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EDITORIAL

Gastrointestinal cancers in the era of theranostics: Updates and future perspectives

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Abstract

Theranostics are one of the practical aspects of personalized medicine. This concept was designed to describe a material combining diagnosis, treatment and follow up of a disease. It evolved and included molecular targeting and nanotechnologies that incorporate both diagnosis and therapeutics. In this editorial, we are presenting briefly the concept and evolution of theranostics, highlighting many applications of theranostics in daily practice and discussing future perspectives and aspects of this model in gastrointestical cancers.

Key words: Theranostics; Gastrointestinal cancer; Nanoparticles; Nanotheranostics; Molecular targeting

Core tip: This editorial presents briefly the concept and evolution of theranostics. It describes the actual use of this treatment modality in gastrointestinal (GI) cancer going from the success story of theranostics in pancreatic neuroendocrine tumors to the promising results in gastric and colon cancer. Future perspectives of theranostics in GI cancers in nanotechnology and biomarkers fields are also reported in the end of this editorial.

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THERANOSTICS: CONCEPT AND EVOLUTION

The Edwin Smith papyrus, dating back to 3000 B.C., describes cancer as an entity that is beyond the reach of any cure[1]. Science has taken us through immeasurable lengths since that categorical statement was drafted. Our present day has witnessed an era of unprecedented advancement in the field of cancer therapeutics.

The dawn of the twentieth century saw the "unintentional" birth of personalized medicine when Beatson first started using oophorectomy as a treatment for breast cancer[2]. Since then, bringing about a true state of precision cancer care, in every sense of the word, has become the holy grail of modern physicians and researchers. The term "theranostics" is simply a by-product of the pharmaceutical industry, in its effort to establish diagnostic tests that also possess the ability to affect the treatment of a certain cancer[3]. Effectively, the need for validated predictive biomarkers was essential in order to transform cancer care into a precise, patient-centred science, in contrast to a crude, reactive, population-based, one size fits all discipline. HER-2 over-expression by breast cancer cells is perhaps the example that portrays a predictive biomarker the best, especially since the approval of Trastuzumab in 1998 drastically changed the treatment paradigm for patients with breast cancer[4,5]. No less can be said about BRAF V600E mutations in melanoma, KRAS/NRAS mutations in colorectal carcinoma, EGFR mutations, ALK gene rearrangement and most recently ROS-1 mutations in Non-Small Cell Lung Carcinoma and many other validated biomarkers with palpable results in different areas of clinical oncology[6-9].

While the definition of theranostics certainly applies to predictive biomarkers commonly used in clinical practice, it is still an evolving concept that encompasses many facades for managing malignant disease. Present and near-future perspectives are looking into theranostic nano-medicine as a tool for achieving a more refined personal medicine, better tailored to the need of each and every patient. This emerging concept would have us probe deeper into the realm of nanoparticles (NP), synthetic materials with dimensions ranging from tens to hundreds of nanometers, which have gained increasing popularity in the past decade for their efficacy in drug delivery with reduced systemic toxicity, such is the case of albumin bound paclitaxel nanoparticles (Abraxane ®)[10]. In contrast, some experimental models of these NP, considered "smart" NP, have no clinical application beyond animal models to date, but the results envisioned are well within grasp for implementation in current practice. "Activatable" NP would respond to changes in the microenvironment to exert their therapeutic or diagnostic mechanism. Therefore, NP could be selective for a certain tumor environment, such as acidic pH resulting from tumor hypoxia and consequent lactic acid production, in order to subsequently release their content[11]. Other forms of NP would use protease that are known to be up-regulated by tumor or irradiation with a predetermined wavelength of light to trigger them into action[12,13]. This creates an opening for the perfection of multi-functional NP with both diagnostic and therapeutic applications simultaneously.

Theranostic NP and their impact on clinical oncology will certainly keep moving forward in the coming years as the need for less invasive and more specific therapeutic alternatives is growing. Our current ambition is aimed at securing NP that would identify the malignant clone and treat it through optimal drug delivery. However, a more futuristic ambition would be to create what is referred to as "nanobots", as these "artificial cells" would continuously circulate in the host's system and activate theranositcs at the earliest disease state.

THERANOSTICS IN GASTROINTESTINAL CANCERS

The success of radiolabeled Somatostatine analogs in the diagnosis and the treatment of gastrointestinal (GI) and pancreatic neuroendocrine tumors widely opened the doors for more trials and protocols based on the Theranostic concept in GI tumors.

Success story: Theranostics in GI and pancreatic neuroendocrine tumors

Neuroendocrine tumors originate from different neuroendocrine cells distributed in the human organism; these cells contain granules secreting amines and peptides[14]. The most frequent sites of these tumors are gastro-intestinal and bronco-pulmonary tracts[15]. NETs are usually considered with favorable prognosis with a five-year survival reaching the 80%[16]. NETs have many specific and particular characteristics including the presence of peptide receptors and transporters at the cell membrane and the neuroamine uptake mechanisms, which lead to the clinical implication of specific radiolabeled ligands for imaging and therapy in these tumors. Somatostatine receptors are expressed in a high percentage of NETs and they became the ideal entity to be targeted in these tumors. Somatostatine targeting has gained much diagnostic and therapeutic value in NET tumors, becoming a model in GI theranostics.

Somatostatine receptor imaging is based on the use of PET or SPECT (scintigraphy) as whole-body techniques; many tracers are included in the panel used for imaging with different degrees of sensitivity and specificity. Octreosan using In-pentetetroide was considered for many years as the gold standard but, presently, new, more reliable tracers exhibit better performance in visualizing NET tumors. Besides the imaging utility, combining somatostatine analogues with therapeutic beta emitters (lutetuin-177 and yttrium-90) is considered an efficient therapeutic option for patient with metastasized and unresectable NETs. Targeting the same marker in imaging and therapeutic in NET, the somatostatine receptors, was considered the first success in the era of theranostics in GI tumors[17].

Table 1 Approved molecular theranostics and nanoparticles in gastrointestinal cancers

	Molecular theranostics	Nanoparticles
Gastric cancer	Her2neu	Polypeptide NP Magnetic NP of iron Triblock copolymer NP
Colon cancer	KRAS	Polymeric nanosphere Micelle particles Metal semi-conductor NP Gold NP
Pancreas cancer	Somatostatine receptors[1]	Iron oxide NP Gold coated iron oxide NP

[1]PNET. NP: Nanoparticles.

Her2neu in gastric cancer and KRAS in colon cancer

In GI cancers, only two molecular mutations are approved as predictive therapeutic targets in daily practice. The Her2neu is a positive predictive factor in advanced gastric cancer and KRAS is a negative predictive factor in metastatic colon cancer.

The overexpression of Her2neu in advanced gastric and gastro-esophageal junction cancer is considered a positive predictive factor to the response to Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2). The TOGA trial showed an overall survival of 13.8 mo in patients with Her2neu overexpression, when treated with trastuzumab associated to chemotherapy in first line treatment, while the overall survival doesn’t exceed one year in the population not receiving trastuzumab[18].

KRAS mutation is a negative predictive factor for the use of Cetuximab, an anti-EGFR, in metastatic colon cancer. KRAS mutated patients will not benefit from Cetuximab as much as the patients with wild type KRAS, these patients will preferentially be treated with bevacizumab[19].

FUTURE PERSPECTIVES OF THERANOSTICS IN GI CANCERS

Nanotheranostics

After the progress in nanotechnology in the last decade, many trials were launched aiming to integrate this technology in theranostics under the name of “nanotheranostics”. The introduction of this new technology in health care routine needs many practical steps in the long way of concretization and daily application. Many nanoparticles were been studying in this domain; gold-based nanoparticles, magnetic nanomaterials and polymeric nanomaterials are the most widely tested associated sometimes to chemotherapeutical agents. These nanotechnologies are being applied first *in vitro*, and subsequently *in vivo* with many positive results (Table 1).

The association of chemotherapeutical agents with nanoparticles avoid the drug degradation, allow higher dose of antitumor agents with less toxicities and a higher penetrance to malignant tissue with more specificity.

Gastro-esophageal cancer

Many combinations based on nanoparticles are being investigated in gastro-esophageal cancer; some nanoplatforms are targeting metaplasia, the precursor of gastric and esophageal adenocarcinoma[20]. The type of nanoparticles studied in theranostics of gastro-esophageal cancer are polypeptide NP[21], magnetic NP of iron[22], triblock copolymer NP[23]. All these NP are not included in clinical trial or for commercial use.

Pancreatic cancer

Pancreatic cancers are known to have one of the poorest prognosis in GI cancers. Treatment of this cancer is limited by resistance of cancer cells to chemotherapy and impaired drug penetration due to the dense stroma formed around the tumor. Nano-sized cytotoxic agents have showed increased drug efficacy, a concrete example is approval of nab-paclitaxel as a therapeutic option in metastatic pancreatic cancer[24].

Different categories of nanoparticles are being investigated in pancreatic cancer; Iron oxide is one of the subtypes with the most promising results in this type of cancer[25]. Many studies are evaluating the different modalities of use of iron oxide nanoparticules as theranostics agents: Iron oxide nanoparticules as vehicule of chemotherapy[26] or gold coated iron oxide nanoparticules[27]. All these studies showed a promising potential of iron oxide nanothenostics in pancreatic cancer. More investigations should be carried out to optimize in order to optimize the parameters and to understand the detailed mechanisms of action of these nanoparticles.

The national cancer institute alliance for nanotechnology in cancer launched a new project to develop a multifunctional theranostic nanoparticle platform that combines demonstrated imaging capability and receptor specificity of the nanoparticles with novel designs for tumor-targeted drug delivery in pancreatic cancer[28]. Rapid diagnosis and treatment using iron oxide theranostics may change the prognosis of pancreatic cancer in the next decade.

Colorectal cancer

Despite the major efforts and the important progress in the treatment of colorectal cancer after the use of targeted therapies, metastatic colo-rectal cancer remains an incurable disease. The nanotheranostics will most probably bring a new hope and add a positive impact on the prognosis and evolution of this disease.

Different new nanoparticles are being designed worldwide to assure a new way of delivering drug with higher doses, less tocixity and more specificity in colorectal cancer. As in pancreatic and gastro-esophageal cancer, many NP specific for colo-rectal cancer as polymeric nanosphere[29], micelle particles[30], metal semi-conductor nanoparticles[31] and gold nanoparticles are being elaborated[32].

One of the ideal examples for theranostics in colon cancer is designed by Soon *et al*[33] who developed a nanoparticle containing a magnetic material core associated with organic fluorescent material and an antibody (Cetuximab) for the specific diagnostic and treatment of these tumors.

NEW MOLECULAR TARGETS

The stratification of cancers into their molecular mutations, alterations or overexpression remains an important step in personalized medicine, before finding the accurate targeted therapy for each mutation. Nowadays, an important number of oncogenic driver alterations implicated in carcinogenesis are detected in lung adenocarcinoma and in breast cancer, but only few targeted therapies are approved in these two cancers. Many new targets are being identified in gastro-intestinal cancers and will probably be incriminated in future theranostics projects.

Next to Her2neu overexpression, MET and FGFR2 overexpression are considered potential therapeutic targets in this type of cancer in gastric cancer due to their role as oncogenic driver alterations. STAT3 seems to be a potential future target in the treatment of pancreatic cancer next to P53 and SMAD4. All these targets and many others will help the development of new treatment modalities based on theranostics[34].

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