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Research Article

Use of Paclitaxel Associated to Lipid Core Nanoparticles (LDE) in the Second or Third Line Treatment of Advanced Pancreatic Adenocarcinoma

Bruna Bighetti[1], Carlos Del Cistia Donnarumma[2], Rodrigo Barbosa Esper[2], Carolina Graziani Vital[3], Aleksandra Tiemi Morikawa[3], José Salvador Rodrigues de Oliveira[1], Raul Cavalcante Maranhão[3,4*], Nora Manoukian Forones[1]

[1]Escola Paulista de Medicina da Universidade Federal de Sao Paulo (EPM-UNIFESP), Sao Paulo, Sao Paulo, Brazil

[2]Instituto Prevent Senior, Sao Paulo, Sao Paulo, Brazil

[3]Instituto do Coracao do Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (InCor-HCFMUSP), Sao Paulo, Sao Paulo, Brazil

[4]Faculdade de Ciencias Farmaceuticas da Universidade de Sao Paulo (FCF-USP), Sao Paulo, Sao Paulo, Brazil

*****Corresponding author:** Raul C. Maranhão at Laboratório de Metabolismo e Lipides, Instituto do Coração (InCor) do Hospital das Clínicas, FMUSP, Av. Dr. Eneias de Carvalho Aguiar, 44, Bloco II, São Paulo, Brazil

Abstract

Background: Previously, we showed that paclitaxel carried in non-protein Lipid Core Nanoparticles (LDE) resembling the lipid structure of LDL has remarkably reduced toxicity in patients with advanced solid cancers, as used in 3rd line chemotherapy or further. The aim was to test LDE-paclitaxel treatment in progressive, advanced pancreatic adenocarcinoma as second or third line of therapy.

Methods: This was a prospective, single-arm study enrolling patients that had been previously submitted to at least one standard chemotherapy scheme. LDE-paclitaxel was administered at weekly infusion of 85mg/m² B.W. dose, with two-week intervals between the 7th and the next dose.

Results: Nine consecutive patients were studied. Maximum 5 cycles were performed before disease progression or death. In none of the patients treatment was discontinued or dose was reduced for drug toxicity. LDE-paclitaxel presented only CTCAE grade 1 and 2 toxicities, anemia and neuropathy being most frequent, with no grade 3 or 4 toxicities. Patient survival after initiation of LDE-paclitaxel use was 4.7 months with no decline in the assessed quality of life indices while they were being treated. Total overall survival was 20.14 months.

Conclusion: LDE-paclitaxel treatment in patients with advanced pancreatic adenocarcinoma at 2nd or 3rd line setting showed remarkably low toxicity and tolerability and the survival data seem satisfactory in view of the previous studies from the literature. Thus, the results pave the way for future clinical trials on LDE-paclitaxel and encourage testing this formulation in 1st line therapy schemes in pancreatic adenocarcinoma.

Keywords: Pancreatic cancer treatment; Solid lipid nanoparticles; Nano emulsions; Drug delivery in cancer

Introduction

Pancreatic adenocarcinoma (PAC) is the eighth leading cause of cancer-related death in men and the ninth in women, with estimated 500,000 new cases diagnosed worldwide in 2020 [1,2]. PAC is usually diagnosed at advanced stages and has poor prognosis due to the extremely aggressive behaviour of the tumor. Surgical resection offers the single chance of cure for PAC, but only 15-20% of cases are potentially resectable at presentation and the prognosis is poor even for those in whom complete resection was successful [3]. In this setting, the overall survival is short and most patients are expected to die from the disease.

In respect to first-line chemotherapy, the FOLFIRINOX regimen is primarily recommended and yields better overall survival, but the toxicity and rate of adverse events are high [4]. In case of intolerance or lack of clinical status to carry out the FOLFIRINOX scheme, the use of gemcitabine can be offered as first line [5]. Use of gemcitabine together with paclitaxel associated to albumin (nab-paclitaxel) is also a first line treatment choice [6]. Second or third lines of chemotherapy may eventually prolong the global survival but are often limited by the low tolerability in those patients with deteriorating clinical state [7].

In pioneer studies, our laboratory has developed formulations of anticancer drugs associated to artificially made lipid nanoparticles that resemble the lipid structure of low-density lipoprotein (LDL) [8,9]. The quasi-spherical nanoparticles are constituted by a monolayer of phospholipids and unesterified cholesterol surrounding a core of esterified cholesterol with small amounts of triglycerides. The nanoparticles, termed LDE, are made without apolipoprotein (apo) B, the protein moiety of native LDL that binds LDL particles to specific receptors on the cell membrane. However, when injected into the bloodstream, LDE acquires apo E which is also recognized by LDL receptors. LDL receptors are strongly upregulated in cancer cells [8,9]. This allows LDE and drugs carried in the nanoparticles to concentrate in different malignant neoplastic tissues, since LDL receptor upregulation is an ubiquitous phenomenon in cancer [10-14]. In experiments with animals with implanted melanoma B17 tumor, the formulation of paclitaxel incorporated to LDE showed increased antitumoral action, as documented by the reduction of tumor growth and of metastases and by prolongation of survival rates of the treated mice, compared with conventional paclitaxel [15]. The toxicity of paclitaxel associated to LDE was pronouncedly reduced, with LD50 ninefold higher than that of paclitaxel using Cremophor L as vehicle [15]. LDE-paclitaxel are stable formulations, with shelf-time up to 4 months without addition of antioxidant compounds when stored at 4 °C.

The pharmacokinetic studies of LDE-paclitaxel in humans confirmed that dissociation of the drug from the nanoparticle vehicle does not occur in the bloodstream and showed that the residence time of the formulation is markedly longer than that of paclitaxel-Cremophor L, which *per se* is a consistent pharmacological advantage over the commercial formulation [12,13]. LDE-paclitaxel had no observable laboratorial or clinical toxicity used as 3rd or later lines of patients with ovarian adenocarcinoma [16] and in end-of-life patients with metastatic cancers [17], as administered as intravenous infusions at 175 mg/m^2 body surface dose every 3 weeks. Uninterrupted treatments up to one year were performed without occurrence of cumulative toxicity [16,17].

In view of the supportive data on the use of LDE-paclitaxel in patients with advanced cancers, as described above, this study was primarily designed to test the toxicity and tolerability of this preparation in the second or third line settings in patients with PAC. As secondary end-points, it was also aimed the evaluation of life quality and patient survival after initiation of treatment.

Materials and Methods

Study design and patients

This was a prospective one-arm, open-label study enrolling consecutive volunteer patients with advanced PAC already submitted to first or second line of chemotherapy. Treatment with LDE-paclitaxel was evaluated by determining the toxicity profile of the drug by clinical and laboratorial exams, by determining the survival period after initiation of the treatment and by application of a quality of life questionnaire (EORTC QLQ-C30).

The patient inclusion criteria were as follows: confirmed histologic diagnosis of advanced PAC; both genders, aged 18-75 years; Eastern Cooperative Oncology Group (ECOG) performance status score 0–2; and adequate haematologic, renal, and hepatic function; having already performed one or more standard chemotherapy regimens for the treatment of the disease. Entry data were collected from clinical records at the participant institutions.

A washout period of at least 15 days after completion of the previous chemotherapy line was kept before starting the LDE-paclitaxel treatment. LDE-paclitaxel at paclitaxel dose 85 mg/m^2 body surface was weekly administered I.V. diluted in 200 mL saline solution. The infusion was made over 90 min, with a two-week interval in the 7th week of treatment. It was previously established that the treatment would be discontinued upon disease progression or at patient request. Patients were submitted to clinical interview and physical examination before every two chemotherapy cycles by one attending oncologist.

The study was in accordance with the Declaration of Helsinki principles and was approved by the Ethics Committee of the Federal University of São Paulo (Protocol nᵒ. 4237198).

Preparation of paclitaxel oleate associated with LDE

To increase the lipophilicity of paclitaxel and thereby to improve the yield of association to LDE and stability of LDE-paclitaxel, we synthesized a paclitaxel derivative, paclitaxel oleate, as previously described [16,17]. The LDE-paclitaxel formulation was prepared from a lipid mixture composed of 135 mg cholesteryl oleate, 333 mg egg phosphatidylcholine, 132 mg Miglyol 812 N, 6 mg cholesterol and 60 mg of paclitaxel and the aqueous phase comprised 100 mg of polysorbate 80 and 10 ml tris–HCl buffer, pH 8.05. Emulsification of all lipids, functionalized drug and the aqueous phase was obtained by high-pressure homogenization using an Emulsiflex C5 homogenizer (Avestin, Ottawa, Canada). After homogenization cycles, the formed nanoparticle was centrifuged and the nanoparticles are sterilized by passage through 0.22-lm pore polycarbonate filter (Millipore, Darmstadt, Germany). The preparations are stored at 4 °C until use. The quantification of paclitaxel in the preparations was performed by high-performance liquid chromatography (Shimadzu, Columbia, MD) developed in isocratic mode, mobile phase 100% methanol and UV–visible detector (227 nm).

Results

Total 9 consecutive patients were studied, 5 of the female and 4 of the male gender, with 63 year average age. Three were at clinical stage II, 3 at stage III and 3 at stage IV of the disease. Six out of the 9 patients had been submitted to resection surgery and none to radiotherapy. Seven of the participants had FOLFORINOX and 2 had gemcitabine as first line chemotherapy. None of the 9 patients used a previous Taxane-based treatment. Three patients had zero ECOG performance status, one ECOG 1 and one had ECOG 2. Four of the participants had been previously treated in first line chemotherapy scheme only and 3 had been treated in second line.

Table 1 shows the toxicity profile of LDE-paclitaxel at the adopted 85mg/m² body surface weekly dose level. Each chemotherapy cycle referred in Table 1 encompasses 6 consecutive weekly LDE-paclitaxel infusions followed by a two-week pause until the next infusion. Maximal 5 chemotherapy cycles were performed, with only one participant reaching the 5ᵗʰ cycle. Altogether, total 24 cycles were performed and in none it was not necessary to reduce the medication dose.

Cycle of treatment	1	2	3	4	5
No. of patients in cycle	9	8	4	2	1
Grade 1/2 toxicities					
Nausea and vomiting	1	1	1	0	0
Diarrhoea	1	0	1	0	0
Fever	0	0	0	0	0
SAH	0	0	0	0	0
Dyspnea	0	0	0	0	0
Alopecia	0	0	0	0	0
Mucositis	0	0	0	0	0
Neuropathy	2	3	2	1	0
Hematologic					
Anaemia	1	3	0	0	0
Neutropenia	0	1	0	0	0
Low platelets	1	1	1	0	0
Hepatic					
AST	0	0	0	0	0
ALT	0	0	0	0	0
Bilirubin	0	0	0	0	0
Renal					
Creatinine	1	1	0	0	0

SAH: systemic arterial hypertension; AST: aspartate transaminase; ALT: alanine transaminase.

Table 1: Events of grade 1 and 2 toxicities registered in each one of the maximum 5 cycles of treatment with LDE-paclitaxel at 85 mg/m^2 B.W. administered in I.V. infusions, with 2 week intervals every 4 cycles. No grade 3 or 4 occurred.

During the treatment with LDE-paclitaxel of the nine patients with PAC no CTCAE grade 3 and 4 toxicities were observed, with exception of one patient who had grade 3 renal toxicity in the first treatment cycle. In fact, it was unlikely that this renal disease event that was diagnosed 15 days after the first LDE-paclitaxel infusion could be accounted for the treatment but rather to the clinical status of the patient. As shown on Table 1, only grade 1 and grade 2 laboratorial toxicities, namely hematologic toxicities were registered in 9 from the total 24 cycles. Hepatic toxicity was not observed. Events of CTCAE grade 1 or 2 clinical toxicities, namely nausea and vomiting, diarrhoea and neuropathy were registered in 13 among the total 24 performed cycles. Alopecia, fever, dyspnea, systemic arterial hypertension and mucositis were not observed.

As shown in Figure 1, the results of the questionnaire evaluation show that the quality of life score remained unchanged during the treatment.
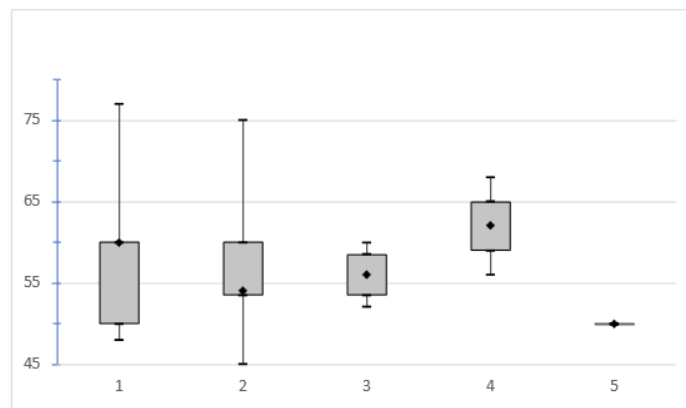

Figure 1: EORTC QLQ-C30 scores as measured at each treatment cycle.

Figure 2 presents the Kaplan-Meier plot of the survival of the patients since the beginning of the treatment with LDE-paclitaxel. The median survival was 4.73 months (CI 95% 0.013; 37.83). Figure 3 shows the survival periods of the patients treated with LDE-paclitaxel in either 2nd or 3rd lines. Apparently, there was no difference between 2nd and 3rd line-treated patients regarding the duration of the treatment periods.
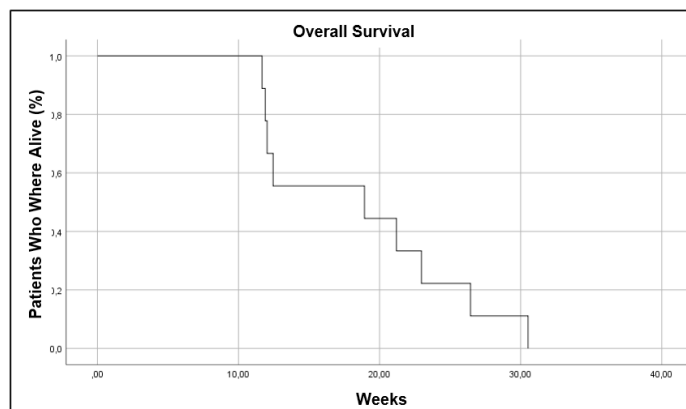

Figure 2: Kaplan-Meier plots of the overall survival of the patients since the beginning of the LDE-paclitaxel treatment (in weeks).
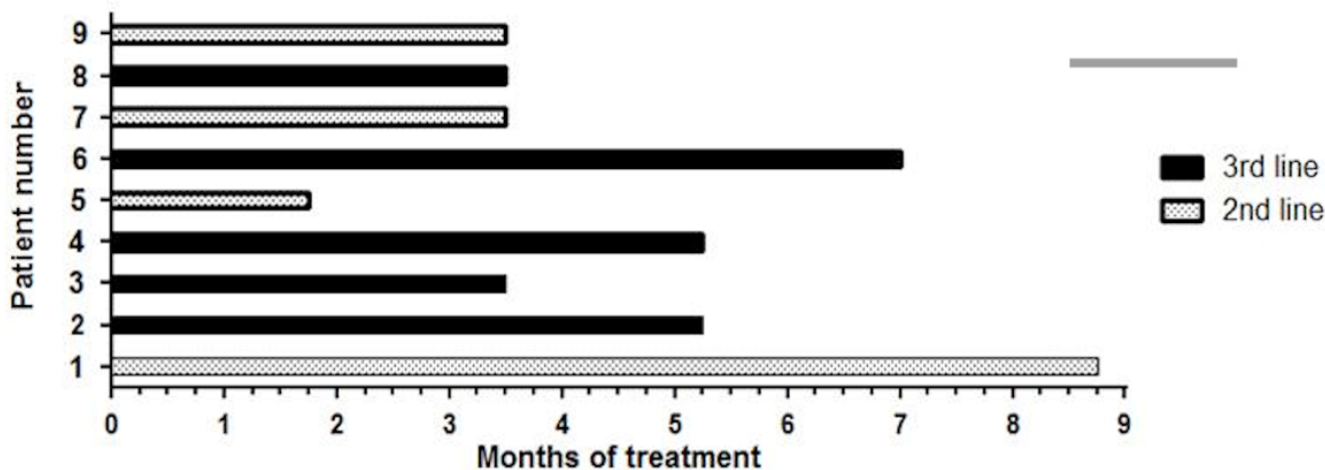
Figure 3: Survival periods of each patient since the beginning of the LDE-paclitaxel treatments, discriminated as 2nd or 3rd line therapy (in months).

The median overall survival since the diagnosis of the disease was 20.14 months (95% CI 16.87; 23.40).

Discussion

The data obtained in this study indicate that LDE-paclitaxel had low toxicity and good tolerability for use in patients with PAC in the 2nd or 3rd line chemotherapy setting at a high dose level of paclitaxel. Apart of the renal disease episode that occurred in one patient and that was most likely not related to the treatment, only CTCAE grade 1 or 2 toxicities were observed. In none of the patients treatment had to be discontinued due to intolerability or toxicity to this paclitaxel formulation. Most frequently, those light, grade 1/2 toxicities were neurotoxicity and myelotoxicity that counted 8 events each over the 24 performed treatment cycles. In fact, those are the most common toxicities occurring with the conventional formulations of paclitaxel.

When confronted to the toxicities of commercial chemotherapeutic agents and with other paclitaxel formulations, the superiority of LDE-formulation was apparent, although the small number of study patients is limiting to warrant more consistent data comparisons. In this respect, grade 3 and 4 neutropenia occurred in up to 35% of PAC patients treated with gemcitabine and up to 45% of patients with the FOLFIRINOX scheme [18]. Grade 3 and 4 anemia and neutropenia also frequently occurred in patients treated with gemcitabine associated with Erlotinib [19]. In most studies, grade 3 or 4 neuropathy also occurred and grade 3 alopecia was common. Symptoms such as grade 3 or 4 nausea and vomiting have been rather frequent in those studies.

In respect to the commercial formulations of paclitaxel, with lower-dose paclitaxel treatment ($50mg/m^2/wk$) Tajima (2018), reported development of grade 3 neutropenia [20]. In second line, Oettle (2000) [21], observed that median weekly dosage 73 mg/m^2 resulted in grade 3 anemia and leukocytopenia and grade 3-4 alopecia. In a phase II trial of nab-paclitaxel as second line therapy, Hosein (2013) [22] reported grades 3-4 neutropenia, neutropenic fever, and anemia occurring in 32%, 11%, and 11% of the patients, respectively.

In our previous studies with LDE-paclitaxel in which this preparation was administered at triweekly paclitaxel dose of $175mg/m^2$, no clinical or laboratorial toxicity appeared. Those studies were performed in women with advanced ovarian carcinoma [16] and in end-of-life patients with lung, breast and prostate carcinomas with bone metastases [17]. The fact that some grade 1 and 2 toxicities appeared in the current study could be ascribed to the use of a higher paclitaxel dose, 85 $mg/m^2/week$, that in a monthly basis was roughly 30% higher than that used in our previous studies. However, the extremely despoiling character of PAC could also have contributed in our study to the surfacing of those light toxicities that otherwise had not appeared at all in the patients with the above-mentioned cancers in whom LDE-paclitaxel was tested [16,17]. It is noteworthy that none of the patients were premedicated with antiemetic, antiallergic or corticosteroid drugs that attenuate some of the expected toxicities related with anticancer agents; those medications are included in the protocols of most clinical trials.

Life quality of the patients under the FOLFIRINOX scheme showed a definite degradation as assessed by standard questionnaire. In smaller proportion this also took place in patients treated with single gemcitabine [4]. In this scenery it is noticeable

that in our study there was no decline of life quality, as accessed by the questionnaire.

Although it was not feasible to objectively evaluate in our patients the treatment responses by imaging exams, the data on the overall survival after the beginning of LDE-paclitaxel therapy suggest that this treatment is not inferior to other chemotherapeutic approaches to the disease. In this respect, in treatments of patients with PAC, Wu (2015) tested Neratinib plus Lapatinib and capecitabine and reported median overall survival 5.2 months [23]; Cardin (2018), 4.57 months with ganetespib [24]; Mie (2021), 4.6 months with erlotinib plus gemcitabine [19]; Mohring (2023) with liposomal irinotecan plus 5-fluorouracil, 9.33 months [25]. Relative to commercial formulations of paclitaxel, in second or third line treatments of PAC, Tajima (2018) reported 0.77 months with low-dose paclitaxel [20] and Hosein (2013) reported 7.3-month overall survival with nab-paclitaxel [22]. Therefore, our results of overall survival after the beginning of the LDE-paclitaxel treatment, 4.7 month-median, were not essentially different from others more recently described in the literature.

Conclusion

In conclusion, the results of the current study show that LDE-paclitaxel has potential to become an interesting choice for the treatment of PAC in 2nd or 3rd lines due to its remarkably low toxicity and tolerability, maintenance of life quality and survival data in the range of those reported in the literature. Thus, our study paves the way for future clinical trials on LDE-paclitaxel and encourage testing this formulation in patients with PAC in earlier line therapy schemes.

Disclosure

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from patients to publish this paper.

Data availability Statement: Data supporting the study results can be provided followed by request sent to the corresponding author's e-mail.

Conflict of interest: None.

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