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Nanomedicine in Pancreatic Cancer: A New Hope for Treatment

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Abstract
Pancreatic ductal adenocarcinoma (PDA) has one of the worst prognosis and higher mortality among most cancers. The diagnosis of PDA is frequently delayed due to a lack of specific biomarkers, and the efficacy of current chemotherapeutic drugs is limited. Moreover, chemotherapy is generally applied in advanced stages, where metastatic spread has already occurred. Nanotechnologybased systems are allowing to advance in the diagnosis and treatment of PDA. New nanoformulations have shown to improve the activity of conventional chemotherapeutic agents, such as gemcitabine, and new antitumor drugs, protecting them from degradation, improving their selectivity, solubility and bioavailability, and reducing their side effects. Moreover, the design of nanocarriers represents a new way to overcome drug resistance, which requires a comprehensive understanding of the tumor microenvironment of PDA. This article reviews the current perspectives, based on nanomedicine, to address the limitations of pancreatic cancer treatment, and the futures lines of research to progress in the control of this disease.

Keywords
Pancreatic ductal adenocarcinoma — chemotherapeutic drugs — nanoparticles — drug resistance — clinical trials — gemcitabine

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Contents

1. Introduction

Pancreatic ductal adenocarcinoma (PDA), more commonly referred to as pancreatic cancer, has one of the highest mortality

rates among all cancers due to its delayed diagnosis and clinical aggressiveness [1]. Despite its relatively low incidence (2.7% of all the cancers detected), PDA represents 4.6% of overall cancer-related mortality (7th most common cause of death) [2], with a mean year survival rate at 1 and 5 years of 30% and 6%, respectively [3, 4]. In spite of the progress made in multimodal therapies, the prognosis of PDA has remained unchanged in the last decades [5, 6]. In addition, the lack of sensitive biomarkers usually leads to diagnosing PDA in advanced stages (i.e. when infiltration of adjacent structures and/or metastases are present), which is directly associated with a poor response to treatment. In fact, it is known that patients with PDA of less than 10 mm have a better prognosis [7, 8]. For these reasons, great efforts are being made to develop new therapies enabling tumor regression and increased survival rates and quality of life in these patients [1]. In this context, nanotechnology represents a novel opportunity to improve treatment response in PDA. The use of biocompatible nanoparticles (NPs) is giving rise to a new generation of nanodrugs with increased activity, reduced toxicity, and more selectivity against PDA cells.

Surgical resection, the preferred treatment for PDA, can only be performed in cases where the tumor is well delimited, which represents a low proportion of patients (20%) [7]. In these cases, surgery is usually complemented with chemotherapy. The use of chemoradiation remains controversial [9]. Hence, after surgery, most patients are treated exclusively with chemotherapy, gemcitabine (GEM) and 5-fluorouracil (5-FU) being the most widely used agents in non-metastatic stages [10], and irinotecan, 5-FU, oxaliplatin, and leucovorin (FOLFIRINOX) in metastatic stages [11]. With GEM, the 5-year survival rate has reached 23% [12], and a nanodrug combining paclitaxel (PTX) and albumin [13] has been used to treat metastatic PDA. Recent studies suggest using new NPs to improve the treatment of PDA, although a considerable variability of results has been reported. This review aims to gather the most relevant data regarding the potential applications and beneficial effects of NPs in the treatment of pancreatic cancer.

2. PANCREATIC CANCER: FROM MOLECULAR PATHOPHYSIOLOGY TO TARGETED THERAPY

Advancements in understanding the molecular biology of PDA is helping to improve the applications of previously known therapeutic targets [14], as well as to determine new molecular targets that may be useful in drug targeting. In this regard, two novel intracellular factors, siRNA and miRNA, have attracted attention. siRNA is a double-helix molecule containing 21-23 nucleotides. In its active form, inside the cytoplasm, also known as RNA-induced silencing complex (RISC), siRNA has the ability to silence and inactivate genes–including cancer-related genes- [8]. In PDA, the genetic targets of siRNA are K-RAS [15] -involved in signaling pathways related to cell growth and proliferation [11]- and Notch -related to the epithelial-mesenchymal transition and thus to malignant transformation [16, 17]-. Furthermore, it has been recently demonstrated that vascular endothelial growth factor (VEGF), an angiogenic factor that boosts tumor expansion, is another target of siRNA [18].

On the other hand, miRNAs are non-coding RNAs consisting of 20-24 nucleotides [19] that participate in the regulation of different tumor processes. Certain miRNAs have been linked with PDA. For example, miR-150, which has tumor-suppressing properties [20], has been shown to inhibit MUC4, a glycoprotein of the cell membrane crucial for the development of metastases in PDA [21]. The blocking of MUC4 inhibits HER2, which participates in the signaling cascade of PDA [22]. Similarly, miR-145 inhibits MUC13, another glycoprotein of the cell membrane that inactivates p53 [23]; miR-34a acts on bcl-2, a key molecule for the permeability of mitochondrial membrane and for the regulation of apoptosis, c-myc, which encodes transcription factors, and cyclin D1, a regulatory protein of the cell cycle [24].

Finally, the application of nanotechnology-mediated gene therapy has made it possible to act on p53, which is mutated in most pancreatic cancer processes and reduces the efficacy of chemotherapy [25] due to its key role in the control of the cell cycle, along with p16 and K-RAS-2.

3. DRUG RESISTANCE IN PANCREATIC CANCER

The development of chemoresistance is one of the main causes explaining the lack of efficacy of some treatments in pancreatic cancer. However, the exact mechanisms underlying drug resistance remain unclear (Fig. 1). It is known that equilibrative and concentrative nucleoside transporters (ENT and CNT, respectively) mediate the cell uptake of GEM. The down-regulation of the expression of hENT1 and hCNT3 by the cell-matrix protein CYR61, which is induced by TGF--ALK5-Smad in the stellate cells of the pancreas, hinders the passage of GEM through the cell membrane and leads to increased resistance to this agent [26]. Inside the cell, GEM is phosphorylated by deoxycytidine kinase (DCK), an enzyme that may contribute to drug resistance. Moreover, multidrug resistance-associated proteins (MRPs), ATP binding cassettes (ABC) transporters, can reduce the intracellular concentrations of GEM [27]. In fact, the expression of MRP1, which is induced by MUC1 and RUNX3, promotes resistance to GEM [28]. In addition, MUC1 stabilizes HIF-1a, a factor that regulates the glycolytic pathway and the de novo synthesis of pyrimidines, increasing the intrinsic levels of deoxycytidine triphosphate (DCTP) which, in turn, reduce the levels of GEM by a mechanism of molecular competition [29]. Some authors have demonstrated alternative splicing of the pyruvate kinase (PKM) gene in PDA cells based on the expression levels of PTBP1 (polypyrimidine-tract binding protein). For this, the modulation of the expression of PKM2 has been linked with the response to GEM and cisplatin by PDA cells [30]. Finally,

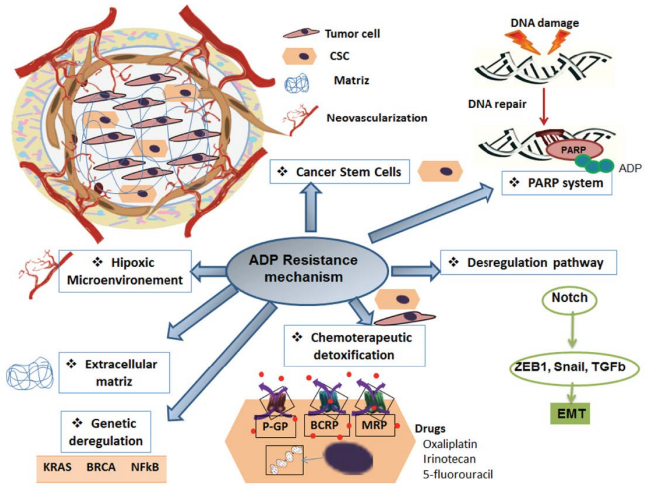

Figure 1. Depiction of the different resistance mechanisms in pancreatic cancer. The extracellular matrix, which is rich in hyaluronic acid and fibronectin, hinders the diffusion of chemotherapy agents. Likewise, the tumor environment is very hypoxic, which favors resistance to treatment. Cancer stem cells have a higher resistance as compared to the rest of the tumor cells, increasing the likelihood of recurrence and metastasis. These phenomena are mainly due to the dysregulation of signaling pathways, such as RAS, PI3K, JNK, Notch. In addition, genetic dysregulation, due to mutations in K-RAS or BRCA or to NF-, reduces the activity of chemotherapy drugs. In pancreatic cancer, the mechanisms of gene repair play a major role in resistance to chemotherapy agents, as is the case with the poly-ADP ribose polymerase (PARP) repair system. Finally, membrane transporters, such as P-glycoprotein, BCRP or MRP, expel the chemotherapy drugs from the cell, thus, impeding their activity. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

the ribonucleotide reductase (RNR) enzyme and, more specifically, the overexpression of two genes that encode for the alpha and beta subunits of this enzyme (i.e., Rrm1 and Rrm2) has been associated with higher resistance to GEM [31].

The epithelial-mesenchymal transition (EMT) has been attracting growing interest in the last years due to its role in resistance to chemotherapy agents. The nucleoside transporters ENT1 and CNT3 were shown to be significantly increased in mice knocked out for Twist and Snail, transcription factors that induce EMT [32]. Likewise, the depletion of Zeb1, a transcriptional repressor of epithelial genes, led to re-sensitization to GEM in PANC-1, a resistant pancreatic cancer cell line [33]. Another study showed that miR-223 governed the EMT-induced resistance to GEM, in part due to the down-regulation of its target Fbw7, and subsequent upregulation of Notch-1 in pancreatic cells [34]. Of note, the tumor microenvironment is enriched in EMT mediators, including cytokines (e.g., TGF-1), growth factors (e.g., EGF receptor), and hypoxia [28].

Finally, different studies indicate that a number of non-coding RNAs have a regulatory role in drug resistance. In PDA, miRNAs regulating the K-RAS, PI3K-AKT, NF-, and Hedgehog signaling pathways have been associated with resistance to GEM. In fact, miR-2 not only induces resistance to 5-FU mediated by PTEN and PDCD4 [35] (tumor-suppressing genes), but also leads to resistance to GEM due to its activity on PTEN, and overexpression of MMP2/9 metalloproteinases and VEGF, which, in turn, induce the PI3K/AKT pathway [36]. On the other hand, miR-506, a tumor suppressor that inhibits the SPHK1/Akt/NF- signaling pathway, is known to be silenced in pancreatic cancer [37]. Similarly, miR-181c has been shown to induce chemoresistance in PDA by repression of Hippo signaling, acting against the proteins that form the core of the kinase [38]. miR-17-92 counteracts quiescence and chemoresistance in PDA stem cells by regulating ALK4, p21, and TBX3 [39]. Moreover, it has been demonstrated that the long non-coding RNA HOTTIP promotes cell proliferation, invasiveness, and chemoresistance, via the modulation of HOXA13 [40].

4. PANCREATIC CANCER AND NANOMEDICINE

Given the current limitations of the therapeutic approaches used in PDA, nanoformulations have emerged as a promising opportunity to improve the outcomes of both traditional and novel drugs against this tumor. Moreover, due to their peculiar physical and chemical properties, nanoformulations can be used not only for the treatment of PDA but also for its detection, generating images that could have a widespread impact on early diagnosis [41].

4.1 Nanoformulations: General Properties

Nanoformulations are nanometric carriers that facilitate the arrival of drugs to target cells, leading to improved efficacy, reduced toxicity, and increased specificity [42]. Their morphological properties (volume and surface) influence the pharmacokinetics and bioavailability of drugs in the body [43]. In addition, their shape (cube, sphere, rods), composition (inorganic, organic, hybrid), and size enable treatment adaptation for different types of cancer [44]. In comparison with conventional anti-tumor drugs, nanoformulations offer several advantages, including i) significant reduction of side effects, as in the case of 5-FU, and increased specificity towards the therapeutic target [45]; ii) increased activity and potential targeting of drugs, as is the case with the association of GEM and anti-CD47 to treat PDA [46]; iii) reduced drug resistance in pancreatic cancer cells [47]; and iv) the possibility of applying combined therapies, including the use of hyperthermia when NPs are hybrid and include magnetic cores [48]. Regardless of their form, NPs are internalized in the cell, generally by endocytosis [49], and reduce the phase I (intracellular reticular system) and phase II (liver) drug metabolism [50]. Furthermore, the load of NPs enables, and requires, balancing bioavailability and internalization [51], i.e., its properties can be modified by a wide variety of molecules in order to

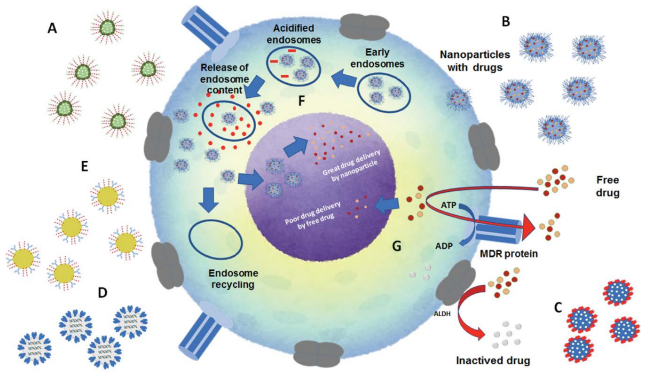

Figure 2. Use of nanoparticles (NPs) in the treatment of pancreatic cancer. A. NK105, a micellar nanoparticle composed of a shell formed by a copolymer of polyethylene glycol (PEG) and a modified poly aspartate chain, trapping inside the chemotherapeutic drug Paclitaxel (PTX); B. NPs coated with poly (lactic-co-glycolic acid) polymers (PLGA) functionalized with Gemcitabine and Simvastatin; C. Nab-paclitaxel (PTX) NPs, formed by an albumin shell and functionalized with PTX; D. Rexin-G, a NP based on gene therapy. This NP contains DNA encoding the mutated cyclin G1 proto-oncogene inside, allowing intracellular coding of a protein capable of replacing the endogenous cyclin G1; E. CYT-6091, an NP composed of a colloidal body of gold, coated with PEG and recombinant tumor necrosis factor (rhTNF); F. Internalization mechanism of the NPs is described above. The NPs are introduced in the cell by endocytosis and then coated inside early endosomes. These are subsequently acidified and cause the covers to break, releasing the endosomal content, and the NP. Finally, this endosome is recycled by the cell itself; G. Mechanisms of drug resistance by tumor cells. Multidrug resistance (MDR) proteins can release drugs inside them outside the cell consuming cellular ATP. In addition, the ALDH enzymes (aldehyde dehydrogenases) can modify and inactivate the free drug. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

improve biofunctionality, internalization, biodistribution, and metabolism [52].

4.2 Nanoformulations: Particular Focus on Pancreatic Cancer

In order to efficiently design nanodrugs against PDA, it is essential to understand the role of the extracellular matrix. The extracellular matrix consists of connective tissue that supports parenchymal cells in a scaffold containing different fibers, including collagen, elastin, fibronectin, laminin, glycosaminoglycans, glycoproteins, and proteoglycans [53]. The histological and molecular properties of this matrix are modified during the development of a tumor [54], with proteinases and especially metalloproteinases being essential mediators in this process. These enzymes facilitate a mechanism for escaping apoptosis via the excision of Fas (CD95) [55], and influence neoangiogenesis, which is essential for tumor growth and metastasis [56]. Hence, acting on the tumor stroma may be a focalized way of treating PDA. In this way, matrix metalloproteinase inhibitors (MMPI) associated with NPs, which allow the binding of drugs such as doxorubicin, represent a promising therapy [57]. In addition, nanodrugs must overcome the stroma barrier, which includes blood vessels surrounded by tumor cells, a high concentration of pericytes, and predominant extracellular compounds such as collagen [58, 59]. The inhibition of transforming growth factor-beta (TGF-) [60], as well as therapies based on cancer stromal targeting (CAST) using antibodies against fibers of collagen and fibrin, have demonstrated to successfully release cytotoxic agents [61].

The progression of PDA can be blocked by NPs associated with siRNA and miRNA. For instance, biodegradable polyester vectors, synthesized by Yang et al. [62] and loaded with siRNA enabled a >70% reduction in the expression of K-RAS and Notch-I. Moreover, it has been demonstrated that these carriers can sensitize cancer cells to GEM [63]. Besides, a significant decrease in the proliferation of PDA cells has been achieved using magnetic NPs with the ability to inhibit the expression of MUC13 and HER-2, and to restore the expression of p53 via miRNA [64]. Analogously, a decreased proliferation of PDA cells has been demonstrated using peptides conjugated with cationic -cyclodextrinpolyethyleneimine (CC9) [50] transporting miRNA-34. In the same way, iron oxide nanoparticles (IONPs) associated with miRNA-21, which has an essential role in the proliferation of pancreatic cancer cells and bound to anti-sense oligonucleotides (ASOs) and GEM, and targeted by CD44v6, have demonstrated high cytotoxicity [65].

4.3 Advances in the Use of Nanoformulations in Pancreatic Cancer

Undoubtedly, significant progress in PDA has been made with the use of nanoformulations. However, most results have been obtained in experimental settings, either in vitro or in animal models. Nevertheless, these advancements make it feasible to assume that, in the mid-term, it will be possible to design clinical strategies based on nanoformulations (Fig. 2). In this section, the main advances in this field will be highlighted.

4.3.1 Solid Lipid Liposomes and Nanoparticles

Liposomes are nanocarriers composed of a lipid bilayer containing water that enables the transport of hydrophilic agents, as well as the incorporation of some hydrophobic molecules on their external surface. Therefore, liposomes can carry molecules such as DNA or RNA inside [66]. Liposomes associated with silica NPs, GEM and PTX bound to albumin were tested in PDA, showing improved delivery of both chemotherapy drugs and suppression of GEM inactivation by regulating the expression of cytidine deaminase (CDA) [67, 68], an enzyme present in the tumor stroma [69]. In addition, solid lipid NPs are lipid compounds stabilized at room temperature using surfactants (e.g., compritol®888 ATO, precirol® ATO5, tripalmitin, stearic acid, glycerol monostearate, and

cetyl palmitate) that protect the encapsulated drug, providing physical stabilization, release control [70], and improved biodistribution. These NPs also show good biocompatibility properties and are not degraded by the reticuloendothelial system [71]. The administration of ferulic acid, acetylsalicylic acid, and solid lipid NPs coated by chitosan led to a synergic inhibition of cell viability in human pancreatic cancer cells, MiaPaCa-2 and PANC-1 [72].

4.3.2 Nanoparticles and Polymeric Micelles

Polymeric NPs have a small size, which allows solving limitations related to low solubility and short in vivo half-life of many drugs [73]. Polylactic-co-glycolic acid (PLGA) NPs are highly biocompatible and have been approved by the Food and Drug Administration Agency (FDA) for human use. PLGA NPs associated with MUC-1 antibodies (TAB004) [74] improved the internalization and specificity of drugs against PDA in murine models [75]. On the other hand, polymeric micelles, i.e., NPs formed by block copolymers [76], enable a sustained release of drugs based on the conditions of the milieu, which represents a major therapeutic advantage [77]. Moreover, the ability of these NPs to incorporate metallic compounds facilitates their visualization, and thus, their diagnostic use. In fact, Zhu et al. developed the HA-VES polymer, loaded with superparamagnetic iron oxide (USPIO) modified with a polypeptide (CKAAKN) specific for cell membrane receptors present in pancreatic tumors, with the aim to detect pancreatic cancer [78]. The incorporation of different magnetic particles will allow creating a contrast agent with high specificity and low toxicity [79].

4.3.3 Polymersomes

Polymersomes are copolymers with both hydrophilic and hydrophobic properties that enable the encapsulation of different drugs simultaneously, in large amounts and with great stability against stress [80]. In PDA, Karandish et al. [81] synthesized a polymersome of N3-polyethyleneglycol (PEG)-polylactic acid (PLA) conjugated to an alkynedexamethasone derivative to improve the nuclear activity of the BBI608 factor, involved in the development of these tumors. Other authors fixed the nuclear localizing peptide, which is activated in the presence of metalloproteinase 7 on the surface of redox-sensitive polymersomes, with the aim to deliver curcumin to the nucleus of the pancreatic cancer cell [82]. Recently, polymersomes of hypoxia-responsive PLAazobenzene-PEG copolymers were tested in PDA with the aim to release drugs only in an environment of oxygen deficiency (90% release in 50 min). In this case, the experiments were conducted using an association of GEM with erlotinib [83]. Other amphiphilic polymersomes, for example, composed of L-lysine hydrochloride, -benzyl (d7) L-glutamate, and ethylene oxide, were loaded with doxorubicin, showing activity comparable to Myocet in human pancreatic cancer [84].

4.3.4 Dendrimers

Dendrimers, large-size molecules with several branches bound to a central core, are being successfully applied in cancer treatment in general, and against PDA in particular. These NPs allow an optimal administration of drugs due to several properties that make them unique, including low molecular weight, spherical shape, and branching distribution. Dendrimers enable an increased effective concentration of drugs and a prolonged release in the presence of an acid or basic environment [42, 85]. PAMAM dendrimers synthesized with PEG containing anionic carboxyl groups conjugated to an antibody against the vascular endothelial growth factor receptor (Flt1), highly expressed in pancreatic cancer cells, improved the internalization and reduced the cytotoxicity of GEM [86]. In addition, a delivery system based on PEG branched with G2 dendrimers through disulfide bonds (PSPG) enabled the combined administration of PTX and siRNA, improving treatment specificity and release of products [87]. Kesharwani et al. developed a dendrimer (PAMAM) with hyaluronic acid, targeted against CD44 and loaded with curcumin and difluorobenzylidene (CDF), showing a high in vitro toxicity in MiaPaCa-2 and AsPC-1 cell lines [88]. Finally, dendrimers have been associated with magnetic NPs in order to facilitate their entry to the fibrous stroma produced by stellate cells. Magnetic NPs conjugated with retinoic acid and PAMAN dendrimers loaded with GEM were used in vitro against the cell lines SU86.86, T3M4, Panc-1, and stroma stellate cells producing high toxicity in these cell types [89].

4.3.5 Nanogels

Nanogels are NPs with low flotation density and high dispersion in aqueous media that enable high loading capacity of anti-tumor drugs. However, due to their hydrophilic nature, the combination of nanogels with highly hydrophobic drugs is limited [90]. Nanogels associated with hyaluronic acid able to recognize CD44, loaded with curcumin bound by reversible ester bonds, showed high cytotoxicity in the MiaPaCa-2 line, and in in vivo tumors derived thereof [91]. Recently, Soni et al. developed polymeric nanogels loaded with cisplatin and associated with the anti-STn antibody (monoclonal antibody TKH2). In combination with free GEM, these nano gels showed to be effective in the T3M4 COSMC KO cell line [92].

4.3.6 Silica Nanoparticles

Silica nanoparticles show good biocompatibility, have a large surface area, and, notably, the size of their pores is variable [93]. In this group, mesoporous silica NPs (MSNPs) are commonly used as drug carriers [94] for anti-tumor agents, such as GEM [95]. In order to block CDA, a GEMinactivating enzyme, PTX and GEM were incorporated into MSNPs (LB-MSNPs). The treatment of mice with subcutaneous xenografts of PANC-1 showed to significantly reduce the tumor as compared to free GEM, LB-MSNP-loaded GEM, or GEM plus Abraxane [68]. This effectiveness has recently been suggested to depend on the pore size of the nanoparticle [96]. Moreover, LB-MSNPs conjugated with irinotecan led to a reduction of spinal, gastrointestinal, and liver toxicity in PDA as compared to a liposomal carrier [97]. Lu et al. added folic acid to

MSNPs loaded with camptothecin, enabling a very significant reduction of the minimum effective drug dose in PDA [98]. Finally, the special properties of these NPs make them ideal for diagnostic use. For instance, MSNs demonstrated to be useful in the detection of PDA using multispectral optoacoustic tomography (MSOT). For such purpose, urokinase plasminogen activator (UPA) was associated with chitosan, which enabled its targeting towards the acid medium of the pancreatic tumor stroma. Using MSOT, the results confirmed a higher accumulation of this compound in PDA in vivo, with low concentrations in the liver and kidneys [99].

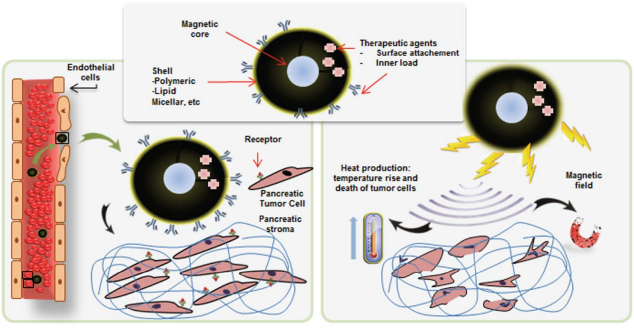

Figure 3. Hyperthermia: action mechanisms of nanoparticles (NPs). The NPs used in hyperthermia have a core with magnetic capacities, such as gold or iron oxide. In addition, they are covered by a lipid, micellar, or polymeric with different properties to improve drug transport or to bind molecules that recognize cancer cells. They reach the injured pancreatic tissue through the bloodstream (EPR effect) and can perform a direct action (i.e., drug). However, this effect is enhanced when a magnetic field is applied, causing an increase in local temperature. The temperature induces the denaturation of stromal proteins that abound in pancreatic cancer, as well as cell membrane proteins, increasing the cytotoxic effect. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

4.3.7 Carbon Nanotubes and Graphene Nanoparticles

Carbon nanotubes are cylindrical structures synthesized using hollow carbon atoms that may have either a simple wall (i.e., formed by a single row of nanographene) or multiple walls (i.e., formed by several layers of graphene concentrically wrapped). This configuration provides them with specific properties, including large surface area, ultralightweight, monolithic and hollow structure, high electrical and thermal conductivity, and outstanding mechanical resistance [42, 100, 101]. Although there are not many studies regarding the use of nanotubes in PDA, immunosensors associated with an anti-CA19-9 antibody are currently being tested for the diagnosis of PDA, offering the advantage of not interfering with other serum molecules [102]. Moreover, recent studies demonstrated that simple-wall nanotubes (SWNTs) are highly effective in photothermal therapy. The presence of antibodies on their surface enabled monitoring the cytotoxicity mediated by photothermal therapy with imaging techniques [103].

On the other hand, graphene is a bi-dimensional material made up of layers of carbon atoms arranged in a regular hexagonal pattern [104]. Its oxide has intrinsic physical and chemical properties, including much lower cytotoxicity than carbon nanotubes. The monolayer configuration of multifunctional graphene oxide was used to silence genes, such as K-RAS and HDAC-1, using siRNA in Mia-PaCa-2 cells, inducing apoptosis, inhibition of cell proliferation, and cell cycle arrest. The synergic combination of gene silencing with NIR thermotherapy, which uses infrared light to transform luminous energy into thermal energy leading to cell death, enabled a reduction greater than 80% of the tumor volume in vivo [105]. Moreover, the use of higher doses of laser (0.75 W/cm2) along with higher doses of reduced graphene oxide (2 mg/kg) enabled an increased treatment temperature and even greater reduction in tumor growth. The combination with a 980 nm laser allowed an ideal temperature, with strong clinical potential in the future [106].

4.3.8 Nanorods, Nanowires and Quantum Dots

Nanorods are being profusely investigated for the treatment of cancer. With variable dimensions from 1 to 100 nm, nanorods are synthesized from semiconductive or metallic materials. In particular, gold has low cytotoxicity and can be applied as a contrast agent or in photothermal therapy [107-109]. These NPs enable a synergic effect of siRNA and doxorubicin in Panc-1 cells, both in vitro and in vivo, leading to the inactivation of K-RAS and cell cycle arrest. The unique properties of nanorods in terms of absorption and scattering of a NIR-window light (665 nm) enable the controlled release of molecules towards tumor cells [110]. Zeiderman et al. synthesized pH-sensitive gold nanorods coated with mesoporous silica and chitosan, and added the pHILP peptide for improved targeting. These NPs were loaded with GEM and resulted to be significantly more toxic for S2Vp10 and MIaPaCa-2 cells than free GEM. Moreover, in vivo targeting of these NPs towards retroperitoneal pancreatic tumors was demonstrated using MSOT [111].

On the other hand, nanowires are structures with a diameter of few nanometers and a high length mainly used for diagnostic purposes. Nanowires are synthesized from silica, germanium, gold, and carbon, among other atoms [112]. The experience with these NPs in pancreatic cancer is scarce; they have been used for the measurement of circulating PDA cells by capture. The combination of EpCAM -a surface marker of circulating tumor cells- with the specific peptide CKAAKN in a silica nanowire demonstrated a high capture efficiency (95.6%). In a clinical trial, including 16 patients with PDA, the use of nanowires allowed the isolation of circulating pancreatic cells to analyze K-RAS mutations, suggesting a strong potential in the diagnosis of PDA [113]. Nanowires based on nickel and gold are being developed for radiofrequency-mediated thermal therapy due to the paramagnetic properties of these metals. Their application showed to cause high mortality in PDA cells with pyknotic nuclei [114].

Quantum dots (QDs) are optical semiconductor nanocrys-

tals with unique electrical and optical properties due to their low weight. QDs are easily detectable because they can emit a characteristic wavelength [115]. Silver-graphene nanodots were applied to enable the administration of anti-tumor drugs in rats. Carboxymethyl insulin improves their biocompatibility as well as the efficacy of 5-FU in pancreatic cancer [116]. Another study demonstrated that NPs of human serum albumin, functionalized with hyaluronic acid and marked with fluorescent QDs, have a strong potential in the administration and visualization of drugs used in PDA, such as GEM [117].

4.3.9 Magnetic Nanoparticles

Iron magnetic nanoparticles (MNPs) have attracted interest for diagnostic and therapeutic purposes. Their versatile surface containing amino and carboxyl functional groups enables the incorporation of ligands against therapeutic targets, reduces agglutination, improves biocompatibility, and takes advantage of their magnetic properties. Magnetite and maghemite are the magnetic materials approved by the FDA, but the latter has a better intrinsic magnetic response for biomedical applications [118]. Some of their applications include cell labeling, classification and manipulation, magnetic guidance for drug release and hyperthermia, and diagnostic validity using magnetic resonance imaging (MRI) [119]. Magnetic NPs were used to introduce miRNA145 -which controls the expression of MUC13- in tumor cells, downregulate MUC13, HER2, and pAKT, and reduce cell proliferation, showing low toxicity and high hemocompatibility [64]. In addition, plasma extracellular vesicles were synthesized by capturing magnetic nanopores to identify pancreatic cancer-specific miRNAs in mice, enabling the identification of precancerous lesions [120].

4.3.10 Nanoparticles and Hyperthermia in Pancreatic Cancer

Hyperthermia consists of a slight increase in temperature (40-43ºC) that causes death in tumor cells. This effect can be boosted using radio and chemotherapy [121]. Photo- and photothermal therapies are based on the absorption of infrared radiation (NIR), enabling the excitation of electrons and subsequent generation of heat, which denaturalizes proteins and breaks nearby cell membranes. Gold-based nanostructures represent the most promising nanomaterials in photothermal therapy, although organic-based and functionalized magnetite nanomaterials may be alternatives [122]. (Fig. 3) shows the hyperthermia effect on the application of NP against pancreatic cancer cells. Iron oxide nanoparticles (IONPs) were used to generate magnetic-flow hyperthermia in MiaPaCa-2 and L929 (murine fibroblasts) cell lines. The cell damage observed correlated with the increase in temperature, treatment duration, cell type, and amount of thermal energy released and caused a 95% death of tumor cells [123]. In vivo studies using paramagnetic IONPs to treat mice with pancreatic cancer and retroperitoneal spread (intraperitoneal graft of PAN02 cells) showed that exposure to magnetic fields not only generated heat but also enabled the migration of NPs toward the tumor. As a result, the survival rate of mice with pancreatic cancer increased by 31% [123].

5. CLINICAL TRIALS IN NANOMEDICINE AND PANCREATIC CANCER

Clinical trials based on the application of nanomedicine to PDA have been increasing in the last years (Table 1). The most recent ones use NPs associated with PTX. In 2008, a phase II clinical trial comparing Abraxane® vs. GEM in 20 patients with PDA (NCT00691054) showed a mean survival rate of 6 months and stabilization in 32% of patients (Hosein PJ y cols, 2013). An ongoing phase Ib/II clinical trial is applying albumin NPs loaded with PTX (NCT0218436) on 43 patients with metastatic PDA in order to determine the maximum tolerated dose, toxicity, and overall survival. Results are currently being analyzed. Likewise, the NCT02336087 clinical trial is using albumin NPs loaded with PTX combined with a dietary supplement in 21 patients with nonresectable PDA to determine potential synergic effects of these molecules. Data collection and analysis are currently being processed. Similar NPs are being tested in patients with PDA in association with GEM (NCT02608229) with the aim to gather data regarding the maximum tolerated dose and response rate, free-progression survival, and overall survival rates. In NCT01161186, a combination of capecitabine, GEM, and albumin NPs loaded with PTX is being used in 15 patients with PDA. The results of this trial will provide relevant information about the optimal dose and safety regarding the administration of these drugs. NCT02194829 is one of the ongoing trials with more patients (133) having metastatic PDA. The trial aims to determine the efficacy of albumin NPs with PTX in combination with GEM, with and without the growth tumor inhibitor WEE1. Although no results are available yet, solid outcomes are expected to be obtained, given the high number of patients recruited in this trial. Furthermore, a relevant study using nab-paclitaxel and gemcitabine compared to gemcitabine alone after surgical removal of pancreatic cancer included 866 patients in the first phase (NCT01964430). The main focus of this trial was to determine improvement in relation to delay or prevention of recurrence or death and the study's estimated completion date is 2022 with a primary completion date in 2018. On the other hand, some trials are in the recruitment phase. This is the case of NCT03410030, which aims to explore the effects of a combined treatment of ascorbic acid with PTX, cisplatin and GEM NPs in patients with metastatic PDA not previously treated; or NCT02394535, a phase I clinical trial analyzing the adverse effects and optimal dose of albumin-PTX NPs with capecitabine and radiotherapy after the first chemotherapy regime in patients with advanced PDA. In 2019, two clinical trials started: NCT04115163, based on the administration of NPs associated with PTX and GEM at different moments (GEM at days 1 and 15, and the nanoformulation at days 3 and 17); and NCT03825328, a phase II clinical trial in patients with pancreatic cancer treated with PTX NPs in combination with GEM and oxaliplatin as the firstline treatment.

Clinical trial number	Status	Intervention	Starting year	End year	Number of patients
NCT00691054	Finished	Abraxane	2008	2012	20
NCT02178436	Active	Albumin NPs loaded with PTX	2014	2018	43
NCT02336087	Active	Albumin NPs loaded with PTX + Diet	2016	2019	21
NCT02608229	Active	Albumin NPs loaded with PTX + Gemcitabine	2015	2019	25
NCT01161186	Active	Albumin NPs loaded with PTX + Gemcitabine +Capecitabine	2010	2012	15
NCT02194829	Active	Albumin NPs loaded with PTX + Gemcitabine + WEE1	2014	2019	133
NCT03410030	Recruiting	Ascorbic acid + PTX NPs + Cisplatin + Gemcitabine	2018		
NCT02394535	Recruiting	Albumin NPs loaded with PTX + Capecitabine + Radiotherapy	2015		
NCT03401827	Recruiting	Albumin NPs loaded with PTX + Gemcitabine	2018		
NCT04115163	New	Albumin NPs loaded with PTX + Gemcitabine	2019		
NCT03825328	New	Albumin NPs loaded with PTX + Gemcitabine +Oxiplatin	2019		

Table 1. Table 1. Recent clinical trials using nanomedicine in PDA.

6. FUTURE PERSPECTIVES

The low efficacy of conventional drugs in pancreatic cancer is forcing to redirect efforts toward the development of new drugs. In spite of research advances regarding the development of new, highly sensitive biomarkers for the detection of PDA, new therapeutic tools are required to improve the prognosis of patients already diagnosed with this cancer. In this context, the development of novel and better nanocarriers is needed in order to improve the properties of antineoplastic drugs with already proven efficacy against pancreatic tumor cells. This would involve therapeutic advantages in terms of bioavailability, effectiveness, and ability to escape the intrinsic or extrinsic resistance mechanisms developed by PDA. Another line of research will consist of the development of nanoformulations that improve the application of gene therapy, an excellent alternative in the treatment of pancreatic cancer. Nanotechnology may help solve some limitations derived from the use of free nucleic acids –mainly related to their electrical charge-, including difficulties in cell uptake, instability in the bloodstream, or poor cell selectivity with regard to drug internalization [124]. In addition, nanotechnology must explore robust strategies based on cell recognition through the addition of antibodies specific to target cells. Nevertheless, nanomedicine presents certain limitations that need to be overcome in order to successfully treat cancer in general and pancreatic cancer in particular. Hence, a deeper knowledge of nanotoxicology will be necessary to determine the long-term effects that result from the accumulation of NPs in the organs, especially in the kidneys. On the other hand, theranostic nanomedicine represents a major challenge that will require new multifunctional NPs that enable the monitoring of drug distribution. A more comprehensive understanding of the molecular biology of pancreatic cells and stroma would certainly help develop more specific NPs, likely improving therapeutic efficacy. Therefore, despite the above-mentioned limitations, nanotechnology represents a promising therapeutic tool in the treatment of pancreatic cancer.

7. AUTHORS INSIGHT ON THE TOPIC

In recent years, cancer therapy is increasingly looking towards nanotechnology as a potential solution to the serious problems associated with the use of cytotoxic drugs and to improve the anti-tumor activity. It is believed that nanotechnology-based approaches within cancer treatment have become essential for the discovery and development of new therapeutic strategies. In addition, these advances are a key element in the expansion and growth of the pharmaceutical industry, which needs to research and develop new designer drugs, precision or personalized cancer therapies, and association treatments. Moreover, the increased incidence of pancreatic cancer in recent years, as well as its resistance and a low response to chemotherapy are two of the main rationales to search for new drug delivery systems that improve its prognosis. The ideal properties of these systems include biodegradability, biocompatibility, high solubility, bioavailability, and stability. It is believed that the success of some nanoformulations (e.g. Abraxane) in certain tumors does not necessarily predict the same outcome in new nanoformulations applied to pancreatic cancer. Therefore, a thorough and detailed investigation and analysis of the trials conducted on these novel nanodrugs in this tumor, which should provide answers not only about the effectiveness of the treatment but also about certain key elements in the evolution of patients, such as where the nanoformulations arrive, how they are excreted and what side effects are caused by their possible accumulation, can be foreseen. All this without forgetting the importance of making the new nanodrugs accessible and affordable to all patients, if the goal is for technological progress to have a real impact on this disease and on society. Therefore, although the immediate outlook is to be close to a promising strategy for improving drug administration in pancreatic cancer, it will be prudent to carry out a comprehensive assessment of its applicability, side effects, elimination processes, and therapeutic advantages. Finally, an interdisciplinary collaboration between experts from different fields will be essential for the optimal applicability of nanotechnology-based strategies in clinical practice.

8. CONCLUSION

Given the clinical and social relevance of PDA, the development of new therapies that improve its prognosis is an essential objective in oncology. This review highlights how the development of nanoparticle systems is helping to optimize the therapeutic efficacy of different anti-tumor drugs and focalize their activity on pancreatic tumor cells. Nanoformulations have the ability to reduce the aggressiveness of current therapies and their adverse effects, while their combination with bioactive materials significantly improves safety and selectivity toward therapeutic targets. Furthermore, certain NPs with specific properties may help in the early and efficient detection of pancreatic cancer, a cornerstone in the management of this entity. In conclusion, the clinical application of nanomedicine is not a distant dream but a near reality and, in the upcoming years, both basic and clinical research will be essential to understand its true relevance in PDA.

9. CONSENT FOR PUBLICATION

Not applicable.

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11. CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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