Nanomedicine and contrast enhanced imaging. Applications in cancer diagnosis and therapy

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Nanomedicine and contrast enhanced imaging. Application in cancer diagnosis and therapy

OBJECTIVE: *Nanotechnology and its applications in medicine made us live a new era of healthcare, particularly in oncology. The objective of this paper is to review the contribution of nanotechnology in clinical use of contrast agents for gastrointestinal cancer diagnosis and follow-up and to offer an overview of the impact of nanotechnology in the management of cancer.*
MATERIALS AND METHODS: *In this regard, we reviewed the main areas of expertise where nanotechnology has contributed to the improvement of diagnostic methods (CE-US, CE-CT, MRI), along with the therapeutic applications that nanoparticles can have. Last but not least, the article highlights the potential that theragnostic molecules can have in the diagnosis and treatment of neoplasia, including those in an advanced stage.*
RESULTS AND CONCLUSIONS: *Nanomedicine has the ability to improve the specificity and sensitivity of cancer diagnosis, together with the enhancing of the systemic cytostatic effect by developing nano bioconjugates that have a wider effect, higher tumor selectivity and thus, lower systemic toxicity.*

KEY WORDS: Ablative treatment, Cancer, Contrast enhanced imaging, Drug delivery, Nanomedicine

Introduction

Cancer is considered to be one of the main leading causes of morbidity and mortality worldwide and it was responsible for 8.8 million deaths in 2012, as reported by World Health Organization (WHO). In 2012, an estimated 14.1 million of new cases of cancer were diagnosed worldwide and this number is expecting to rise about 70% over the next two decades. The International Agency for Research on Cancer reported a total of 32.6 million people living with cancer, as it has been diagnosed within last 5 years. The most diagnosed cancer location is: lung (1.82 million), followed by breast (1.67 million), prostate and colorectal (1.36 million), while the most common causes of cancer deaths are cancer of lung, liver and stomach [1].

Cancer treatment represents a challenge for contemporary medicine due to the growing rate of this disease [2]. The occurrence of peritoneal carcinomatosis causes the infaust evolution of abdomino-pelvine cancers, placing them automatically into a final stage [3]. The development of new methods for treating cancer in general and especially for advanced cancer represents a goal for both clinicians and researchers [4-7].

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Materials and Methods

The objective of this paper is to review the contribution of nanotechnology in clinical use of contrast agents for gastrointestinal cancer diagnosis and follow-up and to offer an overview of the impact of nanotechnology in the management of cancer.

Results and Discussions

Nanotechnology and Cancer

Nanotechnology has many definitions, but all of them refer to the objects that are man-made and contain nano-scale dimensions, having characteristic properties proceeding due to their nano-dimensions. In the recent years, nanotechnology has made essential progresses in medical research providing significant resources with tremendous clinically relevant information, particularly in oncology. Cancer is a serious worldwide health problem, an important number of people being registered to be affected by this disease. Since nanomedicine has serious implication in cancer studies, significant progresses have been made in order to solve the limitations in terms of diagnosis, but especially in treatment of cancer [8]. Diagnosis and the most accurate staging of the disease are decisive, in order to choose the proper treatment for each patient. The clinical diagnostic is indicative for further investigations, most of them being represented by imaging techniques. Diverse medical imaging techniques, providing morphological, functional and metabolic data, are used in all clinical phases of cancer management. It is understandable why continuous researches are mandatory in order to improve these techniques.

Considerable technological progress has been done in the development and application of nanotechnologies. Several clinical trials have been published with eloquent impact for clinicians in this direction. Most of them are based on treatment research, but there are also interests in diagnostic and follow-up.

Cancer Diagnosis

Screening can be done to identify cervical, colon and breast cancers at an early and treatable stage. Screening based on imaging techniques for early detection of cancer is probably the major contributor to reduce the mortality in some certain cancers. Research performed in nanotechnology in this direction, demonstrates that targeted contrast agents can provide rapid and sensitive detection of cancer-related molecules, enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. Another contribution of nanotechnology in favor of cancer diagnostic represents the interest and efforts made in order to improve imaging tests, this subject being discussed further in this article.

Cancer Treatment

In nanomedicine, researchers are developing innovative therapy techniques by direct treatment to the diseased cells, minimizing the damage to healthy tissue. Such situations are met in current methods such as systemic chemotherapy and radiotherapy. Some nanomedicine therapy techniques are only thought, while others are at various stages of testing, or actually being used today. A considerable number of therapeutic NPs, have been approved to be used for cancer treatment (e.g. liposomes, albumin NPs and polymeric micelles), while many other therapeutic modalities that are nanotechnology enhanced are under clinical investigation, including chemotherapy, hyperthermia, radiation therapy, gene or RNA interference (RNAi) therapy and immunoassay [9].

The use of NPs to deliver specific molecules, especially chemotherapeutic drugs to the tumor tissue represents one of the major advantages in therapeutic specificity. Most nanomaterials have been designed with the aim of optimizing the therapeutic effect and reducing the systemic toxicity of the drug they are in combination with [10]. Other NPs, such as cyclodextrin [11], micelles [12] or NPs with a disulfide linker [13], have been designed to improve the response to antineoplastic drugs and to boost their safety and efficacy on drug release into the tumor cells.

Drug Delivery

The use of NPs in drugs and gene delivery has rapidly gained popularity. NPs have been successfully used in association with chemotherapeutic agents in order to improve treatment response and lower their side effects. NPs have also shown potential for the delivery of other anticancer agents, including molecularly targeted agent, in particular kinase inhibitors [14] small interfering RNS (siRNA) [15], mRNA [16] and DNA inhibitor oligonucleotides [17]. The benefits brought by nanoparticles are better solubility and stability of antitumor agents, prevention of early drug degradation and thus minimizing the therapeutic dose and reducing the toxicity. All those properties of the NPs provide an increased level of the chemotherapeutic in the tumor tissue and less in healthy tissue maximizing its outcome and minimizing its side effects.

Drug delivery nanoparticles approved by FDA in clinical use are natural polymers such as liposomes, albumin and polymeric micelles [18] (Fig. 1).

Doxorubicin is one of the most powerful and toxic

chemotherapy drug and has been initially used as treatment for Kaposi's sarcoma. Nowadays it has been encapsulated in liposomes and is FDA approved, commercially known since 1995 as Doxil™ and is being used in treatment of metastatic breast cancer, recurrent ovarian cancer, multiple myeloma and HIV-related Kaposi sarcoma. Another FDA approved drug, in association with pegylatedlyposomes is Irinotecan (Onyvide™ or MM-398), currently used for adjuvant treatment of metastatic pancreatic cancer [20]. Zoledronic acid (ZOL) is known for its high antitumor activity but with a short half-life in plasma, being nowadays used in the treatment of bone metastases from both, solid or hematopoietic tumors [21]. Liposomes have been used in combination with ZOL (LipoZOL), such combination being reported to have better results in antitumor activity and tolerability and has increased the overall survival in preclinical animal model, providing a rationale reason for further exploration [22].

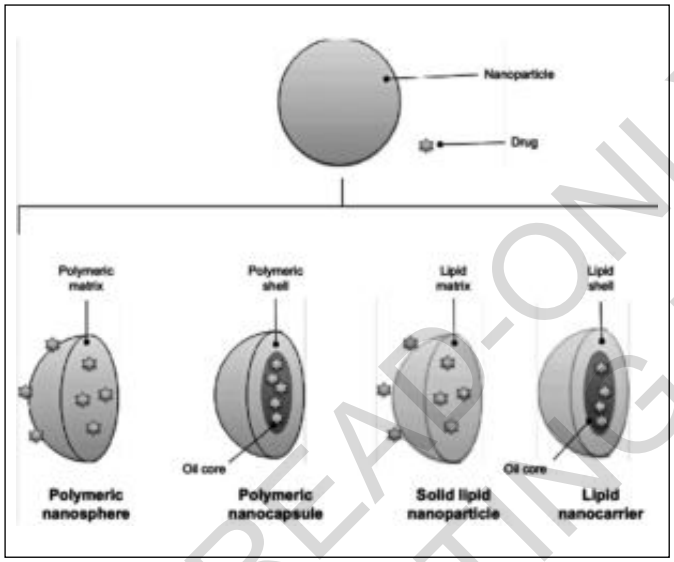

Fig. 1: Schematic differences between nanocapsule, nanostructured lipid carrier, polymeric nanoparticle and solid lipid nanoparticle drug delivery systems, from Fonseca et al, reference [18].

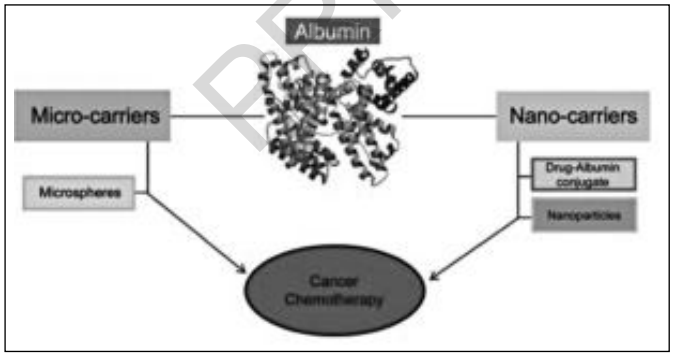

Fig. 2: The schematic illustration of an albumin based nanobioconjugate used in cancer chemotherapy, from Shahzad et al, reference [23].

Albumin NPs used in combination with antineoplastic drug has been shown in preclinical studies, that allows the administration of a greater dose of chemotherapeutics and a better diffusion into the tissue (Fig. 2) [23].
Albumin has been also used in combination with docetaxel (DOC) to enhance the absorption and effectiveness against gastrointestinal cancers [24]. Albumin-based NPs used in combination with Paclitaxel in clinical use under the trade name of Abraxane™ is currently recommended for the treatment of breast, lung and pancreatic cancer. Paclitaxel is also used in treatment of breast and non-small lung cancers (NSCLC), with NPs of polymeric micelles, under the name of Genoxol-PM™ [25].
Immunotherapy is another field where nanotechnology has gather interest, using NPs as a potent antigen or adjuvant for synthetic vaccines [26] or carriers of antineoplastic drugs [27], those application being currently in clinical trials stages.

Thermal Therapy

Thermal therapies are considered minimally invasive procedures and it refers to cooled - or heated - based techniques used in treatment of cancer. Cryosurgery refers to extreme cold destruction of tumors located in liver, prostate or lung. The use of nanoparticles leads to a new concept, called nanocryosurgery and is proposed to improve the traditional technique (Fig. 3) [28].
On the other hand, hyperthermia is other technique capable to damage the tumor cells and avoiding in the same time the healthy tissue, by using temperatures up to 41-45° [29]. Magnetic NPs are capable to induce localized hyperthermia in addition of the alternating magnetic field, being able to destroy the tumors and sensitizing it to radiation or chemotherapies [30]. In this regard, a new treatment using an aqueous dispersion of iron oxide NPs, is nowadays used in the treatment of glioblastoma, an aggressive tumor of the brain, under the name of NanoTherm™. It is directly injected into the tumor and an alternating magnetic field is then applied creating heat, offering thus a local treatment [31].

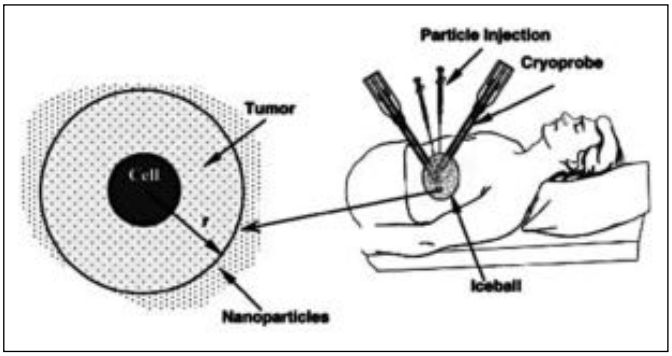

Fig. 3: Nanocryosurgery and its mechanisms. Schematic representation, from Yan et al, reference [28].

Radiotherapy

The applications of nanomedicine and the use of NPs, such as hafnium oxide NP used in treatment of soft tissue sarcoma, augmented to radiotherapy, are currently in clinical studies [32]. Nanoparticles are used to enhance the therapeutic effects of radiation in cancer treatment [33].

Nanotechnology and Contrast Agents

Nanotechnology is a multidisciplinary field and nanomedicine has benefited and been influenced by its findings for many years. Nowadays, nanomaterials (NMs) benefits of scientist and physician attention, in order to develop new non-invasive strategies for the diagnostic and treatment of cancer. By understanding tumor pathology and nanoparticles (NPs) structure and biocompatibility, a wide range of NMs has been designed to reach tumors, having different and sometimes unique properties making them useful for different applications.

NPs vary in size and shape along with physical and therapeutic properties. NMs used for diagnostic and therapy of cancer, are organic substances (e.g. micelles, liposomes, natural and synthetic polymers including dendrimers), anorganic substances (e.g. quantum dots), metallic nanostructures and metal oxides (e.g. iron oxides, phosphors and zeolites) [34]. It has been taken advantages of the NPs properties, being often used as delivery vehicles by encapsulating a diagnostic or therapeutic compound that may otherwise demand superior properties which can cause systemic side effects.

Nowadays, emerging researches that are made in nanotechnology are providing scientists and clinicians with a remarkable access to information with excellent clinical potential. Nanomaterials have also evolved, being recognized as a novel biomaterial with promising applications in drug delivery [35].

Contrast agents are used in medical imaging to increase the sensitivity and specificity of the imaging tool. An ideal contrast agent must be able to selectively accumulate in the targeted tissue and interact with it, in order to improve the image contrast [8].

Ultrasonography

Ultrasonography (US) is one of the most used imaging techniques in medicine, thanks to its wide availability and portability; it is accessible at relative low cost and does not expose the patient to ionizing radiation. US issued in all clinical departments, emergency room and even in the operating theatre in order to confirm a diagnosis or to estimate its severity. On the other hand, US is one of the easiest and fastest method to assess the patient's response to the treatment. The progresses made recently, in terms of image processing and transducer design and the novel 3D US and progresses made in the field of interventional US, have greatly enriched the use of US in diagnosis and treatment [36].

Another decisive contribution to clinical US, in terms of resolution and sensitivity, has come with the use of US contrast agents [37]. Contrast agents commercially used for US are microbubbles, with size in micrometer range, and are mainly composed of insoluble gas and an encapsulating shell [38]. The thin shell coating of the microbubbles, are generally made of lipids, polymers, proteins, while the inner core consists of high molecular weight gas such as nitrogen, per-fluorocarbon of sulfur hexafluoride (Fig. 4) [39,40].

The currently used US contrast agents for clinical imaging are SonoVue™, Definity™, Luminity™ and Sonazoid™ [41,42]. These agents possess a short circulation time (few minutes) and a relatively large size (two to ten micrometers) and thus, do not permit an adequate diffusion into tumor tissue owing an endothelium pore in the range 380-780nm [43] Theoretical, NPs can exceed the shortcomings of microbubbles, due to their smaller sizes [44]. It has been shown that US alone can improve through thermal or mechanical processes, the delivery of the NP alone. The ultrasonic heating has a direct effect on tissue itself by changing blood flow and vascular pressure, or it can activate an agent such as thermally sensitive NPs or nanodroplet [45,46].

Protein based contrast agents possess a good biocompatibility being widely used in clinical diagnosis and research, but because of their relatively poor stability, they are not good competitors for functional modification. Thus, Wang et. al. [47] designed albumin shelled microbubbles with encapsulated gold nanorods (AuMBs), for both US photoacoustic imaging and photothermal therapy. In vivo studies, showed that targeted AuMBs come with a significant improvement of the retention time for longer US imaging and the identification of the angiogenesis of the tumor.

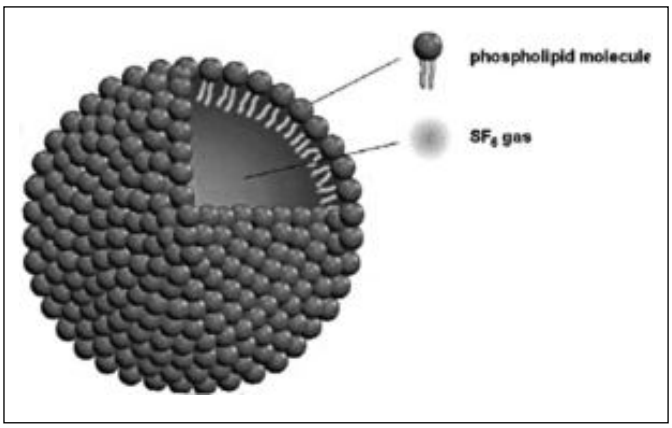

Fig. 4: Composition of an ultrasound contrast agent microbubble (SonoVueÒ), from Greis, reference [39].

Lipid-based contrast agents used in US are intensively studied due to their exceptional echogenicity. The drawbacks of these agents come from their incapacity to incorporate the NPs, considering the instability of their soft shells [48].

Progresses have been made in terms of contrast agents, as clinical trials are looking forward to demonstrate the benefits of molecularly targeted microbubble contrast agent [49]. The use of molecularly targeted microbubbles is a novel and promising technique to visualize, characterize and quantify the biological process at the molecular level [50,51]. A recent published study showed that the three-dimensional (3D) molecularly targeted US with VEGFR2-targeteted micro-bubbles, provide complementary molecular and functional in vivo imaging formation on antiangiogenetic treatment effects using a murine model of human colon cancer compared with quantitative immunofluorescence as the ex vivo reference standard [52].

The use of US microbubble as a contrast agent has been expanded beyond their primary role in diagnostic, being today in clinical studies in the field of drug and gene therapy [53].

Computed Tomography (CT)

Computed tomography (CT) is one of the most used clinical imaging tools, being useful for diagnosis of disease, prediction of therapy and treatment assessment. Contrast agents, such as barium sulfate suspensions and iodine-based compound, are used in order to increase the sensitivity of the CT. The limitations of these contrast agents (e.g. short circulation time, serious adverse effects, nonspecifically distribution throughout intravascular and extravascular spaces) motivated scientists to develop contrast agents in nanometer size providing thus several advantages over the widely used iodinated solutions. Notably is the fact that their surface can be modified to enhance the specificity by attaching targeting. The most frequently used contrast generating elements used in CT scans are iodine [54], gold [55] or bismuth [56]. Elements such as bromine, platinum [57] based on heavy atoms such as tantalum [58] or lanthanides have been reported in literature as generators of contrast [59]. Other types of nanoparticles with promising result as contrast agents for CT are mainly lipid-based structures (emulsions, micelles, lipoproteins, liposomes) or solid core based (metal, metal alloy or metal salt).

The use of NPs contrast agents for CT was first reported in the early 1980s [60-62]. without benefit of much attention for further studies. Although, in the last seven years, a tremendous attention was given to nano-based contrast agents for medical imaging with hundreds of articles with significant clinical impact being published within this period [63].

One of the most appropriate NPs, serving as a contrast agent for CT scans that can overcome some limitation of iodine-based agents, are gold NPs due to their high X-ray absorption coefficient [64].

Magnetic Resonance Imaging (MRI).

The most commonly used compounds for contrast enhancement in MRI scans are Gadolinium (III) based contrast agents. Gadolinium ions (Gd) are strongly paramagnetic due to their unpaired electrons and they are providing a positive contrast on T1 images. Gd (III) ions bind with a chelate agent that decreases its toxicity, but maintaining in the same time its properties, forming thus a complex molecule. Other contrast agents used for MRI scans are iron oxide and iron platinum, both with super-paramagnetic properties. Iron-oxide NPs have been approved by FDA, since 1990s, for clinical use [65]. SPIOs can provide a safe and strong negative contrast enhancement of the targeted lesion in T2-weighted MRI, being widely used as contrast agent [66].

The traditional method of performing MRI has been improved by using a polymeric based NPs to incorporate gadolinium, a positive magnetic resonance agent [34].

Fluorescence

Bovine serum albumin coated gold nanoclusters have some unique properties which allow them to be ideal candidates in studies regarding the interaction between nanoclusters and different cells. The most important properties are represented by their small size, in situ fluorescence and biocompatibility. The fluorescent properties are used to track them into the living tissue. Tumoral cells express a large amount of glucose uptake, which is necessary for the high energetic needs which assure the uncontrolled growth and the capacity of angiogenesis and metastasis. There are studies which were conducted to show that glucose coated gold nanoclusters can be safely developed in order to target the tumoral cells. Also, bovine serum albumin coated gold nanoclusters were synthesized as control. The study conclude that glucose coated gold nanoclusters present a better uptake into cancerous cells [67].

Future Perspectives

Theranostic Nanostructures Used for Diagnosis and Treatment of Hepatic and Pancreatic Tumors

Theranostics is a unique cancer treatment strategy, which combines the imaging diagnosis and imaging guided therapy simultaneously, solving thus the challenges of

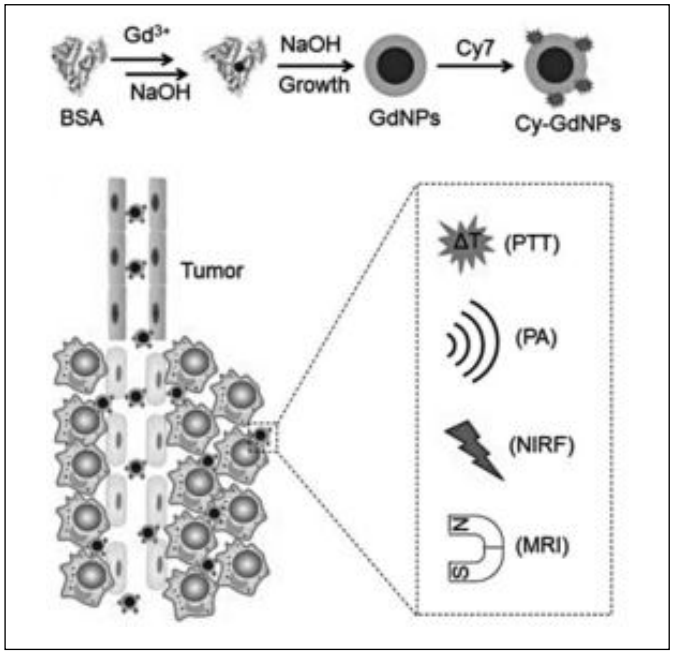

Fig. 5: Preparing a theranostic nanoparticle based form bovine serum albumin, as template for multimodal (NIRF/PA/MR) imaging-guided photothermal tumor ablation. Schematic representation, from An et al, reference [68].

cancer heterogeneity and adaptation. NPs are ideal competitors for this challenge, owing a significant biocompatibility and appropriate optical, electronic, magnetic and structural properties (Fig. 5) [68].
Theranostic medicine proposes to study one single nanoparticle (NP) based agent, capable of diagnosis, through imaging studies, therapy through delivery drugs in a targeted way and monitoring response of the therapy. The theranostic nanoparticles are defined as NP with double functions (for both therapeutic and diagnostic purposes) and are commonly applied to simultaneous drug delivery and molecular imaging.

Hepatic Tumors

The incidence of hepatocellular carcinoma (HCC) is increasing over the past decades [69]. Recently researchers worldwide focus on developing a new strategy of treating HCC, theranostic nanomedicine. This new way of treatment is a promising approach which aid the conventional chemotherapy, the early detection of cancer and also the measurement of therapeutic response [70]. Also, there are efforts made to improve the success rate of radiofrequency ablation. This can be performed by using certain temperature-sensitive nanoparticle that releases the chemotherapeutic agent at a specific temperature. The use of a peptide which has the ability to penetrate the tumoral cell in addition to a thermo-sensitive doxorubicin loaded nanoparticle was used in an experimental study combined with radiofrequency ablation on a mouse model [71].

Pancreatic Tumors

Pancreatic cancer remains a disease with high mortality rate, despite the advances made in diagnosing and treating this disease. Most of the pancreatic tumors are diagnosed in advanced stages, unresectable and drug-resistant. Recently, the attention was guided for developing new nanoparticle drug carriers with enhanced tumor accumulation and reduced side-effects. This is due to the fact that conventional chemotherapy demonstrated to have reduced efficiency because of the barriers developed by pancreatic tumoral cells which block the drug delivery. The nanoparticles were developed to have a large surface area and biocompatibility and also a high capacity of loading drugs. Some of these nanoparticles have also imaging contrast agents' properties and can be used both for diagnosing and treating pancreatic cancer. The most important function of theranostic nanoparticles is the fact that they allow monitoring the drug delivery [72].
A new perspective for the treatment of pancreatic ductal adenocarcinoma is represented by the use of small interfering RNAs, toxins, antibodies and antisense nucleotides, which are all potential agents in developing theranostic molecules [73-75].
First of all, NPs were used as drug carriers for efficient delivery of conventional chemotherapeutic agents [19]. Human albumin encapsulated with Paclitaxel, Abraxane® has been recently approved by FDA to be used in combination with gemcitabine for treating advanced stages of pancreatic ductal adenocarcinoma (Fig. 6) [76].
The use of Abraxane® improved the overall survival rate with 1.8 months when compared to the use of gemcitabine alone [72]. Paclitaxel was used as a chemotherapeutical agent because of its effect on gemcitabine-resistant tumor cells. Improved tumor growth inhibition is obtained by systemic delivery of paclitaxel encapsulated in poly(ethyleneoxide) copoly (D, L-lactide), unde MRI guidance and combined with ultrasound enhanced intratumoral accumulation by increasing blood vessel and cell membrane permeability [77].

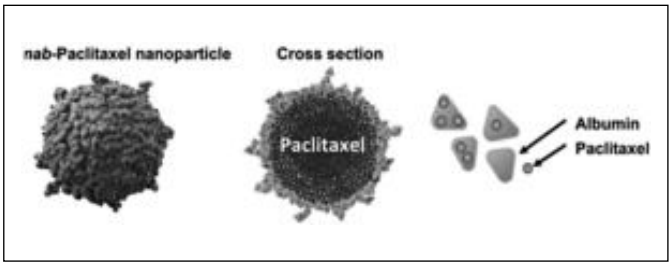

Fig. 6: Cytotoxic "Abraxane®" drug' schematic representation, from Desai, reference [75].

Some pancreatic ductal adenocarcinomas are drug-resistant because of the dense stroma that blocks drug complexes to reach the tumoral cells. This leads to the development of nanoparticles which target tumor stromal fibroblasts and macrophages. Such nanoparticles offer the opportunity to obtain an enhanced drug delivery into tumor cells. Pancreatic cancer cells express IGF-1 receptor at a high level. Iron-oxide nanoparticles carrying anthracycline doxorubicine was developed and have proven to deliver nanoparticle-drug complexes into IGF-1 receptor-expressing tumor cells [78].

A great therapeutic approach for diseases caused by genetic mutations or abnormal gene expression, such as cancer, is represented by the use of small RNA molecules which specifically modify the expression of a targeted gene.

An extremely important aspect of developing this technique is represented by the poor stability of RNA in vivo, when passing the cell membrane. To enhance this researcher developed certain nanomaterials which provide carriers for delivery small RNA [79]. Single wall carbon nanotube was used to deliver small RNA into pancreatic tumoral cells due to its unique shape [80]. In addition to the inhibition of tumor growth, knocking down the expression of critical genes appears to enhance the efficiency of chemotherapy. This is shown by the induced apoptosis and the increased citotoxic effect obtained in pancreatic tumoral cells when AURKA genes are silenced [81]. Also, it was observed that the down-regulation of ITCH sensitizes the tumoral cell to chemotherapeutic agents and RNA based therapy act as a booster when used together with conventional chemotherapeutic agents [82].

In conclusion, the use of targeted nanoparticle drug carriers represents a promising approach when treating pancreatic cancer by selective delivery of potent antitumoral agents with reduced systemic toxicity.

Mapping of Peritoneal Carcinomatosis

Detecting peritoneal metastases and residual tumor implants is a continuous target for worldwide medical practitioners [5,7,8,83,84]. It also represents a very important subject for most of the researchers who activate in the field of cancer. In current surgical practice, the detection of peritoneal carcinomatosis is made only by palpation and visual assessment. In order to obtain a more accurate mapping of peritoneal metastases, new techniques, such as indocyanine green fluorescence imaging, can be used (Fig. 7) [85].

The main advantages of using indocyanine green in order to detect peritoneal carcinomatosis are represented by its safety and large availability. There is a study that aims to verify if peritoneal lesions detected on preoperative imaging or during surgical interventions can be positively identified by using indocyanine green fluorescence imaging. Fluorescence imaging encountered poor results in patients with extended peritoneal lesions. This is due to the long duration of the surgical act due to the need of extensive resections of the peritoneum combined with

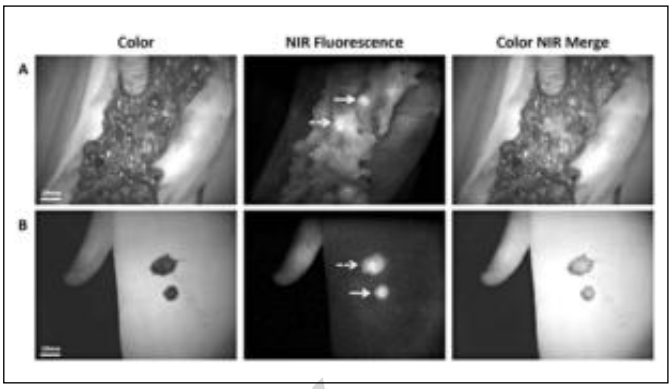

Fig. 7: Identification of ovarian cancer omental metastases using NIR fluorescence imaging, from Tummers et al, reference [85]: A) identification of 2 ovarian cancer metastases located in the greater omentum (arrow and dashed arrow) using NIR fluorescence imaging; B) imaging of the same two NIR fluorescent lesions removed from the omentum (arrow and dashed arrow).

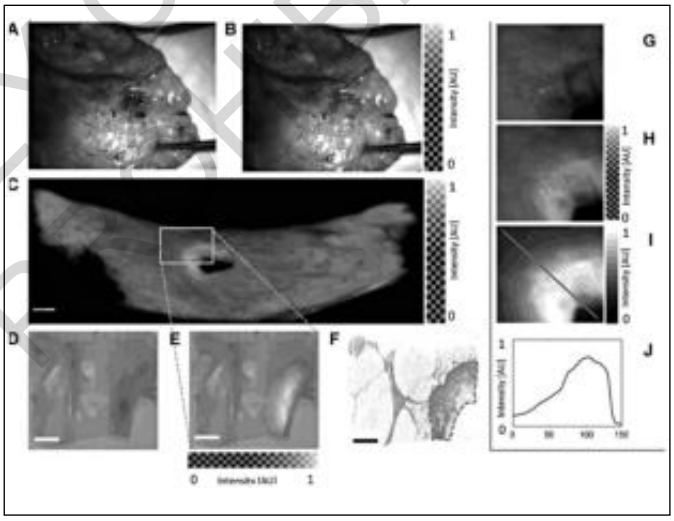

Fig. 8: Spatial patterns of bevacizumab-IRDye800CW distribution in an invasive ductal carcinoma, from Koch et al, reference [90]: intraoperative image (in situ).
A) hybrid color image; B) fluorescence image of deep-seated tumor; C) necrosis in the core of the tumor (scale bar, 10 mm); D) color image of the paraffin-embedded tissue sample (scale bar, 5 mm); E) H&E staining of 4-µm thick paraffin slice corresponding to the field of view in D. The green dotted line marks the tumor border according to histopathology (scale bar in D-F, 5 mm); F) magnifications of color images obtained from the region outlined by the rectangle in subfigure C; G) magnifications of pseudo-color overlay images obtained from the region outlined by the rectangle in subfigure C; H) magnifications of raw fluorescence images obtained from the region outlined by the rectangle in subfigure C (I); fluorescence intensity profile along the blue line shown in I (J).

the difficulty of fluorescence measurement in the massively invaded areas [86]. However, there are recent studies that prove a significant benefit of cytoreductive surgery only in patients with peritoneal carcinomatosis index lower than 17 [87]. Even if indocyanine green allows detecting tumoral tissue, it has a limited specificity. New perspectives are represented by the development of specific molecules such as a combination between antitumoral antibodies and a fluorophore. The use of this type of molecules represents a major step forward in the field of the detection of peritoneal spreading [88]. A recent clinical study reports the use of IRD-800CW-labeled bevacizumab for the detection of peritoneal carcinomatosis of colorectal origin. The results of this study were encouraging, with no false negative results. However, there was a high rate (47%) of false positive records (Fig. 8) [89, 90].

A main challenge for both clinical practitioners and researchers is represented by finding a way to discriminate between malignant tissue after neoadjuvant chemotherapy and benign tissue. In order to find a method, there are studies who analyze the use of indocyanine green fluorescence imaging for detecting peritoneal carcinomatosis. Indocyanine green fluorescence imaging was also evaluated for the detection of remnant tumoral tissue in scar tissue. A pilot study concludes that intraoperative indocyanine green fluorescence imaging was not efficient for discriminating between benign and malignant scars in patients who received neoadjuvant chemotherapy [91]. As a result to this finding, a new fluorescence imaging technique is necessary to be developed.

Conclusions

The evidence presented in the literature clearly indicates that, on selected cases with specific histopathological results, the outcome of patients with advanced cancers, even with peritoneal carcinomatosis, could be improved. For that, an aggressive treatment is often necessary: ablative techniques, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy.

Both systemic chemotherapy and intraperitoneal chemotherapy have a number of limitations, primarily linked to neoplastic cell resistance and non-selective cytotoxicity with consecutive systemic toxicity. In addition, knowing that any tumoral residue can compromise the survival after this procedure, the intraoperative acknowledgement of all neoplastic implants is mandatory.

Nanotechnology can represent a solution in this field of area, by improving the currently used contrast agents, in the idea of developing theranostic structures with large applicability in the perioperative period, regarding diagnosis, treatment and remote monitoring of patients with this advanced stage of neoplastic disease. In this regard, ablative techniques used for the treatment of visceral tumors (liver metastases, primary liver tumors, pancreatic tumors) could be improved by using these "magic bullets", with applications in imagistic diagnosis, cytoreductive therapy and local cytostatic effect: see nanobioconjugates based on metals with thermoablation properties, linked to specific antibodies and controlled release of cytostatic agents.

Radical treatment of peritoneal carcinomatosis is the other area in which theranostic molecules will play an important role by concomitantly achieving a precise mapping of neoplastic tumor implants (e.g. fluorescence, IR spectrum) and a cytostatic effect amplified by the association of specific molecules (tumor antibodies, AuNPs, etc.).

And last but not least, in addition of improving these local techniques, nanomedicine has the ability to enhance the systemic cytostatic effect by developing nanobioconjugates that have a wider effect, higher tumor selectivity and thus, lower systemic toxicity. All this could invariably lead to an increase in therapeutic resources for patients diagnosed with advanced neoplasms, and ultimately to a increased survival period and a better quality of life.

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Riassunto

La nanotecnologia e le sue applicazioni in medicina ci hanno fatto vivere una nuova era dell'assistenza sanitaria, in particolare in oncologia. L'obiettivo di questo articolo è esaminare il contributo della nanotecnologia nell'uso clinico di agenti di contrasto per la diagnosi e il follow-up del cancro gastrointestinale e per offrire una panoramica dell'impatto della nanotecnologia nella gestione del cancro.

A questo proposito, abbiamo esaminato le principali aree di competenza in cui la nanotecnologia ha contribuito al miglioramento dei metodi diagnostici (CE-US, CE-CT, MRI), insieme alle applicazioni terapeutiche che le nanoparticelle possono avere. Ultimo ma non meno importante, l'articolo evidenzia il potenziale che le molecole teragnostiche possono avere nella diagnosi e nel trattamento delle neoplasie, comprese quelle in stadio avanzato.

RISULTATI DELLO STUDIO: la nanomedicina ha la capacità di migliorare la specificità e la sensibilità della diagnosi del cancro, insieme al potenziamento dell'effetto citostatico sistemico sviluppando nano bi-oconiugati che hanno un effetto più ampio, una maggiore selettività tumorale e quindi una minore tossicità sistemica.

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