVA, univariate analysis; MVA, multivariate analysis; LDH, lactate dehydrogenase; mOS, median overall survival.

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significant prognostic factors for OS in this setting.

A similar study by Sinn *et al.* (15) on 208 advanced PDAC patients who received second line chemotherapy showed that poor KPS (Karnofsky Performance Status), CA 19-9 and duration of first-line treatment were prognostic factors associated with OS. These results are comparable to what observed in our analysis. However, in our study the prognostic value of duration of first-line chemotherapy was not confirmed as an independent prognostic factor at multivariate analysis. In a large retrospective analysis by Vienot *et al.* on 261 advanced PDAC patients treated with second line chemotherapy, age, smoking status, liver metastases, performance status, pain, jaundice, ascites, duration of first-line, and type of chemotherapy regimen were identified as prognostic factors for OS. Interestingly, the authors developed a prognostic model which allowed to identify three risk groups (low, intermediate and high risk) with different survival (16). Performance status and duration of first-line chemotherapy were confirmed as prognostic factor also in our study, while age, pain and smoking status were not found to be significantly associated with prognosis in our analysis.

Another study by Kasuga *et al.* (17) assessed prognostic factors in second line treatment in 61 patients gemcitabine refractory patients. Interestingly, the study showed significant prognostic value for ECOG PS and CA 19-9 as in our analysis. The prognostic role of ECOG PS in this setting has been confirmed also in a recent systematic review and meta-analysis of randomized controlled trials in PDAC (18). In addition, the study also demonstrated prognostic value of modified Glasgow prognostic score (mGPS), an inflammation-based prognostic score based on C-reactive protein and albumin. In our study, a different inflammation biomarker, namely NLR, was found to be related to poor prognosis at univariate analysis but this was not confirmed at multivariate analysis.

Inflammation response in tumor microenvironment has several tumor promoting effects including inhibition of apoptosis or enhancement of angiogenesis and multiple clinical studies have demonstrated negative prognostic factors for inflammation-related biomarkers in different tumors, including advanced chemotherapy refractory PDAC (19).

It is to notice that the variables analyzed in our study can be easily determined and, in particular, LDH and CA 19-9, are part of routine laboratory evaluations. CA 19-9 is the most extensively studied and validated biomarker in PDAC. In a large meta-analysis, Ballehaninna *et al.* (20) concluded that normal (<37 U/mL) or moderately elevated pre-operative CA 19-9 serum levels (<100 U/mL) independently predict improved OS, whereas elevated Ca19-9 serum levels (>100 U/mL) were associated with a poor prognosis. Moreover, CA 19-9 has already been identified as a potential independent prognostic factor also in PDAC patients receiving second-line chemotherapy (6,21).

With regard to the LDH, the upper limit of the standard (250 U/L) was defined as cut-off for this study and was found to be significantly associated to median OS in both univariate and multivariate analysis. To date there are only a few reports that describe the potential prognostic role of LDH in patients with pancreatic cancer. A retrospective analysis on 127 pancreatic cancer patients, including 56 patients with metastatic disease, demonstrated a significant prognostic value of LDH levels in metastatic setting. In particular LDH high value was associated with shorter OS when compared to normal values (10 *vs.* 39 months, P=0.0001) in this study and prognostic value was also confirmed at multivariate analysis. However, in this study no data about second line chemotherapy were available (22). In our study ECOG PS, duration of PFS to first-line chemotherapy, single metastatic site, NLR, CA 19-9 and LDH showed significant correlation with the median OS at univariate analysis. High levels of LDH and CA 19-9 as well as ECOG PS remained independent prognostic factors for OS also at multivariate analysis. Meta-analysis (23) of two international phase III studies in which 34 prognostic factors, including CA 19-9 and LDH, evaluated in 436 metastatic patients treated with gemcitabine-based chemotherapy showed that serum CA 19-9 (HR =1.38; 95% CI, 1.12–1.70, P=0.028) and LDH levels (HR =2.08; 95% CI, 1.50–2.88, P<0.001) were highly significant prognostic factors. However even in this study there were no data about second line chemotherapy. Contrary to other prospective studies (7,8,21,24) NLR demonstrated no independent prognostic value in our analysis. Also, Maréchal *et al.* (25) reported that ECOG performance status and albumin level were independent prognostic factors in chemo-naive and gemcitabine refractory patients with advanced pancreatic cancer. Indeed, a poor performance status associated with high CA 19-9 value and LDH may reflect an inherent aggressiveness of pancreatic cancer, an increased disease burden and may also be related to the inability to complete the prescribed treatment. Moreover, association between high LDH serum levels and tumour angiogenesis may also explain the prognostic role of LDH in PDAC such as in different solid tumors including for example biliary tract cancer (26) considering that tumor angiogenesis and tumour-induced hypoxia are in fact usually related to poor prognosis and clinical outcome. This monocentric study cannot be exempt from the limits derived mainly from his retrospective nature. Another limit is the heterogeneity of the

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chemotherapy regimens used, that were chosen by the treating oncologist on the basis of clinical factors, as well as the lack of patients treated with innovative cytotoxic agents that showed promising results in second-line setting, for example irinotecan nanoliposomal, which has been shown to significantly prolong median OS in combination with 5-FU in pretreated advanced pancreatic cancer patients. Moreover, not all potential prognostic factors emerging from scientific literature such as reactive protein C, uric acid (27), and coagulation factors (28) have been taken into account. However, this retrospective study, despite its inherent intrinsic limitations, confirms the important role of CA 19-9 as biomarker in advanced pancreatic cancer also in second line setting and highlights the potential role of another serum marker, LDH, as a prognostically relevant factor in this disease. It is therefore a further confirmation of how prognostic and predictive factors can play a crucial role in improving outcome in second line setting after the failure of first-line chemotherapy. It can also be a valuable tool for future stratification procedures in clinical trials and for selection of high and low risk patients in different therapeutic strategies. Patient selection could be the key to maximizing the benefits of available therapeutic options. However, these results should be confirmed in prospective trial of second-line chemotherapy for advanced PDAC. Such prospective studies should be large-scale, with homogeneous disease stages and standardized cutoff levels to facilitate comparative analysis of results, determine the exact role of these variables in terms of clinical significance and facilitate an appropriate evaluation of new therapeutic strategies.

Conclusions

Our study shows that three clinical-laboratoristic features (ECOG PS, CA 19-9 value and LDH value) may be significant independent prognostic factors for OS in evaluation of second-line chemotherapy in pancreatic cancer. No significant impact on prognosis was observed for the other variables evaluated [gender, stage of disease, metastatic localization, presence or absence of peritoneal involvement, surgery on the primary tumor, age, hemoglobin levels, NLR, sodium (Na+) levels, mono-chemotherapy *vs.* combination therapy and PFS after first line chemotherapy].

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Footnotes

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.08.34). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were retrieved from institutional database and patients' clinical records. The study was approved by local ethics committee (AOU Ospedali Riuniti, No. 214341). Informed consent was waived.

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