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Phytosome complex of curcumin as complementary therapy of advanced pancreatic cancer improves safety and efficacy of gemcitabine: Results of a prospective phase II trial

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ABSTRACT

A large body of biomedical evidence indicates that activation of Nrf2 by curcumin increases the nucleophilic tone and damps inflammation cumulatively supporting the malignant phenotype. Conversely, genetic analyses suggest a possible oncogenic nature of constitutive Nrf2 activation since an increased nucleophilic tone is alleged increasing chemoresistance of cancer cells. Aiming to contribute to solve this paradox, this study addressed the issue of safety and efficacy of curcumin as complementary therapy of gemcitabine on pancreatic cancer. This was a single centre, single arm prospective phase II trial. Patients received gemcitabine and Meriva®, a patented preparation of curcumin complexed with phospholipids. Primary endpoint was response rate, secondary endpoints were progression free survival, overall survival, tolerability and quality of life. Analysis of inflammatory biomarkers was also carried out. Fifty-two consecutive patients were enrolled. Forty-four (13 locally advanced and 31 metastatic) were suitable for primary endpoint evaluation. Median age was 66 years (range 42–87); 42 patients had Eastern Cooperative Oncology Group performance status 0–1. The median number of treatment cycle was 4.5 (range 2–14). We observed 27.3% of response rate and 34.1% of cases with stable disease, totalizing a disease control rate of 61.4%. The median progression free survival and overall survival were 8.4 and 10.2 months, respectively. Higher IL-6 and sCD40L levels before treatment were associated to a worse overall survival ($p < 0.01$). Increases in sCD40L levels after 1 cycle of chemotherapy were associated with a reduced response to the therapy. Grade 3/4 toxicity was observed (neutropenia, 38.6%; anemia, 6.8%). There were no significant changes in quality of life during therapy. In conclusion, the complementary therapy to gemcitabine with phytosome complex of curcumin is not only safe but also efficiently translate in a good response rate in first line therapy of advanced pancreatic cancer.

Abbreviations: CM, complementary medicine; CT, computerized tomography; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30; FDA, Food and Drug Administration; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin, and fluorouracil; GEM, gemcitabine; Nab-P + G, nanoparticle albumin-bound paclitaxel and GEM; NF-κB, nuclear factor-kappa B; NRM, Nuclear Magnetic Resonance; OS, overall survival; PC, pancreatic cancer; PFS, progression free survival; QoL, quality of life; RR, response rate

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1. Introduction

Pancreatic cancer (PC), a big killer in medical oncology, is the fourth cause of cancer-related death. The median overall survival (OS) of patients treated with gemcitabine (GEM) as a single agent is 5.7 months [1], and the recently introduced combination of nanoparticle albumin-bound paclitaxel and GEM (nab-P + G) increases the OS to rates ranging from 8.5 to 10.7 months [2–4]. Although the increased toxicity profile, this combination has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as first line treatment for locally advanced and metastatic PC [5].

Millions of cancer patients use complementary medicine (CM), principally during chemotherapy with the intent to ameliorate the symptom control and compliance of therapies [6–8]. Nutritional supplement or specific foods known for a suitable anti-cancer effect [9] are eligible for the use as CM.

Curcumin, the most abundant polyphenolic compound among curcuminoids present in Curcuma longa, a plant used as spice in Asian countries, and as a relevant component of Ayurvedic medicine, has anti-inflammatory, and potential anticancer properties [10–18].

Compelling evidence indicates that curcumin, besides showing positive effects in vitro and animals models (almost 10.000 refs in PubMed) is also bioavailable in humans, at least when administered is specific formulations such as in a form complexed with lipids [19–21].

Used as food supplement, curcumin is safe, while just a grade 1–2 diarrhea and nausea has been reported after ingestion of daily doses up to 8000 mg used in clinical trials [22].

Recent critical reviews of the paradoxical mechanism of nutritional antioxidants activating Nrf2, suggested that curcumin contributes to support the homeostasis between inflammation and its negative feedback regulation [23,24]. This complies with the observation that curcumin suppress cell proliferation and induce regulated cell death, seemingly by inhibiting the nuclear factor-kappa B (NF-κB) [25] through the decreased activity of IKK and Akt [26]. This is expected to have an impact on several inflammation-related markers [27,28] while also accounting for the regulation of immune response mediated through the transcriptional regulation of inflammatory cytokines [29,30].

This hypothesis is supported by recent evidence from meta-analyses of randomized controlled trials suggesting a significant effect of curcumin in lowering circulating inflammatory cytokines levels, an effect more evident in patients with higher degrees of systemic inflammation [31,32].

Besides this evidence, it has been shown that in PC cells curcumin potentiates the anticancer activity of GEM via inhibition of NF-κB, proliferation, angiogenesis and expression of Cdc20, which is associated to enhanced cell proliferation and invasion [33,34]. Although all these effects can be rationalized by the increase of nucleophilic tone due to Nrf2 activation, this has been also alleged as detrimental for cancer therapy. Genetic studies on some cancers, indeed, point out constitutive Nrf2 activation as a possible cause of an increased resistance to chemotherapy [35,36]. This paradoxical dual function of Nrf2 in cancer has been critically discussed considering the relevance of the context of the experimental approaches leading to seemingly conflicting data [36,37]. Notably, also the difference has to be considered between constitutive activation and functional regulation through nucleophilic tone.

The present phase II clinical study was aimed to contribute to solve this issue. The study was designed to test the safety and activity of curcumin as nutritional complement to GEM in patients affected by locally advanced or metastatic PC. We used a formulation of a curcuminoid mixture with soy lecithin at a weight ratio 1:2, patented as Meriva® by Indena S.p.A.

Besides clinical evidence, we also investigated the role of inflammation asking whether circulating inflammation-related biomarkers [38–42] can predict the outcome of the disease.

Results clearly indicate that the use of curcumin as Meriva® is safe and increases the efficiency of GEM translating in a response rate (RR) in the first line therapy of advanced PC superior to that described to GEM as single agent and similar to that produced by the more toxic treatment with nab-P + G.

2. Patients and methods

2.1. Patient selection

This study was a prospective phase II, single arm, single center trial. The study was conducted in accordance with Helsinki Declaration and was approved by the Local Ethics Committee. All patients provided written informed consent before study participation. Previously untreated patients were eligible if they met following inclusion criteria: cytologically or histologically confirmed locally advanced or metastatic PC; previous adjuvant treatment (chemotherapy, radiotherapy) completed at least six months prior to data collection; age > 18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; life expectancy > 12 weeks; adequate blood cell counts (neutrophil count $> 1.5 \times 10^9$L, platelet count $> 100 \times 10^9$ L, hemoglobin > 9 g/dL), adequate hepatic function (bilirubin ≤ 3 mg/dL, alanine aminotransferase and aspartate aminotransferase levels up to 2.5x the institutional national limits); adequate renal function (creatinine ≤ 2 mg/dL); ability to answer European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) questionnaire [43]. Exclusion criteria included concurrent malignancies except cancer of uterine cervix, basal and squamous cell skin cancer, known presence of central nervous system metastases, intercurrent significant systemic illness (infection, cardiac and renal diseases).

2.2. Treatment protocol

Treatment consisted of GEM 10 mg/m^2/min infused over 100 min and diluted in 500 mL normal saline on days 1, 8, 15 in the dose-intense schedule [44] and Meriva® 2000 mg/die continuously (4 capsules, each of 500 mg, every day). Each cycle was given every 28 days.

The pretreatment evaluation included: physical examination; Computerized Tomography (CT) or Nuclear Magnetic Resonance (NMR) imaging scan of chest, abdomen, pelvis; full blood counts, hepatic and renal function tests, glucose, electrolytes, and CA 19-9.

Quality of life (QoL), physical examinations, full blood counts and CA 19-9 were recorded before the beginning of each study cycle; CT or NMR scans and QoL assessment were performed every 3 months. Follow-up evaluations included physical examination, blood chemistry and CT or NMR imaging scan every two months. Response and progression were evaluated using the RECIST 1.1 criteria [45]. Treatment was continued until progression, chemotherapy delay > 2 weeks, unacceptable toxicities, patient refusal. Meriva® was continued after completion of nine cycles. Premedication included dexamethasone 8 mg or metoclopramide 10 mg, intravenously.

2.3. Correlative study on inflammation-related biomarkers

Blood was drawn from 34 patients for the determination of inflammation-related biomarkers before starting therapy (baseline) and during the treatment (at the end of any 28-day treatment cycle until patient progression). Aliquots of serum and EDTA plasma samples were stored at −80 °C until analysis. Plasma CRP levels were measured by immuno-turbidimetric method using the automated analyzer AU 5822 (Beckman Coulter Inc, CA, USA). Serum sCD40L levels were measured by Quantikine Human CD40 Ligand/TNFSF5 Immunoassay (R&D Systems Inc., MN, USA). Serum cytokines (IL-8, IL-6 and MIP-1) and adhesion molecules (sE-selectin, VCAM-1, ICAM-1) levels were measured using the multiplexing (xMAP) technology with Magnetic Luminex Assays (R&D Systems Inc., MN, USA), respectively: Human Cytokine Premixed Kit A Performance Assay and Human Premixed

Multi-Analyte Kit Screening Assay. All assays were performed following the manufacturer's instructions. All samples were analyzed in duplicates and the researcher was blinded to outcome group. The lower limits of the assay sensitivity were as follows: CRP, 1 mg/L; sCD40L, 4.2 pg/mL; IL-8, 1.8 pg/mL; IL-6, 1.7 pg/mL; MIP-1α, 16.2 pg/mL; sE-selectin, 0.1 ng/mL; VCAM-1, 0.24 ng/mL, ICAM-1, 0.09 ng/mL. The intra and inter-assay coefficient of variation were < 3% for CRP, < 10% for ELISA and < 20% for multiplex analysis.

2.4. Toxicity evaluation and dose modification

All patients who received at least one dose of treatment were considered evaluable for safety. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 [46].

On day 1, the patient was required to have an absolute neutrophil count ≥1500 and platelets ≥100,000 to receive treatment. The dose of GEM was reduced by 25% in case of grade 2–3 thrombocytopenia or neutropenia, and it was discontinued if patients developed a grade 4 hematologic toxicity. Treatment of common adverse effects seen with this regimen was allowed using standard interventions.

2.5. Statistical analysis

The primary endpoint was the response rate (RR). Sample size was calculated to reject a 10% RR in favor of a target RR of 25%, with a significance level of 0.05 and a power of 80% by using Simon 2-stage design [47]. In the initial stage, a total of 18 assessable patients were evaluated for response. If > 2 responses were observed, then 25 additional patients were selected to enter the second stage to achieve a sample size of at least 44 patients.

Secondary objectives included overall progression free survival (PFS), OS, tolerability, QoL and inflammatory biomarkers. PFS was calculated from the start of therapy until tumor progression in any site or death in the absence of progressive disease. OS was calculated from the start of therapy to the date of death. The Kaplan-Meier method was used for survival analysis. Survival curves were compared using Log Rank (Mantel-Cox) test. Uni-variate, followed by multi-variate analyses, were performed using a Cox regression model with a backward selection procedure, and independent prognostic factors of OS were identified. For multivariate analysis, basal median levels of biomarkers were used as cutoff value to enable the analysis of biomarkers as dichotomized variables. Mann–Whitney *U* test was used to assess differences in basal biomarker levels between groups of patients grouped according to the response to treatment and Wilcoxon test to assess differences between paired pre and post-treatment values of biomarkers inside a group of patients (favorable or non-favorable response to treatment). Mixed Model Analysis for repeated measures was performed to evaluate QoL. The software Stata/IC 13.1 (StataCorp LP, College Station, TX) was used to perform statistical analyses, with significance defined as a p-value ≤0.05.

3. Results

3.1. Patient characteristics

Between October 2012 and February 2015, 52 consecutive patients were enrolled in the Rare Tumor Unit of Veneto Institute of Oncology, Padua, Italy. Patient and disease characteristics are shown in Table 1. Forty-four patients (29 males and 15 females) were suitable for primary endpoint evaluation. Median age was 66 years (range 42–87); 13 and 31 patients had a histologically confirmed locally advanced or metastatic PC, respectively; all patients but two had ECOG PS 0-1.

Table 1
Patients' Characteristics.

Characteristic		N	%
Patients		44	100
Age	Media ± SD	66.43 ± 10.50	
	Median (range)	66 (42–87)	
Gender	Male	29	65.9
	Female	15	34.1
Stage of disease	Locally Advanced	13	29.5
	Metastatic	31	70.5
ECOG PS	0	34	77.3
	1	8	18.2
	2	2	4.5
Best Response	PR	12	27.3
	SD	15	34.1
	PD	17	38.6

Abbreviations: N, number; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; SD, stable disease; PD, progression disease; IL, interleukin; VCAM, Vascular cell adhesion protein 1; ICAM, Intercellular Adhesion Molecule 1; sE-selectin, soluble E-selectin; sCD40L, soluble CD40 ligand; CRP, C-reative protein.

3.2. Clinical efficacy and prognostic analysis of OS

The data regarding the activity and toxicity of GEM and Meriva® combination were reported in abstract form in ASCO meeting 2016 [48]. The median number of chemotherapy cycle was 4.5 (range 2–14). We observed a partial response in 27.3% of patients, a stable disease in 34.1%, with a disease control rate (DCR) of 61.4%. Progression occurred in 17 patients (38.6%). At a median follow-up time of 26 months, 37 patients (84.1%) were dead, with a median OS of 10.2 months (95% CI, 8.8–11.7; Fig. 1) and with a median time to progression of 8.4 months (95% CI, 5.0–11.8; Fig. 2).

According to the stage of disease, a median OS of 16 months was observed in patients with locally advanced pancreatic cancer, and of 8.5 months in patients with metastatic disease (Fig. 3).

Supplementary Table 1 summarizes the biomarker levels found in the overall patient series. MIP-1α serum levels of all samples were lower than the limit of detection.

Patients which did not respond to treatment had significantly higher basal levels of IL-6 (p = 0.03), sCD40L (p = 0.05) and CRP (p = 0.03) (Supplementary Table 2). In order to investigate if variations of biomarker levels could be associated to response to the therapy, basal values were compared to those obtained after the 1 st and the 3rd chemotherapy cycles, according to RECIST timing for the assessment of response.

In patients responding to the therapy no significant variations of biomarkers were found between baseline levels and those after either 1 or 3 chemotherapy cycles (Supplementary Table 3).

In patients not responding to the therapy, the evaluation was feasible only between values at baseline and after 1st cycle, because the 3rd cycle was not administered due to the progression status (Supplementary Table 4). In these patients, a significant increase was observed after the 1st cycle of chemotherapy only for sCD40L (p = 0.02).

Pretreatment variables associated to worse prognosis in univariate analysis were the presence of distant metastases, increased basal levels of IL-6, sCD40L and CRP (Table 2). Age, sex, ECOG PS and basal levels of IL-8, VCAM-1, ICAM-1 and sE-Selectin were not associated to survival and were therefore not included in multivariate analysis.

At multivariate analysis (Table 2) metastatic disease and high baseline levels of IL-6 or sCD40L were identified as independent predictors associated with worse OS (p = 0.007 and p = 0.002, respectively).

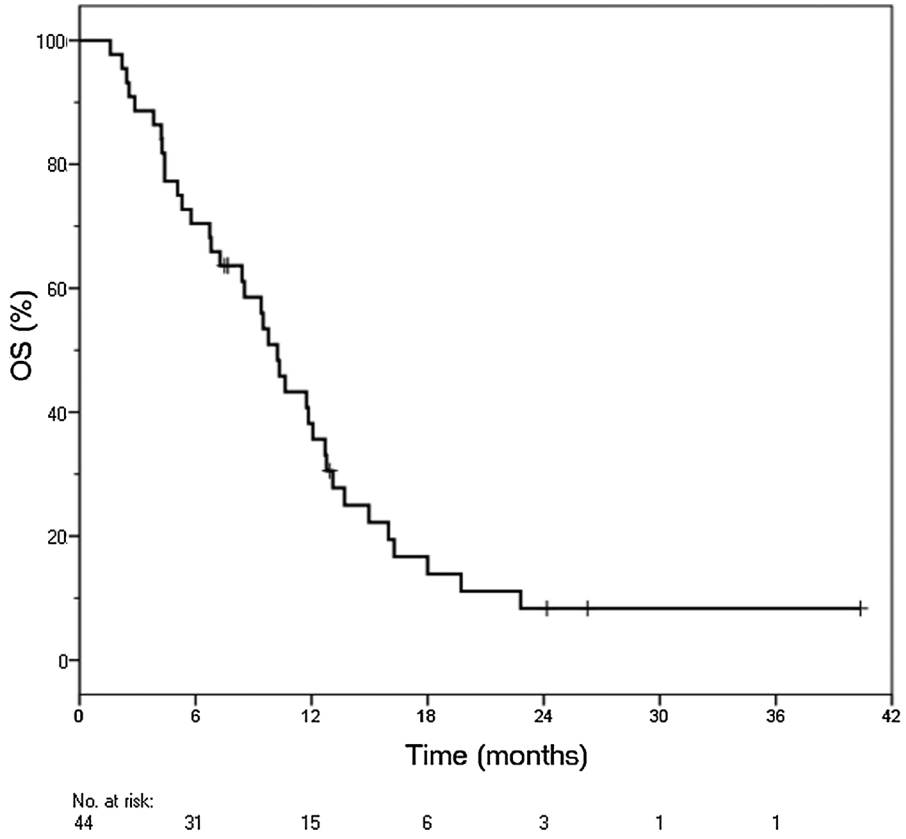

Fig. 1. Cumulative survival: median OS.

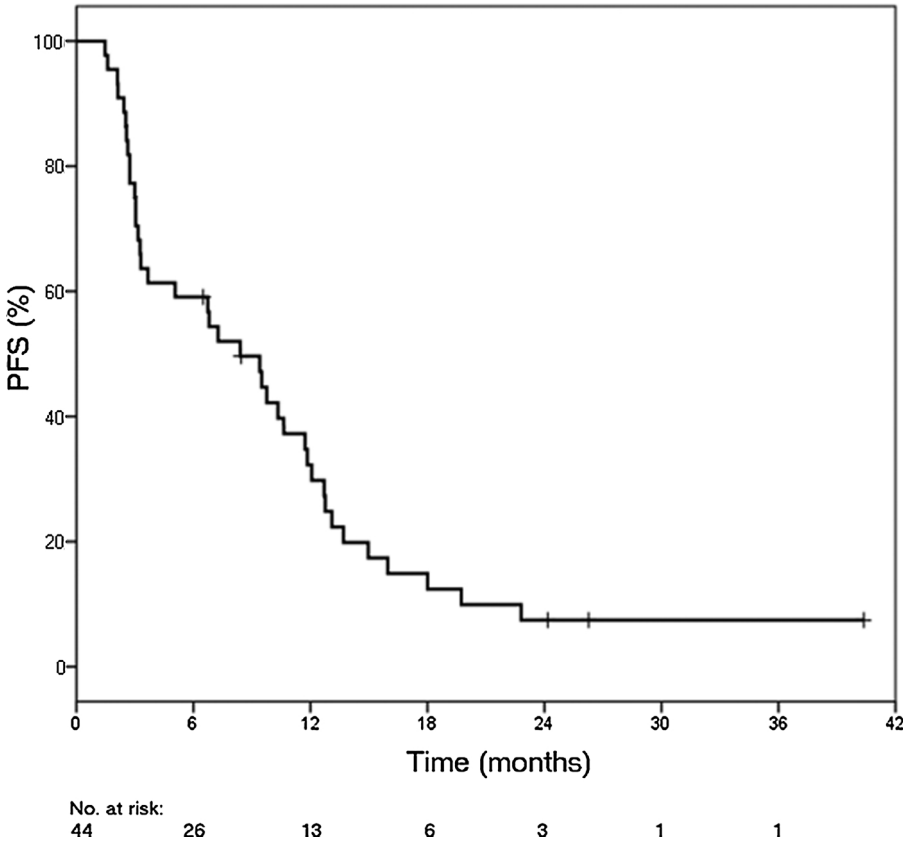

Fig. 2. PFS of all patients.

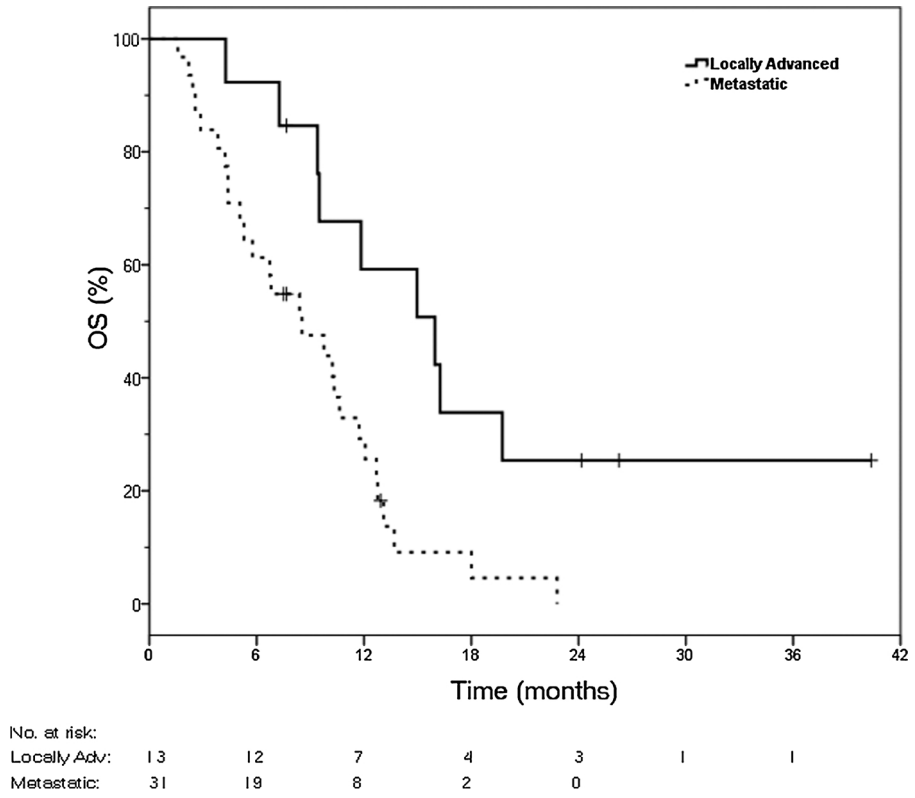

Fig. 3. Median OS according metastatic vs locally advanced disease: 8.5 vs 16 months. Log Rank (Mantel-Cox); p-value 0.005.

3.3. Toxicity

The principal toxicity observed was hematological, as expected according to the dose-intense schedule of GEM. A grade 1–2 and 3–4 anemia was respectively observed in 14 out of 44 treated patients (31.8%) and 3/44 patients (6.8%); grade 1–2 and 3–4 neutropenia respectively in 10/44 (22.7%) and 17/44 patients (38.6%), while a grade 1–2 and 3–4 thrombocytopenia was respectively observed in 14/44 patients (31.8%) and in 3/44 treated patients (6.8%). As for non-hematological toxicity a grade 1–2 fatigue was reported by 13/44 patients (29.5%), and grade 1 nausea and vomiting in 8/44 patients (2%). We observed a grade 1–2 oral mucositis in 3 patients (6.8%), grade 1–2 and 3–4 diarrhea respectively in 4 (9%) and 1/44 patient (2.2%).

3.4. Quality of life

Overall, 35 patients (79.5%) completed the baseline QoL questionnaire and 30 (68.2%) filled it at least for three cycles. Missing data were dependent on patient's death before the next scheduled assessment or patient's unwillingness to complete questionnaire. Mixed

Table 2
Univariate and Multivariate Analysis for overall survival with Cox regression.

Variables	Regression Coefficient (b)	Standard Error SE (b)	p-value	HR	95% CI for HR	
					Lower	Upper
Univariate Analysis						
Age	0.001	0.015	0.925	1.001	0.973	1.03
Male vs. Female	0.056	0.342	0.871	1.057	0.541	2.065
Metastatic vs. Locally Advanced	1.088	0.402	0.007*	2.969	1.35	6.528
ECOG PS 1-2 vs.0	0.496	0.375	0.186	1.641	0.787	3.423
IL-6 ng/mL	0.041	0.017	0.018*	1.041	1.007	1.077
IL-8 ng/mL	0.002	0.001	0.107	1.002	1	1.004
VCAM-1 ng/mL	0	0.001	0.955	1	0.999	1.001
ICAM-1 ng/mL	0	0.001	0.921	1	0.998	1.002
sE-selectin ng/mL	0.049	0.031	0.121	1.05	0.987	1.116
sCD40L ng/mL	0.159	0.057	0.006*	1.172	1.048	1.312
CRP > 6 vs ≤ 6 mg/L	1.047	0.454	0.021*	2.849	1.171	6.934
Multivariate Analysis						
Metastatic vs Locally Advanced	1.91	0.60	0.002*	6.78	2.08	22.13
IL-6 ≥ 5.88 vs < 5.88 ng/mL	1.66	0.50	0.007*	4.79	1.79	12.84
sCD40L ≥ 3.38 vs < 3.38 ng/mL	1.73	0.53	0.002*	5.64	2.01	15.82
CRP > 6 vs ≤6 mg/L	0.26	0.49	0.6	1.29	0.49	3.40

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; IL, interleukin; VCAM, Vascular cell adhesion protein 1; ICAM, Intercellular Adhesion Molecule 1; sE-selectin, soluble E-selectin; sCD40L, soluble CD40 ligand; CRP, C-reative protein.
*p ≤ 0.05.

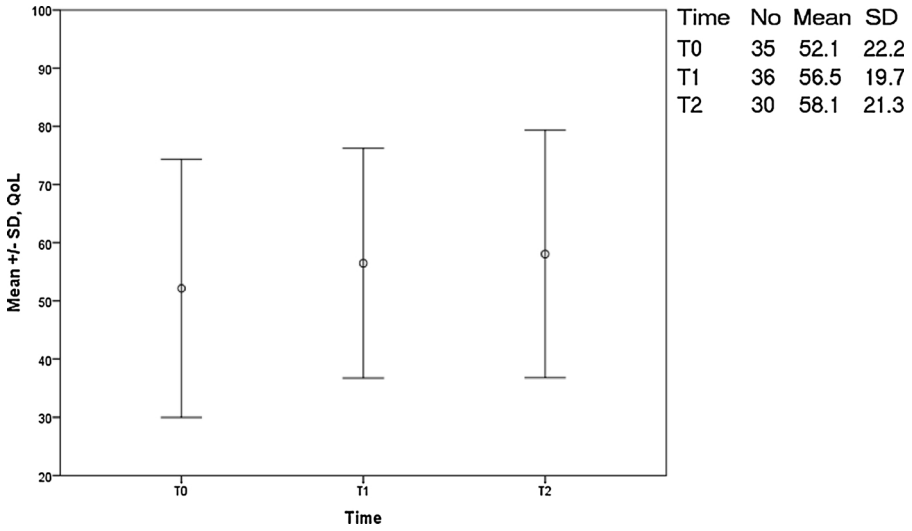

Fig. 4. QoL analysis for all patients.

model analysis for repeated measure showed no decrease of QoL ($p = 0.497$) during treatment (Fig. 4).

4. Discussion

In the attempt to improve the performance of chemotherapy in the treatment of PC, innovative treatments have been introduced aiming to increase OS preserving QoL and limiting severe side effects. A dose-intense schedule of prolong infusion of GEM has been used, but an increment of the adverse effects was also observed [36]. The combination of oxaliplatin, irinotecan, leucovorin, and fluorouracil (FOLFIRINOX) had a good performance status ECOG (ECOG PS 0-1), and a median OS of 11.1 months, median PFS of 6.4 months. However still high toxicity was observed [49]. The combination of nab-P + G, increased the OS rates ranging from to 8.5–10.7 months with a more manageable toxicity [2–4] and this is now accepted as the new standard of care.

This study provides first preliminary evidence that the association of curcumin (Meriva®) to the GEM as single agent regimen is as effective as the combination of nab-P + G with the advantage of producing less toxicity (absence of neurotoxicity and lower hematological toxicity).

PC was a typical pathology for testing the efficiency of a CM. To this purpose, corroborated by a long series of pre-clinical data [25,27,50–53], we planned the use of curcumin as CM to the treatment of PC with GEM. The minimal aimed outcome was a decrease of side effects associated to a preservation of QoL. On a theoretic background, indeed, the working hypothesis was in contrast with some in vitro studies suggesting that curcumin could lower the efficiency of the chemotherapy. Thus a relevant aim of this clinical trial was the contribution to solve this paradox.

The study included a careful analysis of the biomarkers of inflammation linking the effect of curcumin to inflammation and thus to clinical outcome.

Cancer-related inflammation has been suggested as a hallmark of cancer and recent studies have identified the role of local immune response and systemic inflammation in cancer progression and patient survival in different types of tumors [54,55]. Inflammation within the PC microenvironment, seemingly due to activation NF-κB activation, has been mechanistically linked to tumor progression and chemoresistance [56]. Activating Nrf2, curcumin down-regulates NF-κB controlled genes involved in inflammation, proliferation, survival, invasion, angiogenesis, and metastasis [27,30,50,51,57]. On the other hand, systemic inflammation also affects patient's response to chemotherapeutic agents [58]. In a mouse model of PC, systemic inflammation reduces the therapeutic efficiency of GEM and in PC cells tumor-associated pro-inflammatory macrophages induce GEM resistance [59]. These mechanisms seemingly impact on the response to chemotherapeutic agents and survival [59–61]. Previous clinical trials have already tested the effect of curcumin on PC. In a phase II clinical trial curcumin (at 8000 mg/day) gave positive effects via reduced activation of NF-κB in peripheral mononuclear cells in PC patients with no treatment-related toxic effects [62]. Moreover, in GEM-resistant PC patients, curcumin increased the median survival time [63].

In this study we report the results of the use of curcumin Meriva® 2000 mg/day continuously (4 capsules, each of 500 mg, every day) as CM to GEM in 44 consecutive patients affected by locally advanced or metastatic PC.

In this phase II study we observed a DCR of 61.4%, with a median PFS of 8.4 months, and a median OS of 10.2 months. OS observed in the present study was higher than that historically observed with GEM in classic schedule (OS 5.7 months) or that obtained in studies using GEM as single agent in the phase III trial (OS 6.7 months) [3,44], suggesting that the complementary administration of phytosome complex of curcumin increases the efficacy of first line therapy with GEM in advanced PC. The association of curcumin (Meriva®) and GEM lead to OS rates comparable to that found in different studies with nab-P + G combination (8.5–10.7) [2,64], with the advantage of absence of neurotoxicity and lower hematological toxicity. Remarkably, Meriva® did not lead to an increased toxicity and QoL was preserved.

We also found that increased pretreatment level of CRP, IL-6 and sCD40L predicts a poor response. Consistently, higher pretreatment level of IL-6 or sCD40L was associated to a worse OS as well as increased sCD40L level after 1 cycle of chemotherapy. These results comply with the known relevance of inflammatory indicators as prognostic or predictive markers in PC and other tumors [38,40,64–70]. CD40-sCD40L interaction is seen associated to the promotion of tumor cell growth and angiogenesis. sCD40L emerged as suitable biomarker in metastatic PC treated with FOLFIRINOX or nab-P + G [41].

Our evidence confirms the relevance of inflammation in PC clinical outcome and corroborate the working hypothesis, born from in vitro studies, that the positive effect of curcumin is due to the control of inflammation brought about by Nrf2 activation and NF-κB inactivation [71–73]. Moreover, our findings reinforce pre-clinical evidence that the complementary therapy to other chemotherapeutic agents with curcumin exhibits beneficial efficacy and safety during anti-cancer therapy [74,75].

Our data suggest that curcumin in complexed form with phospholipids (Meriva®) can be used in the treatment of PC as a complementary

therapy to GEM. No evidence, indeed, for a decrease of the suspected efficiency of the chemotherapy or a decrease of QoL was observed.

Our data show that the use of Meriva® as CM was safe and translate in good RR in first line therapy of advanced PC.

Author contributions

Conception and design: Davide Pastorelli, Massimo Gion, Aline S. C. Fabricio, Fulvio Ursini.*Administrative support*: Pasquale Fiduccia, Simona D'Ippolito, Caterina Soldà.*Provision of study materials or patients*: Davide Pastorelli, Petros Giovanis, Simona D'Ippolito, Caterina Soldà, Andrea Buda, Cosimo Sperti, Romeo Bardini, Gianfranco Da Dalt.*Collection and assembly of data*: Giulia Rainato, Aline S. C. Fabricio, Pasquale Fiduccia, Simona D'Ippolito, Davide Pastorelli.*Data analysis and interpretation*: Pasquale Fiduccia, Giulia Rainato, Aline S. C. Fabricio, Massimo Gion, Davide Pastorelli, Fulvio Ursini*Manuscript writing*: Davide Pastorelli, Aline S. C. Fabricio, Massimo Gion, Fulvio Ursini.*Final approval of manuscript*: All authors.*Accountable for all aspects of the work*: All authors.

Conflict of interest

The author(s) indicated no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.phrs.2018.03.013.

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