Emerging therapeutic nanotechnologies in pancreatic cancer: advances, risks and challenges

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Historical perspective

Pancreatic cancer is one of the most lethal cancers with extremely poor prognosis. This cancer is considered the fourth common cause of cancer-related mortality in the western world and it is predicted to become the second leading cause by 2030 [1,2].

Despite significant developments in cancer treatment, the median survival after diagnosis still ranges between 2 and 8 months; the 5-year survival rate is less than 5%, and thus early diagnosis is crucial [2,3].

Exocrine pancreatic cancer constitutes the majority of pancreatic malignancy (up to 95%), in which pancreatic adenocarcinoma is responsible for nearly 90% of the pancreatic cancer cases [2,4].

Combinational chemotherapies, like 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (named as FOLFIRINOX), are being used for pancreatic cancer treatment; however, gemcitabine remains the first-line treatment, yet it is only effective in 23.8% of these cases [2,5]. The main reason for low efficacy of gemcitabine is due to its' chemical instability and poor cellular uptake, resulting in a very short half-life and low bioavailability. This fact leads to a frequent administration of high doses, leading to adverse systemic toxicity of healthy cells [6].

Therefore, more effective strategies are essential in order to fulfill the immediate need for more effective pancreatic cancer therapies [2]. Here, nanotechnology may provide new opportunities to overcome the complexities of pancreatic cancer [7].

Current scenario of pancreatic cancer approaches

Malignant pancreas neoplasms are mainly classified based on cellular differentiation of the neoplastic cells (ductal, acinar or neuroendocrine), combined with the macroscopic tumors appearance (solid or cystic) [8].

There is no consistent screening test currently available to screen the general population and to early detect pancreatic cancer. Although, several screening tests, such as blood markers (CA19-9, SPAN-1, CA-50, DUPAN-2), cell-surface-associated mucins, carcinoembryonic antigen, or heat shock proteins, are being studied to help in the identification or earlier diagnosis of pancreatic cancer for the general population [9].

Epidemiology data indicate that only 20% of patients with early disease diagnosis are fit for radical surgical resection, based on their staging. Nevertheless, adjuvant treatment is considered necessary [10].

The pancreas is located within the abdomen, surrounded by several other organs, major blood vessels and several tissue types, as well as near the lymphatic system. This allows pancreatic cancer to spread quickly to neighboring areas [2].

Beside standard chemotherapy that has been used in pancreatic cancer treatment (gemcitabine, 5-fluorouracil or combination therapy) and surgical resection, there are also other treatment options, such as radiotherapy or neoad-

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juvant chemoradiation [3]. Immunotherapy is also an emergent optimistic approach and is making huge progress in molecular subtypes, dominant mechanisms of immunosuppression and penetrant germline risk factors [11].

Nanotechnology in cancer treatment

Most of the current chemotherapeutic agents do not significantly differentiate between cancerous and normal cells, which limits the drug maximum tolerable dose [12]. Nanotechnology has emerged as a rising approach for drug delivery, opening up new landscapes in medicine, through the introduction of smart drug-delivery systems and increasing numbers of nanotherapeutics and nanodiagnostics that are being commercialized or have reached clinical stage [3,13].

Unlike traditional drug-delivery systems, it is possible to modify nanocarrier physiochemical properties, such as composition, size, shape and surface properties (charge, functional groups, coating and attachment of targeting ligands), which can improve their solubility and stability, obtain a controlled release and site-specific delivery of therapeutic agents and decrease toxicity [14]. These properties are attractive in oncology. Moreover, it is possible to encapsulate multiple active pharmaceutical compounds in a single nanoparticle, which could potentially offer synergistic effects to promote the therapeutic efficacy, while limiting the risk of resistance [13].

Due to abnormal characteristics of the tumor, namely in the lymphatic system, fluid retention occurs, the interstitial pressure increases, and an external convective interstitial fluid flow occurs. Also, tumor microvessels demonstrate an enhanced permeability and the transport of macromolecules across microvasculature may occur through open interendothelial junctions or transendothelial channels, known as passive targeting. This fact results in enhanced permeation and retention effect, allowing the accumulation of the nanocarriers in the tumor site in higher concentration than in the plasma or in other tissues [15]. Enhanced permeation and retention effect is a size-dependent phenomenon in which particles ranging from 10 to 400 nm can target the tumor through this mechanism [3].

In order to achieve an active targeting ligands such as antibodies, peptides or other small molecules are generally attached to these nanocarriers' surface because they recognize specific receptors in the tumor [15]. Thus, it is essential that the specific ligand site be present and accessible on the targeted cells to nanoparticles binding [13].

However, it is also important to consider the interstitial fluid pressure (IFP) as a significant physiological barrier. IFP can make the internalization of macromolecular therapeutics difficult, since a high IFP induces fluid flow from the high-pressure core to the tumor periphery. Therefore, intratumoral drug accumulation and distribution are key factors to the nanoparticle development and new nanocarriers must be developed under this consideration [3].

Nanotechnology in pancreatic cancer

Advances in the clinical use of nanotechnology can open up new pathways for the treatment of pancreatic cancer. A large number of nanoparticle–drug combined formulations are at different stages of clinical trials [3,16]. These nanoparticle–drug combined formulations include liposomes, polymeric nanoparticles, small interfering ribonucleic acid (siRNA) nanoparticles, amphiphilic polymers nanoparticles, inorganic nanoparticles, dendrimers, carbon nanotubes, hybrid nanoparticles, quantum dots and magnetic and gold nanoparticles [2,3,7].

Abraxane® (an albumin-bound nanoformulation of paclitaxel) was approved in 2013 by the US FDA as the frontline treatment for patients with advanced stage metastatic pancreatic cancer in a combination with gemcitabine, presenting a 1-year survival rate improvement. In 2015, a second nano-based formulation (MM-398) was approved by the FDA in a combination regimen with FOLFIRINOX. It is used as a second-line therapy for metastatic pancreatic adenocarcinoma, showing a median overall survival improvement of 2–4 months, when compared with those treated with only FOLFIRINOX. However, MM-398 monotherapy did not result in any statistically significant efficacy improvement compared with FOLFIRINOX [17].

There are many other studies reporting the successful use of numerous nanoformulations in pancreatic cancer therapy, for example, the development of a chitosan grafted with poly(ethyleneimine) arms and candesartan conjugate or graft amphiphilic poly (allylamine) derivative capable of solubilizing hydrophobic drugs [2,3].

Additionally, gold nanoparticles have presented an effective targeting to overexpressed EGFR in pancreatic cancer cells, being biologically viable and highly adaptable for conjugation with a large number of compounds that have amine or thiol groups using functionalization through Au–SH, Au–NH₂ interactions [3].

Recently, new clinical trials are ongoing to evaluate the safety and efficacy of systemic siRNA delivery using modified nanoparticles [3]. In addition, Bisht *et al.* demonstrated that curcumin-loaded polymeric nanoparticles

(NanoCurc™) have significantly reduced the primary tumor growth, systemic metastases and they have harnessed the potential effects of gemcitabine in both subcutaneous and orthotopic pancreatic cancer xenograft models [18].

Challenges to overcome in the development of nanomedicines

Authorities for drug approval are receiving a large and growing number of nanomedicine submissions and their current approach to regulating nanomedicines has been questioned. They are being encouraged to establish specific regulatory guidelines. Though prior to doing so additional data need to be collected and appropriate testing criteria needs to be established [19].

The characterization of new nanomaterials in terms of safety and toxicity is a significant challenge for the development of nanotherapeutics, since it is difficult to make a generalized statement about the safety of those systems, because they include a diversity of nanoparticles and materials [20]. Thus, the application of nanotechnology to medicine may exacerbate some concerns about risk minimization, creating a sense of urgency for reforming current regulations [19].

Nevertheless, despite the success of some nanopharmaceuticals sales (\$178 billion expected by 2019), financial issues are still another barrier in the development of these systems, as it is not so easy to demonstrate their efficacy and safety to be granted regulatory approval using the same guidelines as traditional medicines [20].

Most of the nanopharmaceuticals currently approved are based on conventional drugs that have existing approval and are based in a simple nanoformulation composition. Few nanotherapeutics in development will ultimately receive regulatory approval.

Conclusion

Nanotherapies may hold the key to reduce the damage of the adjacent healthy tissues and limit other side effects of cytotoxic agents by encapsulating drugs into a nontoxic nanoformulation that can pass through immunogenic and stromal barriers. Nanotherapies can really target the drug with high specificity to the tumor site, leading to an extension of the survival rate of pancreatic cancer patients with lower morbidity.

Nanotherapeutics development still faces many challenges, even though these systems may provide unique solutions for clinical needs and significantly alter clinical practice.

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References

- 1 Teague A, Lim KH, Wang-Gillam A. Advanced pancreatic adenocarcinoma: a review of current treatment strategies and developing therapies. *Ther. Adv. Med. Oncol.* 7(2), 68–84 (2015).
- 2 Manzur A, Oluwasanmi A, Moss D, Curtis A, Hoskins C. Nanotechnologies in pancreatic cancer therapy. *Pharmaceutics* 9(4), 39 (2017).
- 3 Rebelo A, Molpeceres J, Rijo P, Reis CP. Pancreatic cancer therapy review: from classic therapeutic agents to modern nanotechnologies. *Curr. Drug Metab.* 18(4), 346–359 (2017).
- 4 Zhou J, Lindsey E, Stojadinovic A *et al.* Incidence rates of exocrine and endocrine pancreatic cancers in the United States. *Cancer Causes Control* 21(6), 853–861 (2010).
- 5 Zhu Q, Pan X, Sun Y *et al.* Biological nanoparticles carrying the *Hmda-7* gene are effective in inhibiting pancreatic cancer *in vitro* and *in vivo*. *PLoS ONE* 12(10), 1–12 (2017).
- 6 Birhanu G, Javar HA, Seyedjafari E Zandi-Karimi A. Nanotechnology for delivery of gemcitabine to treat pancreatic cancer. *Biomed. Pharmacother.* 88, 635–643 (2017).
- 7 Sielaff CM, Mousa SA. Status and future directions in the management of pancreatic cancer: potential impact of nanotechnology. *J. Cancer Res. Clin. Oncol.* 144(7), 1205–1217 (2018).
- 8 Hackeng WM, Hruban RH, Offerhaus GJA, Brosens LAA. Surgical and molecular pathology of pancreatic neoplasms. *Diagn. Pathol.* 11(47), 1–17 (2016).
- 9 Ilic M, Ilic I. Epidemiology of pancreatic cancer. *World J. Gastroenterol.* 22(44), 9694–9705 (2016).
- 10 Karanikas M, Esemipidis A, Tzoutze Memet Chasan Z *et al.* Pancreatic cancer from molecular pathways to treatment opinion. *J. Cancer* 7(10), 1328–1339 (2016).

- 11 Collisson EA Olive KP. Pancreatic cancer: progress and challenges in a rapidly moving field. *Cancer Res.* 77(5), 1060–1062 (2017).
- 12 Sinha R. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. *Mol. Cancer Ther.* 5(8), 1909–1917 (2006).
- 13 Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv. Drug Deliv. Rev.* 66, 2–25 (2014).
- 14 ud Din F Aman W, Ullah I *et al.* Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int. J. Nanomedicine* 12, 7291–7309 (2017).
- 15 Alexis F, Rhee JW, Richie JP, Radovic-Moreno AF, Langer R, Farokhzad OC. New frontiers in nanotechnology for cancer treatment. *Urol. Oncol.* 26(1), 74–85 (2008).
- 16 McCarroll J, Teo J, Boyer C, Goldstein D, Kavallaris M, Phillips PA. Potential applications of nanotechnology for the diagnosis and treatment of pancreatic cancer. *Front. Physiol.* 5(2), 1–10 (2014).
- 17 Adisheshaiah PP, Crist RM, Hook SS, McNeil SE. Nanomedicine strategies to overcome the pathophysiological barriers of pancreatic cancer. *Nat. Rev. Clin. Oncol.* 13(12), 750–765 (2016).
- 18 Bisht S, Mizuma M, Feldmann G *et al.* Systemic administration of polymeric nanoparticle-encapsulated curcumin (NanoCurc™) blocks tumor growth and metastases in preclinical models of pancreatic cancer. *Mol. Cancer Ther.* 9(8), 2255–2264, (2011).
- 19 Ventola CL. The nanomedicine revolution: part 3: regulatory and safety challenges. *P T* 37(11), 631–639 (2012).
- 20 Ventola CL. Progress in nanomedicine: approved and investigational nanodrugs. *P T* 42(12), 742–755 (2017).