Advanced Drug Delivery Reviews 108 (2017) 13–24

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Nanomedicine-based intraperitoneal therapy for the treatment of peritoneal carcinomatosis — Mission possible?☆

George R. Dakwar [a], Molood Shariati [a], Wouter Willaert [b,c], Wim Ceelen [b,c], Stefaan C. De Smedt [a,*], Katrien Remaut [a,c,**]

[a] Ghent Research Group on Nanomedicines, Laboratory for General Biochemistry and Physical Pharmacy, Faculty of Pharmacy, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[b] Department of Surgery, Laboratory of Experimental Surgery, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
[c] Cancer Research Institute Ghent (CRIG), Ghent, Belgium

ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form 1 July 2016
Accepted 5 July 2016
Available online 13 July 2016

Keywords:
Peritoneal carcinomatosis
Intraperitoneal delivery
Sustained release
Biodistribution
Nanomedicines

ABSTRACT

Intraperitoneal (IP) drug delivery represents an attractive strategy for the local treatment of peritoneal carcinomatosis (PC). Over the past decade, a lot of effort has been put both in the academia and clinic in developing IP therapeutic approaches that maximize local efficacy while limiting systemic side effects. Also nanomedicines are under investigation for the treatment of tumors confined to the peritoneal cavity, due to their potential to increase the peritoneal retention and to target drugs to the tumor sites as compared to free drugs. Despite the progress reported by multiple clinical studies, there are no FDA approved drugs or formulations for specific use in the IP cavity yet. This review discusses the current clinical management of PC, as well as recent advances in nanomedicine-based IP delivery. We address important challenges to be overcome towards designing optimal nanocarriers for IP therapy in vivo.

Contents

Abbreviations: CRS, cytoreductive surgery; HA, hyaluronic acid; IP, intraperitoneal; IPEC, intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemoperfusion; IFP, interstitial fluid pressure; MDR, multi drug resistance; MPs, microparticles; NPs, nanoparticles; PTX, paclitaxel; PC, peritoneal carcinomatosis; PIPAC, Pressurized IntraPeritoneal Aerosol Chemotherapy; VEGF, vascular endothelial growth factor.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Editors' Collection 2016".

* Corresponding author. Tel.: +32 9 2648076; fax: +32 9 2648189.
** Correspondence to: K. Remaut, Ghent Research Group on Nanomedicines, Laboratory for General Biochemistry and Physical Pharmacy, Faculty of Pharmacy, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium. Tel.: +32 9 2648046; fax: +32 9 2648189.
E-mail addresses: stefaan.desmedt@ugent.be (S.C. De Smedt), Katrien.Remaut@ugent.be (K. Remaut).

http://dx.doi.org/10.1016/j.addr.2016.07.001
0169-409X/

1. Introduction

Primary cancer occurring in organs confined to the peritoneal cavity (e.g. ovary, liver, colon, and pancreas) might lead to the migration of cancer cells to the peritoneal cavity. Attachment of free-flowing cancer cells to the mesothelial layer of the peritoneal membrane results in the formation of peritoneal carcinomatosis (PC). In the USA alone, there are about 250,000 cases of cancer originating from organs in the peritoneal cavity (e.g., ovarian, pancreatic, colorectal, gastric and liver) [1]. Unfortunately, most primary tumor sites do not cause clear clinical symptoms that enable the early detection of the peritoneal spread of cancer cells. The detection of PC thus mostly occurs at a later disease stage when a large amount of tumor nodules is already distributed over the peritoneal surfaces. The presence of these multiple peritoneal metastases confers a poor prognosis [2].

Selected patients with PC benefit from surgical cytoreduction, aiming to remove all visible peritoneal metastases. Depending on the histology and grade of the disease, either perioperative or postoperative intravenous (IV) chemotherapy can be administered. Despite macroscopically complete cytoreductive surgery (CRS), many patients develop recurrent PC [3]. Hence, active adjuvant treatments are needed to remove persisting minimal residual disease and improve the survival of patients diagnosed with PC. The past decade has witnessed a significant progress in developing IP adjuvant techniques. Most newly developed techniques focus on the local administration of chemotherapeutics. The rationale for IP therapy is the ability to achieve a high locoregional (peritoneal) drug concentration, while avoiding systemic toxicity [4]. Conventional chemotherapeutics might, however, rapidly leak from the peritoneal cavity and display little specificity towards cancer cells. Therefore, the use of nanomedicines to prolong the residence time in the peritoneal cavity and to specifically target tumor cells is being explored. In this review we aim to discuss the progress, barriers and challenges in employing nanomedicines for IP therapy of PC, with a special focus on strategies that are employed to increase the residence time of nanomedicines in the peritoneal cavity. To do so, we first focus on the main techniques that are currently used in the clinical management of PC using local administration of conventional chemotherapeutics. We also address the challenges and hurdles in tailoring nanomedicines for IP delivery in vivo, including biodistribution and tumor penetration. Finally, we discuss ongoing clinical trials with nanomedicines for PC therapy and reflect on the possible strategies to overcome current limitations upon administration of nanomedicines.

2. Anatomy and role of the peritoneal membrane

The peritoneal membrane covers the visceral, abdominal and pelvic organs and has a total surface of 1.5 m^2 on average [5]. It is composed of several layers of connective tissue as demonstrated by Baron [6]. The first layer is comprised of mesothelial cells interconnected by tight junctions, which secrete surface hyaluronan as depicted in Fig. 1A. The mesothelial layer functions as a barrier that protects from physical damage and surface adhesion [7]. A submesothelial basement membrane separates the mesothelial layer from the interstitial space, which contains fibroblasts, collagen and other molecules as a first "defense line" against macromolecules (Fig. 1A). The last layer consists of negatively charged endothelial cells — a second "defense line" that prevents the passage of large macromolecules into the peritoneal cavity (Fig. 1A).

Under normal conditions (Fig. 1A), the oncotic pressure that is exerted by plasma proteins (mainly albumin) across the peritoneal membrane (between the endothelial layer and the mesothelial layer) restricts the diffusion of water into the abdominal cavity due to the reabsorption of water that occurs into the capillaries from the interstitial space [8]. In the majority of the PC cases, however, this homeostasis is disrupted by an increased microvascular permeability which is believed to be mainly induced by the vascular endothelial growth factor (VEGF) [9,10]. Together with the secretion of cytokines and chemokines in the surrounding of the peritoneum, the structure of the membrane is altered leading eventually to a net change in the flow direction of the fluid (i.e. oncotic pressure) into the peritoneal cavity and consequently, to the formation of an albumin-rich ascites fluid in the peritoneal cavity (Fig. 1B). The exact mechanism by which the ascites fluid accumulates in the abdomen is very complex, and not fully elucidated yet. It is hypothesized that different factors play an important role in the formation of the ascites fluid, such as lymphatic obstruction and osmotic water transport following the leakage of proteins from microcapillaries into the peritoneal cavity [11].

Interestingly, it has been shown that the peritoneal membrane does not correspond to the classic semi-permeable model, but rather is highly permeable to both water, small solutes and proteins [7]. In fact, the peritoneal membrane does not represent a substantial physical

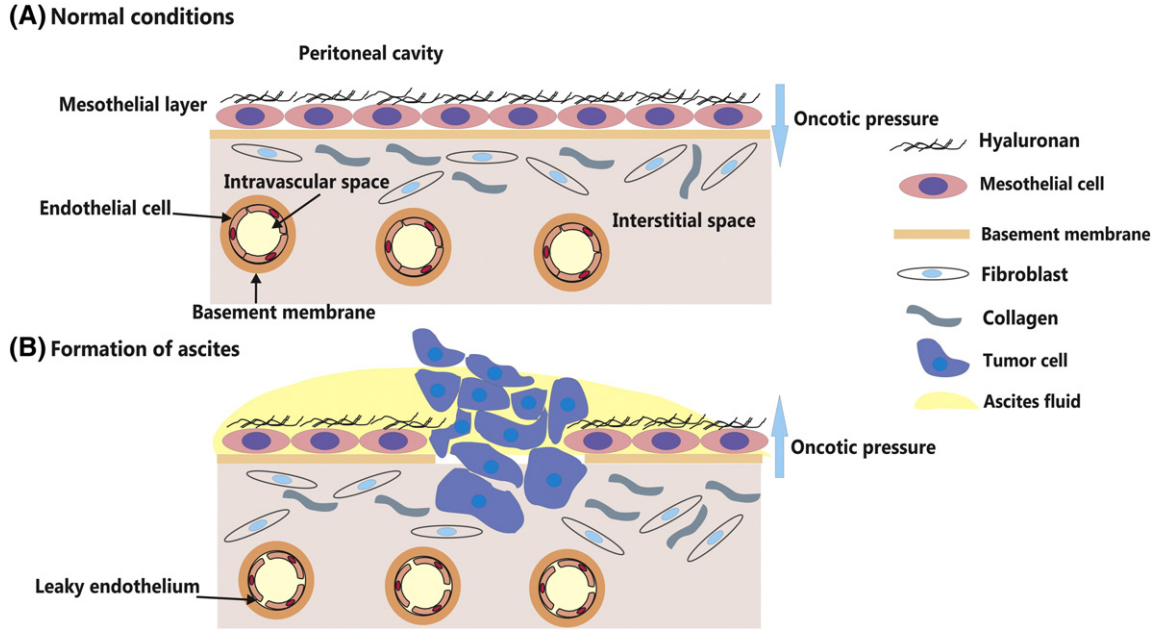

Fig. 1. The peritoneal membrane and formation of ascites fluid. (A) Structure of the peritoneal membrane under normal conditions and (B) disruption of the peritoneal membrane in peritoneal carcinomatosis, leading to the formation of ascites.