

Curcumin Combination Chemotherapy in Pancreatic Cancer

Shazia Tahira

Abstract

Pancreatic cancer is one of the most lethal cancer and there is innate resistance to standard chemotherapy regimens in pancreatic cancer. Gemcitabine was approved in 1996 for the chemotherapeutic treatment of metastatic pancreatic cancer. FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel combination therapies have shown superiority to gemcitabine monotherapy but are more toxic than gemcitabine monotherapy. Therefore, gemcitabine monotherapy is still one of the standard treatments for pancreatic cancer for patients who can't tolerate the toxicity of other chemotherapeutic regimens. The effectiveness of standard chemotherapeutic drugs is limited in pancreatic cancer due to drug resistance, and undesirable side effects. There is a likelihood that the combination of standard chemotherapy with natural compounds having anti-cancer potential like curcumin will increase the effectiveness of treatment as well as reduce the toxic side effects of standard chemotherapeutic agents. Curcumin is a polyphenolic compound isolated from the rhizome of *Curcuma longa* (turmeric) and is considered a promising anticancer agent. Here, a review is presented about the potential use of curcumin with standard chemotherapy in pancreatic cancer as there is a potential in different combination regimens of curcumin in pancreatic cancer to increase median survival in pancreatic cancer in comparatively less toxic, novel ways. Also, curcumin combination chemotherapy may lead to the improvement of cancer and chemotherapy-related symptoms. The poor bioavailability of curcumin has been the major obstacle for its clinical application. To overcome this problem, several curcumin preparations have been developed including cost-effective preparation methods to increase the bioavailability of curcumin. Different studies have shown that gemcitabine curcumin combination regimen can effectively increase survival with less toxicity in patients who are resistant to gemcitabine and can't even tolerate the toxicity of other chemotherapeutic combination regimens. Although clinical trials are needed, Paclitaxel and curcumin cobound albumin nanoparticles also have the potential to become another alternative chemotherapeutic regimen for pancreatic cancer. For those patients who can tolerate gemcitabine paclitaxel regimen toxicity, there can also be a future possibility of using paclitaxel and curcumin cobound albumin nanoparticles with gemcitabine and this triple therapy may have enhanced therapeutic effects with comparatively less toxic effects. Curcumin has shown its effectiveness with the constituents of FOLFIRINOX in other types of cancers, therefore there is a need for curcumin FOLFIRINOX combined clinical trials in pancreatic cancer as curcumin has the potential to increase the effectiveness of FOLFIRINOX as well as reduce its toxic side effects.

Key Words pancreatic cancer, pancreatic ductal adenocarcinoma, curcumin combination chemotherapy, curcumin gemcitabine combination chemotherapy, albumin co-bound paclitaxel and curcumin, FOLFIRINOX

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Introduction

Pancreatic cancer is one of the most lethal and deadly cancer, being the seventh most common cause of cancer-related mortality worldwide, with an overall 5-year survival rate of 9% [1]. It is projected to become the second most common cause of cancer death in the USA by 2030 [2]. The most common type of pancreatic cancer (more than 90% cases) is infiltrating pancreatic ductal adenocarcinoma. Pancreatic ductal adenocarcinoma is characterized by glandular neoplastic epithelial cells typically surrounded by an intense desmoplastic stromal reaction [1].

Pancreatic ductal adenocarcinoma is an aggressive disease. Even with surgical resection, the 5-year survival rate is 30%. This suggests that pancreatic cancer metastasizes early in the course of the disease. There is innate resistance to standard chemotherapy and radiotherapy regimens in pancreatic ductal adenocarcinoma. The intense desmoplastic stromal reaction in pancreatic ductal adenocarcinoma limits the effective delivery of therapeutic agents within the tumor [1].

Gemcitabine was approved in 1996 for the chemotherapeutic treatment of metastatic pancreatic cancer. Prior to gemcitabine, fluorouracil was used as the standard chemotherapeutic treatment for metastatic pancreatic cancer. Gemcitabine alone has since long been the standard chemotherapeutic agent for metastatic pancreatic cancer [3]. Many studies have been conducted to develop regimens that are more effective than gemcitabine monotherapy. Combination therapies including FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel showed superiority to gemcitabine monotherapy [4,5]. Both these regimens are combination therapies of cytotoxic agents. The prognoses were prolonged by 4.3 months by FOLFIRINOX and 1.8 months by gemcitabine plus nab-paclitaxel, therefore, these two regimens have become the two standard front-line treatments for metastatic pancreatic cancer. Nab-paclitaxel was approved to be used in combination with gemcitabine as first-line treatment for metastatic pancreatic in 2013. But FOLFIRINOX and gemcitabine plus nab-paclitaxel combination therapies are more toxic than gemcitabine monotherapy [4,5]. There are many metastatic pancreatic cancer patients with poor performance status. Therefore, these two combination therapies can be used only in selected metastatic pancreatic cancer patients who maintained good performance status, while the remaining ones are still treated with gemcitabine monotherapy [6].

The effectiveness of standard chemotherapeutic drugs is limited in pancreatic cancer due to drug resistance, and undesirable side effects. There is a likelihood that the combination of standard chemotherapy with natural compounds having anti-cancer potential like curcumin will increase the effectiveness of treatment as well as reduce the toxic side effects of standard chemotherapeutic agents. Curcumin is a polyphenolic compound isolated from the rhizome of *Curcuma longa* (turmeric) and is considered a promising anticancer agent. Here, a review is presented about the potential use of curcumin with standard chemotherapy in pancreatic cancer.

Standard First Line Chemotherapeutic Agents in Pancreatic Cancer

Gemcitabine

Gemcitabine has been the standard chemotherapeutic agent for pancreatic cancer for many years [7]. Before gemcitabine, fluorouracil was the standard treatment for metastatic pancreatic cancer. Gemcitabine was synthesized during the early 1980s as an antiviral drug, but during the 1990s, pancreatic cancer trials found that gemcitabine increased survival time significantly, and it was approved in the UK in 1995 and approved by the FDA in 1996 for the treatment of pancreatic cancer. In one study, Gemcitabine was superior to 5-FU (fluorouracil) in providing a clinical benefit among advanced pancreatic ductal adenocarcinoma patients with pain symptoms (clinical benefit rate = 23.8% versus 4.8%; $p = 0.0022$) and modestly prolonged median survival from 4.4 to 5.6 months ($p = 0.0025$) [3]. Due to the development of resistance to gemcitabine, several more aggressive regimens were developed and tested to overcome resistance mechanisms by the cancer cells and increase chemotherapy effectiveness [7]. Most guidelines consider FOLFIRINOX and nab-paclitaxel plus gemcitabine as the accepted treatment for the first-line therapy of pancreatic cancer in patients who can tolerate their toxicity with a trend towards better survival outcomes for FOLFIRINOX [7]. New drug combinations are associated with increased response rate but at the expense of higher toxicities, therefore, gemcitabine monotherapy is still one of the standard treatments for pancreatic cancer for patients who can't tolerate the toxicity of other chemotherapeutic regimens which may include FOLFIRINOX or nab-paclitaxel [6].

FOLFIRINOX

FOLFIRINOX is a chemotherapy regimen for the treatment of advanced pancreatic cancer. It is a combination made up of four drugs: folinic acid (leucovorin), fluorouracil (5-FU), irinotecan and oxaliplatin. In 2011, Conroy et al. showed that FOLFIRINOX produced the longest improvement in survival in a phase III clinical trial of patients with advanced pancreatic cancer and patients on the FOLFIRINOX treatment lived approximately four months longer than patients receiving the standard gemcitabine treatment (11.1 months compared with 6.8 months) [4]. But treatment with FOLFIRINOX also resulted in more toxic outcomes like neutropenia (45.7% for FOLFIRINOX vs. 21.0% for gemcitabine), febrile neutropenia (5.4% vs. 1.2%), thrombocytopenia (9.1% vs. 3.6%), diarrhoea (12.7% vs. 1.8%) and peripheral neuropathy (9.0% vs. 0%), while the incidence of elevation of alanine aminotransferase was decreased (7.3% vs. 20.8%) [4]. Therefore only patients with good performance status are candidates for this regimen [4].

Nab-Paclitaxel

Paclitaxel is one of the commonly used antimetabolic chemotherapeutic agents for treating many types of cancers, such as ovarian, breast, lung, pancreatic, and other cancers, by preventing microtubule depolymerization, arresting mitosis at the G2/M stages of the cell cycle and also inducing apoptosis-mediated cell death [8]. Three paclitaxel formulations are commercially available, Taxol (cremophor formulated), Abraxane (nanoparticle albumin-bound), and Genexol-PM (PEGPLA micelles). In 2013, the U.S. FDA approved the use of nanoparticle albumin-bound

paclitaxel (nab-paclitaxel) with gemcitabine in pancreatic cancer. This regimen is somewhat less toxic but also a bit less effective alternative to FOLFIRINOX for treating late-stage pancreatic cancer. In 2012, a trial demonstrated that nab-paclitaxel in combination with gemcitabine improved the response rate (7% in gemcitabine alone vs 23% in combination), progression-free survival (PFS) (from 3.7 months to 5.5 months), and OS from 6.7 months to 8.5 months, compared to single-agent gemcitabine [5]. This combination increased the haematological toxicity profile and caused more myelosuppression and also increased non-haematologic clinical toxicity such as peripheral neuropathy and fatigue, as compared with the gemcitabine monotherapy, however, these side effects appeared to be reversible [5]. The toxicity profile for both nab-paclitaxel plus gemcitabine and FOLFIRINOX is similar. However, haematological toxicities and growth factor usage were higher in the FOLFIRINOX regimen, whereas nab-paclitaxel plus gemcitabine demonstrated higher rates of neuropathy [9]. Compared to FOLFIRINOX treatment the overall nab-paclitaxel plus gemcitabine treatment was found to be well-tolerated and manageable in most advanced pancreatic ductal adenocarcinoma patients [9]. Studies have shown that locally advanced and metastatic pancreatic ductal adenocarcinoma, which were primarily resistant to FOLFIRINOX treatment, still responded to combination treatment with nab-paclitaxel and gemcitabine, with a manageable toxicity profile [10-12].

Combination of Pancreatic Cancer Chemotherapy with Curcumin

The effectiveness of chemotherapeutic drugs is limited in pancreatic cancer chemotherapy due to development of drug resistance, and undesirable side effects. The combination of therapies with natural compounds with anti-tumor potential has shown to enhance the effectiveness of standard chemotherapeutic regimens and decrease the toxic outcomes. There is a hope that natural compounds like curcumin can benefit pancreatic cancer patients who are already receiving aggressive standard chemotherapy a further increase in treatment efficacy without adding up on toxicity. Curcumin shows potential as an anti-cancer agent and has been considered an attractive anti-tumor, chemo-preventive, antioxidant and anti-inflammatory agent [8].

Curcumin is a pharmacologically active polyphenolic compound and Biopharmaceutics Classification System (BCS) Class IV substance isolated from the rhizome of *Curcuma longa* (turmeric) belonging to family Zingiberaceae. The rhizome of *Curcuma longa* has been traditionally used as a natural spice and foodstuff.

Studies from in vitro and in vivo revealed that curcumin exerts many pharmacological activities with less toxic effects. Curcumin is cytotoxic to many cancer cell lines including pancreatic cancer cells and exerts chemopreventive activities in nature to a wide variety of cancer cell lines and animal tumor models via multiple molecular mechanisms targeting all stages of carcinogenesis [13]. In pancreatic cancer, curcumin induces apoptosis and inhibits cell growth and invasion in vitro, inhibits tumor growth and angiogenesis in vivo and targets cancer stem cells [14]. Cancer stem cells, a subset of cancer cells, may cause not only tumor initiation and heterogeneity, but also treatment resistance, cancer recurrence, and metastasis.

Although more research needs to be done, earlier research shows that chemopreventive agents, such as curcumin, target cancer stem cells mediated through the inhibition of multiple signaling pathways [15]. Li et al first identified pancreatic cancer stem cells [16]. In their study, Ning et al. showed that curcumin can be a potential therapeutic for use against pancreatic cancer stem cells as pancreatic cancer stem cells were more sensitive to curcumin than conventional chemotherapy [17]. Curcumin has a wide range of targets and affects many cellular signaling pathways. Among them are the WNT/ β -catenin, NOTCH, TGF/ β Smad, SHH, STAT3, PI3K/AKT and NF- κ B/COX-2 signaling pathways, most of which play important roles in cancer development and progression [14]. Curcumin inhibits nuclear factor-kappa beta, which is involved in the pathogenesis of several malignancies [18]. Li et al. showed that curcumin downregulates NF- κ B binding and IkappaB kinase activity in pancreatic cancer cell lines that lead to a time-dependent decrease in cancer cell proliferation and increased apoptosis [19]. Curcumin also inhibits the production of many cytokines, such as tumor necrosis factor (TNF)- α and interleukin-1 β [20].

It is very important to maintain quality of life during pancreatic cancer chemotherapy. The decrease in toxic side effects and the improvement of cancer or chemotherapy-related symptoms could increase the compliance to chemotherapy and that largely affects the efficacy of chemotherapy and overall survival. Curcumin has been shown to improve depressive-like behaviors in mice with an increase in serotonin, noradrenaline, and dopamine levels in the brain [21,22]. Curcumin also attenuate hyperalgesia in a mouse model of neuropathic pain [23]. Kanai et al also reported an improvement of pancreatic cancer or chemotherapy-related symptoms (e.g. fatigue, pain, constipation) in several patients after the initiation of curcumin intake [24].

Increasing Bioavailability of Curcumin

Many studies have demonstrated that curcumin could be a promising anticancer agent due to its good bioactivity; however, poor bioavailability has been the major obstacle for its clinical application. Curcumin is a polyphenol and is highly lipophilic and sparingly soluble in water and very little is absorbed when it is ingested [25]. Because of its poor absorption efficiency, it is difficult for orally administered curcumin to reach blood levels sufficient to exert its bioactivities [26]. To overcome this problem, several curcumin preparations have been developed to increase the bioavailability of curcumin and tested as potential medical agents in humans.

Sasaki et al. developed a highly absorptive curcumin dispersed with colloidal nano-particles and named it Theracurmin [27]. The absorption efficacy of Theracurmin was investigated and compared with that of curcumin powder. The area under the blood concentration-time curve (AUC) after the oral administration of Theracurmin was found to be more than 40-fold higher than that of curcumin powder in rats. Then, healthy human volunteers were administered orally 30 mg of Theracurmin or curcumin powder. The AUC of Theracurmin was 27-fold higher than that of curcumin powder. These findings demonstrate that Theracurmin shows a much higher bioavailability than currently available preparations. Thus, Theracurmin may be useful to exert clinical benefits in humans at a lower dosage.

In another study, a highly bioavailable curcumin called Theracurmin was developed using submicron particle formation and surface controlled technology [25]. In a human study, the area under the blood concentration-time curve (AUC) after oral administration of Theracurmin was 27-fold higher than that of commercially available curcumin. Preclinical safety tests were conducted and no adverse effects were confirmed. The effects of Theracurmin on pancreatic cancer and other diseases were also evaluated in this study.

Sunagawa et al. performed a double-blind, 3-way crossover study to evaluate the absorption efficiency of three types of curcumin drug-delivery systems [26]. They compared plasma curcumin levels after the administration of Theracurmin (curcumin dispersed with colloidal submicron-particles) and 2 other capsule types of curcumin drug-delivery systems, BCM-95 (micronized curcumin with turmeric essential oils) and Meriva (curcumin-phospholipid). Nine healthy subjects were administered these 3 preparations of curcumin drug-delivery systems, at commonly used dosages. The maximal plasma curcumin concentration (0-24 h) of Theracurmin was 10.7 to 5.6 times higher than those of BCM-95 and Meriva, respectively. Moreover, the area under the blood concentration-time curve at 0-24 h was found to be 11.0- and 4.6-fold higher with Theracurmin than BCM-95 and Meriva, respectively. These data indicate that Theracurmin exhibits a much higher absorption efficiency than other curcumin drug-delivery system preparations.

Kanai et al. conducted a phase I study on Pancreatic or biliary tract cancer patients who failed standard chemotherapy [28]. They selected Theracurmin containing 200 mg of curcumin (Level 1) as a starting dose, and the dose was safely escalated to Level 2, which contained 400 mg of curcumin. Theracurmin was orally administered every day with standard gemcitabine-based chemotherapy. In addition to safety and pharmacokinetics data, NF- κ B activity, cytokine levels, efficacy, and quality-of-life score were evaluated. Ten patients were assigned to level 1 and six were to level 2. Peak plasma curcumin levels (median) after Theracurmin administration were 324 ng/mL (range, 47-1,029 ng/mL) at Level 1 and 440 ng/mL (range, 179-1,380 ng/mL) at Level 2. No unexpected adverse events were observed and 3 patients safely continued Theracurmin administration for >9 months. The study concludes that repetitive systemic exposure to high concentrations of curcumin achieved by Theracurmin did not increase the incidence of adverse events in cancer patients receiving gemcitabine-based chemotherapy.

Some types of pancreatic cancer cells overexpress the epidermal growth factor receptor (EGFR), which is a potential target for anticancer agents. Le et al. examined the effect of epidermal growth factor (EGF)-conjugated liposomes containing curcumin (EGF-LP-Cur) on three different EGFR-expressed human pancreatic cancer cell lines, BxPC-3, Panc-1 and Mia Paca-2 [29]. They demonstrated that it is feasible to prepare liposomal vesicles of EGF-LP-Cur and that it is stable in the liquid vehicle at ambient conditions for three weeks. In addition, the formulation of curcumin had higher cytotoxicity on BxPC-3 than on any other cells. It is also shown that the cellular uptake of curcumin on BxPC-3, which is essential for cytotoxicity, is associated with the EGFR-mediated mechanism of action. Their results showed that

targeting EGFR with EGF-conjugated curcumin liposomes enhanced the antitumor activity of curcumin against human pancreatic cancer cells.

Nanosuspension is one of the most promising strategies to improve the oral bioavailability of insoluble drugs. Wang et al. developed curcumin nanosuspensions to enhance curcumin oral bioavailability using a cost-effective method different from conventional techniques [30]. The low-cost and time-saving method was highly suitable for fast and inexpensive preparation. In vitro dissolution degree of the prepared curcumin nanosuspensions using TPGS or Brij78 as a stabilizer was greatly increased. Pharmacokinetic studies demonstrated that the oral bioavailability of curcumin was increased 3.18 and 3.7 times after administration of Curcumin/TPGS nanosuspensions or Curcumin/Brij78 nanosuspensions when compared with the administration of Curcumin suspension.

Ozawa et al. evaluated the role of curcumin internal metabolite, curcumin β -D-glucuronide (curcumin monoglucuronide) [31]. They orally administered highly bioavailable curcumin to rats and confirmed that curcumin is conjugated when it passes through the intestinal wall. Curcumin β -D-glucuronide was then orally administered to rats. Despite its high aqueous solubility compared to free-form curcumin, it was not well absorbed. Later when curcumin β -D-glucuronide was injected intravenously into rats, high levels of free-form curcumin, thought to be sufficiently high to be pharmacologically active, were observed. The in vivo antitumor effects of curcumin β -D-glucuronide following intravenous injection were then evaluated in tumor-bearing mice with the HCT116 human colon cancer cell line. The tumor volume within the curcumin β -D-glucuronide group was significantly less than that of the control group. Moreover, there was no significant loss of body weight in the curcumin β -D-glucuronide group compared to the control group. The study concluded that curcumin β -D-glucuronide could be used as an anticancer agent without the serious side effects that most anticancer agents have.

Curcumin in Combination with Gemcitabine

Even though new drug combinations have been developed with better response and survival rate, gemcitabine monotherapy is still one of the standard treatments for pancreatic cancer for patients who can't tolerate the toxicity of other chemotherapeutic regimens. Different studies have been done to evaluate the safety and feasibility of complementary therapy using curcumin with gemcitabine-based chemotherapy with the hope that it can increase treatment efficacy without adding further toxicity.

Kunnumakkara et al. showed that curcumin potentiates the antitumor effects of gemcitabine in pancreatic cancer by suppressing proliferation, angiogenesis, NF- κ B, and NF- κ B-regulated gene products [32]. Curcumin and gemcitabine together inhibit the expression of NF- κ B-dependent gene products VEGF, cyclin D1, c-myc, ICAM-1, MMP-9, COX-2, survivin, Bcl-2, Bcl-xL, and IAP-1 in pancreatic tumor tissues.

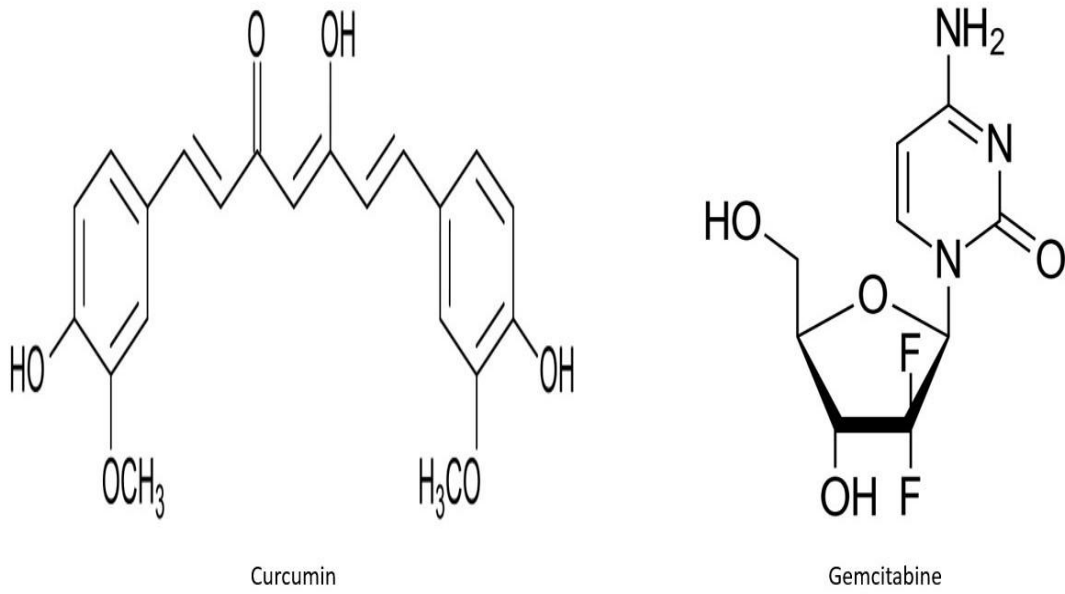


Fig 1. The Structure of Curcumin and Gemcitabine

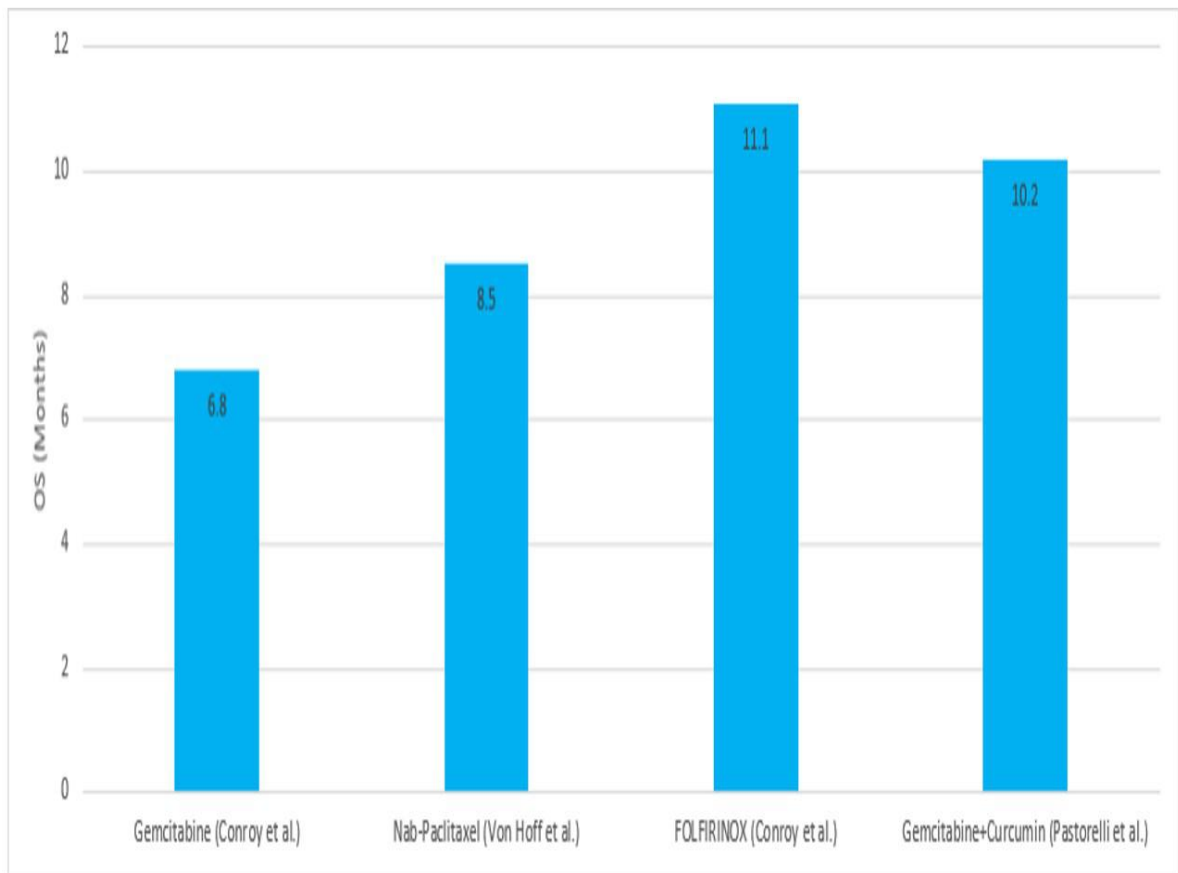


Fig 2. Overall Survival (OS) in Months Comparison of Gemcitabine, Nab-Paclitaxel, FOLFIRINOX and Combined Gemcitabine Curcumin in Metastatic Pancreatic Cancer

Yoshida et al. reported the re-sensitization of chemoresistant PDAC cells by curcumin through the inhibition of the PRC2-PVT1-c-Myc axis [33]. Using gemcitabine-resistant pancreatic ductal adenocarcinoma cell lines, they found that curcumin sensitized chemoresistant cancer cells by inhibiting the expression of the PRC2 subunit EZH2 and its related lncRNA PVT1. Curcumin was also found to prevent the formation of spheroids, a hallmark of CSCs, and to down-regulate several self-renewal driving genes. They confirmed their in vitro findings in a xenograft mouse model where curcumin inhibited gemcitabine-resistant tumor growth. Overall, this study indicates clinical relevance for combining curcumin with chemotherapy to overcome chemoresistance in pancreatic ductal adenocarcinoma.

Epelbaum et al. did a study to evaluate the activity and feasibility of gemcitabine in combination with curcumin in patients with advanced pancreatic cancer [34]. Patients enrolled in the study received 8,000 mg of curcumin by mouth daily, concurrently with gemcitabine 1,000 mg/m² IV weekly × 3 of 4 wk. The compliance for curcumin at a dose of 8,000 mg/day, when taken together with systemic gemcitabine was low in this study as out of seventeen patients, 5 patients (29%) discontinued curcumin after a few days to 2 wk due to intractable abdominal fullness or pain, and in 2 other patients, the dose of curcumin was reduced to 4,000 mg/day because of abdominal complaints. One of 11 evaluable patients (9%) had a partial response, 4 (36%) had stable disease, and 6 (55%) had tumor progression. Time to tumor progression was 1–12 mo (median 2.12), and overall survival was 1–24 mo (median 5).

Kanai et al. conducted a phase I/II study in which gemcitabine-resistant patients with pancreatic cancer received 8 g oral curcumin daily in combination with gemcitabine-based chemotherapy [24]. The primary endpoint was safety for phase I and feasibility of oral curcumin for phase II study. The median compliance rate of oral curcumin was 100% (Range 79–100%). Median survival time after initiation of curcumin was 161 days (95% confidence interval 109–223 days) and 1-year survival rate was 19% (4.4–41.4%). Plasma curcumin levels ranged from 29 to 412 ng/ml in five patients tested. Although the quality-of-life score was not included in the pre-specified endpoints in this study, several patients reported an improvement of cancer or chemotherapy-related symptoms (e.g. fatigue, pain, constipation) after the initiation of curcumin intake.

Soldà et al. evaluated the possible synergistic activity of curcumin extract, conjugated with phospholipids to enhance bioavailability, and gemcitabine in advanced pancreatic cancer in a phase II trial [35]. Previously untreated patients with histologically confirmed metastatic or locally advanced pancreatic cancer received gemcitabine (1000 mg/m² in 100 minutes on day 1, 8, 15 every 28 days) and curcumin (2000 mg/die, continuously) until progression or unacceptable toxicities or patients refusal. Primary endpoint was response rate RR (according to RECIST criteria version 1.1); secondary endpoints were progression-free survival PFS, overall survival OS, tolerability and quality of life QoL. Serum samples collection for inflammatory biomarkers was also performed. The overall RR was 28,2% (all partial responses), stable disease (SD) was reported in 33,3% of cases with a disease control rate (RR + SD) of 61,5%. Grade 3/4 hematological toxicities included neutropenia (41%, but no febrile neutropenia were observed) and anemia (7,7%). Neither grade 3/4 non-hematological toxicities nor treatment-related deaths were reported.

In another phase II trial conducted by Pastorelli et al., patients received gemcitabine and Meriva®, a patented preparation of curcumin complexed with phospholipids [36]. 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. 27.3% response rate was observed and 34.1% of cases were 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.

Soldà et al. presented a case of a patient with locally advanced disease treated who could undergo surgery after 14 cycles of therapy with gemcitabine and curcumin conjugated with phospholipids (Meriva®) [37]. Treatment was well tolerated without severe toxicities or impairment of quality of life. At the time of the case presentation, 9 months from surgery and 28 months from initial diagnosis, the patient was disease-free and in good clinical condition.

Paclitaxel and curcumin co-bound albumin nanoparticles

Nanoencapsulation has emerged as a potent strategy to enhance the therapeutic potential of conventional drugs. Co-delivery of nanoparticle-based curcumin and chemotherapy has shown efficacy for improving intracellular drug concentration and enhancing the synergistic effect in cancer therapy by sensitizing cancer cells towards chemotherapeutic drugs [38].

Albumin is a natural biocompatible and biodegradable protein that possesses many chemical groups for functionalizing drug or ligand attachments such as amines, carboxylates, and thiols on its surface. Albumin is sometimes used as a carrier protein for nano-delivery systems. Albumin nanoparticles are considered to be an effective way to load water-insoluble anticancer drugs and target tumors via the gp60-mediated pathway. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel or protein-bound paclitaxel) is approved by the FDA to use with gemcitabine for treating late-stage pancreatic cancer. Kim et al. (2016) prepared an albumin nanoparticle formulation for co-loading paclitaxel and curcumin, via nanoparticle albumin-bound technology using high-pressure homogenization [8]. The paclitaxel/curcumin co-bound albumin nanoparticles had a slightly greater particle size of ~250 nm than that of plain paclitaxel albumin nanoparticles and curcumin albumin nanoparticles (~234 and ~134 nm, respectively), with spherical surface morphology and stable size maintenance. The loaded paclitaxel and curcumin were released gradually from the paclitaxel/curcumin albumin nanoparticles over the one day test period. Paclitaxel release was slightly faster than curcumin release from the paclitaxel/curcumin albumin nanoparticles ($97.7 \pm 1.7\%$ and $76.2 \pm 0.5\%$, respectively). These two drugs appeared to be released independently without any significant interaction between the two. This one day period was considered sufficient for exhibiting an anti-tumor effect

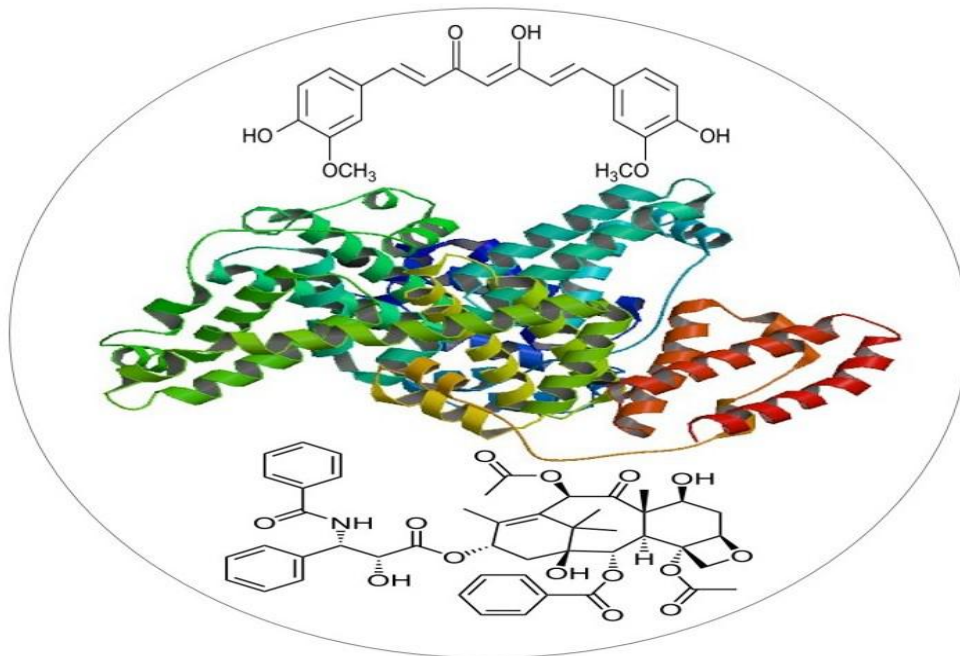


Fig 3. Albumin co-bound Paclitaxel and Curcumin (Paclitaxel-Nab-Curcumin)

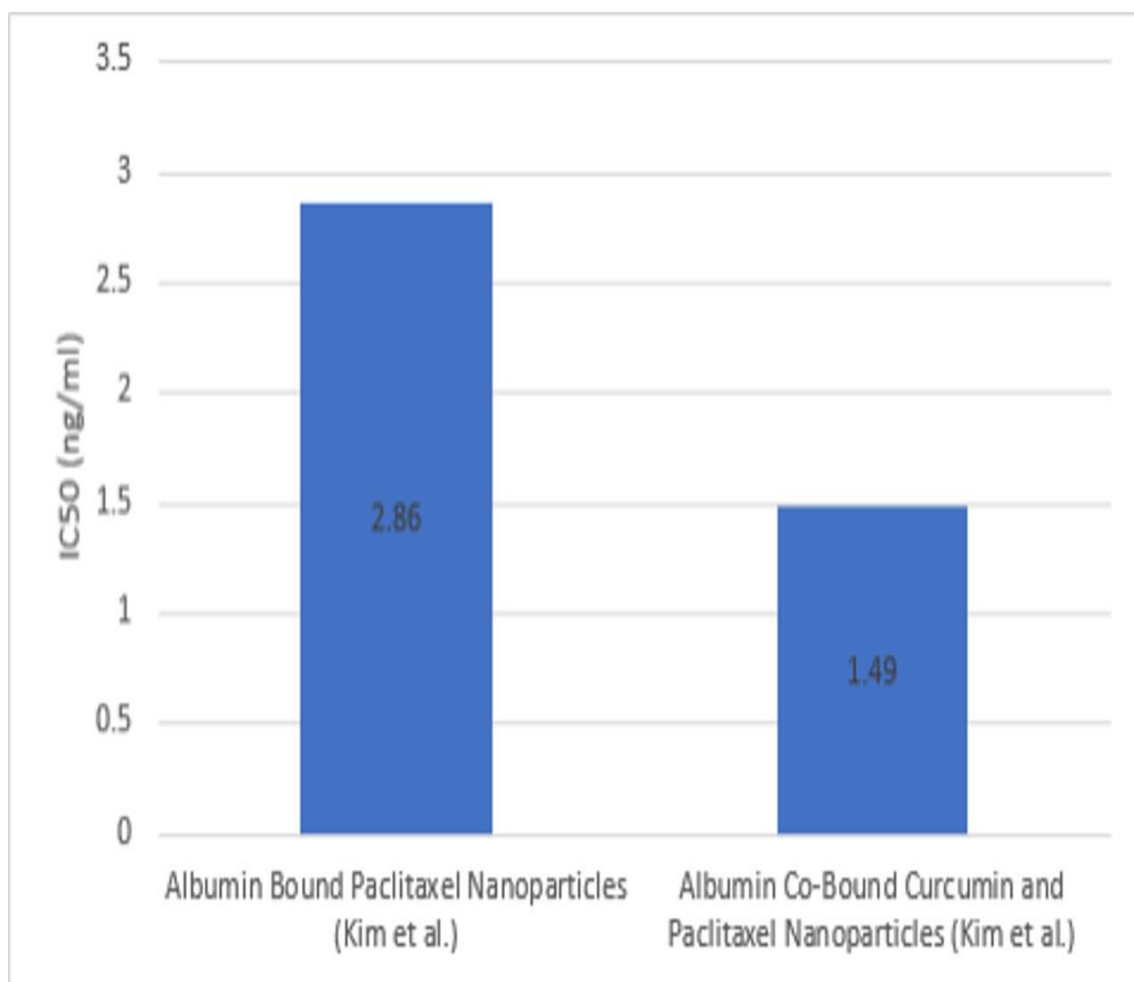


Fig 4. Comparison of IC₅₀ Values of Albumin Bound Paclitaxel Nanoparticles (2.86 ± 0.11 ng/ml) and Albumin Co-Bound Curcumin and Paclitaxel Nanoparticles (1.49 ± 0.02 ng/ml) after a 24 hour exposure

in vivo because many studies have shown that intravenously injected albumin nanoparticles are delivered to tumor sites within 3~12 h via an enhanced permeability and retention effect. The cytotoxicities of paclitaxel albumin nanoparticles or paclitaxel/curcumin albumin nanoparticles in Mia Paca-2 cells were assessed using the MTT assay. Paclitaxel/curcumin albumin nanoparticles appeared to be efficiently internalized into Mia Paca-2 cells and co-treatment with paclitaxel and curcumin using albumin nanoparticles markedly decreased Mia Paca-2 cell viability. The IC₅₀ values of plain paclitaxel albumin nanoparticles and paclitaxel/curcumin albumin nanoparticles after a 24 h exposure were 2.86 ± 0.11 and 1.49 ± 0.02 ng/ml, respectively showing a 71% increase in cytotoxicity. The enhanced cytotoxicity of paclitaxel/curcumin albumin nanoparticles seemed to be due to the combined treatment of paclitaxel and curcumin. Co-treatment of chemotherapeutics has resulted in enhanced antitumor effects in vitro and in vivo. The combined use of paclitaxel and gemcitabine displays a synergistic antitumor effect in pancreatic cancer. Similarly, paclitaxel/curcumin albumin nanoparticles seemed to be synergistically effective for killing Mia Paca-2 cells. These results suggest that paclitaxel/curcumin albumin nanoparticles can be a new potential anticancer agent for combination therapy. This system offers the clinical possibility of an improved anti-tumor pharmaceutical to synergistically suppress pancreatic tumors and may allow reduced chemotherapeutic doses.

Curcumin in Combination with FOLFIRINOX

Not much work has been done related to the use of curcumin in combination with FOLFIRINOX (folinic acid, fluorouracil, oxaliplatin, irinotecan) in pancreatic cancer. But there are several studies supporting the use of curcumin with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and irinotecan in other types of cancers. Curcumin acts synergistically with FOLFOX in gastric cancer in vitro and in vivo by inducing apoptosis via Bcl/Bax-caspase 8,9-caspase 3 pathway [39]. Curcumin is found to be a safe and tolerable adjunct to FOLFOX chemotherapy in metastatic colorectal cancer and by itself or together with FOLFOX, reduce/eliminate colon cancer stem cells, and enhances the effects of FOLFOX in mediating growth inhibition of colon cancer cells by attenuating EGFR and IGF-1R signaling pathways [40-42]. Curcumin inhibits cancer stem cells and the addition of curcumin to FOLFOX enhanced anti-proliferative and pro-apoptotic effects leading to reduced expression of stem cell-associated markers ALDH and CD133 in ex vivo model of colorectal liver metastases [43]. Curcumin enhances the efficacy of irinotecan-induced apoptosis of colorectal cancer in vivo, restores the irinotecan-induced autophagy of small intestinal epithelium, attenuates resistance to irinotecan through induction of apoptosis of cancer stem cells in chemoresistant colon cancer cells and enhances the effects of irinotecan on colorectal cancer cells by inhibiting cell viability and inducing cell cycle arrest and apoptosis, and these effects may be mediated, in part, by reactive oxygen species generation and activation of the endoplasmic reticulum stress pathway [44-46]. In one colorectal cancer study, curcumin also reduced irinotecan-induced diarrhea [44]. There is a need for combined curcumin FOLFIRINOX clinical trials in pancreatic cancer to know if curcumin can enhance the effectiveness of FOLFIRINOX in pancreatic cancer and reduce FOLFIRINOX toxicity.

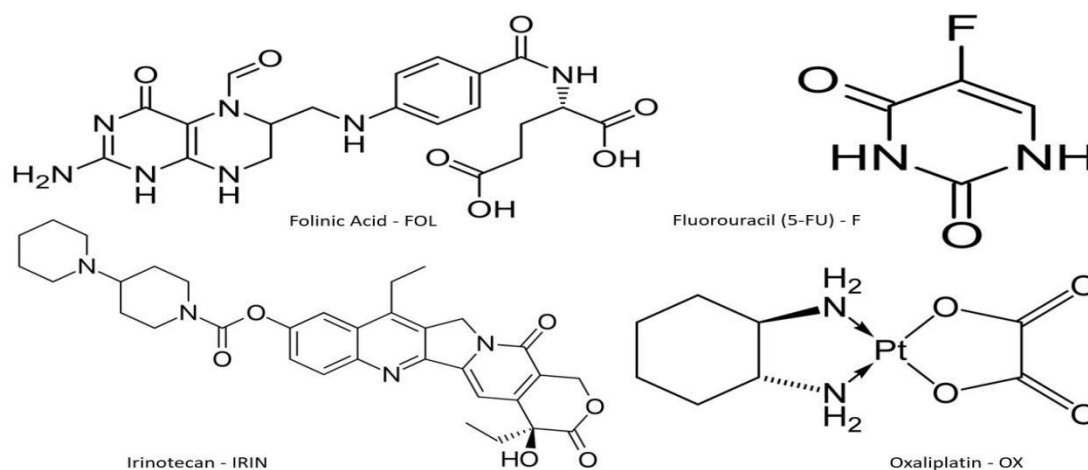


Fig 5. FOLFIRINOX (Folinic Acid, Fluorouracil, Irinotecan, Oxaliplatin)

Conclusion

Currently, neither surgical resection nor any chemotherapeutic agent can ensure a complete cure for pancreatic cancer but there is a potential in different combination regimens of curcumin in pancreatic cancer to increase median survival in pancreatic cancer in comparatively less toxic, novel ways. Also, curcumin combination chemotherapy may lead to the improvement of cancer-related symptoms and drug induced chemotherapy-related symptoms including sensitivity to pain, fatigue, depressive behaviors, constipation, and diarrhea. The poor bioavailability of curcumin has been the major obstacle for its clinical application. To overcome this problem, several curcumin preparations have been developed including cost-effective preparation methods to increase the bioavailability of curcumin. Different studies have shown that gemcitabine curcumin combination regimen can effectively increase survival with less toxicity in patients who are resistant to gemcitabine and can't even tolerate the toxicity of other chemotherapeutic combination regimens including gemcitabine nab-paclitaxel combination regimen and FOLFIRINOX. In some of these studies, gemcitabine curcumin combination therapy has shown an improvement over gemcitabine nab-paclitaxel combination therapy with comparatively better progression-free survival rates and overall survival rates and that may make it a potentially better and less toxic alternative to gemcitabine nab-paclitaxel combination. Although clinical trials are needed, with enhanced cytotoxicity, paclitaxel and curcumin cobound albumin nanoparticles also have the potential to become another alternative chemotherapeutic regimen for pancreatic cancer. For those patients who can tolerate gemcitabine paclitaxel regimen toxicity, there can also be a future possibility of using paclitaxel and curcumin cobound albumin nanoparticles with gemcitabine and this triple therapy, that is, gemcitabine in combination with paclitaxel-nab-curcumin, may have enhanced therapeutic effects with comparatively less toxic effects. Curcumin has shown its effectiveness with the constituents of FOLFIRINOX in other types of cancers, therefore there is a need for curcumin FOLFIRINOX combined clinical trials in pancreatic cancer as curcumin has the potential to increase the effectiveness of FOLFIRINOX as well as reduce its toxic side effects.

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