Drug-eluting stent in malignant biliary obstruction

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ABSTRACT

Endoscopic stent insertion is the treatment of choice for patients with malignant biliary obstruction. However, conventional stents enable only mechanical palliation of the obstruction, without any anti-tumor effects. Drug-eluting stent (DES), which was first introduced in coronary artery disease, are currently under investigation for sustaining stent patency and prolonging patient survival by inhibiting tumor ingrowth in malignant biliary obstruction. Many factors affecting efficient drug delivery have been studied to determine how drugs with anti-tumor effects suppress tumor ingrowth, including the specific drugs incorporated, means of incorporating the drugs, mode of drug release, and stent structure. Advances have resulted in the construction of more effective non-vascular DES and ongoing clinical research. Non-vascular DES is expected to play a vital role in prolonging the survival of patients with malignant biliary obstruction.

Keywords: Drug-eluting stent, malignant biliary obstruction, Paclitaxel, Gemcitabine, Pluronic F-125.

1. INTRODUCTION

Drug-eluting stent (DES) consists of a polymer-attached drug and polymer that controls the drug release on a covered or uncovered stent, which serves as the platform. Stent intervention is most common in coronary artery diseases, and DES is being developed to reduce restenosis, which occurs in 15–30% of patients. In addition to vascular DES, much effort has been put into developing non-vascular DES to prevent stent stenosis by cancer in malignant biliary disease. Non-vascular DES is far different from those of the vascular tract. Vascular DES is designed to deliver drug locally to inhibit intimal thickening and hyperplasia by interfering with the cellular

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pathways involved in inflammation, migration, proliferation, and secretion of the extracellular matrix [1]. In addition, non-vascular DES must suppress tumor proliferation and mucosal hyperplasia.

2. DRUG ELUTING STENT

2.1 History of DES

The notion that DES can sustain stent patency by suppressing tumor proliferation in malignant biliary obstruction developed in the mid-1990s [2]. First, the feasibility of non-vascular DES was suggested in a porcine bile-duct model. Paclitaxel-coated stents consistently resulted in near-complete inhibition of stent ingrowth, compared with non-drug-coated stents for 6 months after insertion [3]. In humans, non-vascular DES was first tried in unresectable adenomatous esophageal cancer [4]. Although no conclusion was reached regarding the effect of DES at preventing tumor ingrowth, the study demonstrated that DES was safe and did not cause complications. Subsequently, a new percutaneous transhepatic biliary drainage tube coated with carboplatin (carboplatin-coated tube; CCT) continuously released a fixed amount of carboplatin for 4 weeks and showed antitumor effects on human cholangiocarcinoma cell line HuCC-T1 *in vitro* [5]. This study proposed a new therapeutic method using DES in unresectable cholangiocarcinoma. In addition, paclitaxel incubation resulted in the dose-dependent inhibition of the proliferation of human epithelial gallbladder cells, human fibroblasts, and pancreatic carcinoma cells. This inhibitory effect of paclitaxel on the cell lines could serve as the foundation for developing drug-coated or drug-eluting stents for malignant biliary strictures [6]. Based on the existing research, an animal study was conducted on porcine bile ducts using metallic stent covered with a paclitaxel-incorporated membrane (MSCPM-1), which was a type of paclitaxel-coated DES. The MSCPM-1 inserted the normal porcine bile duct resulted in epithelial denudation, mucin hypersecretion, and epithelial metaplasia when stents containing 20% wt/v paclitaxel were used. The absence of transmural necrosis and perforation proved the safety of MSCPM-1. *In vitro* experiments [7] with MSCPM-1 could serve as a basis for developing new, safe treatment modalities for malignant biliary obstruction. In a canine model, although paclitaxel-eluting covered metallic stent (PECMS) was inserted in the normal bile duct without technical complications, the local drug delivery from the PECMS produced no significant histological changes [8]. A human pilot study with MSCPM-1 demonstrated that the endoscopic insertion of MSCPM-1 was technically feasible, safe, and effective in patients with malignant biliary obstruction. In addition, MSCPM-1 might have local antitumor activity via the steady release of paclitaxel. However, a comparison study of MSCPM-1 versus covered metal stent

(CMS) revealed no significant discrepancy in survival or stent patency [9]. This might be due to the biodegradation of the polyurethane membranes by hydrolysis and oxidation, and contact with continuous bile flow. Degraded membranes lead to the formation of micro-cracks and holes in the stents, resulting in stent occlusion via tumor ingrowth [10]. The second-generation MSCPM-2 was invented to overcome these limitations, while maintaining continuous drug release, and was tested in porcine bile ducts [10]. The new paclitaxel-eluting stent with 10% Pluronic F-127 proved to be safe and provided enhanced local drug delivery in this study. This stent is now being evaluated in a large-scale clinical trial. Recently, studies using DES coated with gemcitabine (GEM) instead of paclitaxel have been conducted. An animal study of GEM-incorporating self-expanding metal stent (GSEMS), indicated that their safety for use in normal bile ducts. The 10% GEM eluting GSEMS produced mild histological changes in the stented segments and adjacent tissue [11]. Sub-tumor insertion of the 12% GEM-eluting covered nonvascular stent membrane was more efficiently inhibited the growth of CT-26 colon cancer [12]. Research into DES using various anti-tumor agents and stent structures in malignant biliary obstruction is underway.

2.2 Necessity of DES

Pancreatic and bile duct cancer are common causes of malignant biliary obstruction. Pancreatic cancer is resectable in 10–20% of patients at diagnosis and has a poor prognosis. The chances of resection in bile duct cancer have increased with technical advances in surgery, but the prognosis remains poor. The duration of patency is important for patients with a short life expectancy, because the quality of life and cost-effectiveness of treatment are determined mainly by stent occlusion [13]. The treatment of choice for unresectable malignant biliary obstruction is endoscopic stent insertion. Self-expanding metal stents (SEMS) are superior to plastic stents in patency and efficacy, but they confer no improvement in survival. In addition, uncovered SEMS can become occluded over time because of tumor overgrowth, ingrowth, and/or biliary sludge. Covered SEMS developed to prevent tumor ingrowth can occasionally migrate. Moreover, metal stents merely promote biliary drainage and have no antitumor effect. Therefore, the local application of antitumor agents via SEMS has been proposed as a possible method to prevent tumor ingrowth in SEMS.

2.3 Development of DES

There are three general techniques for incorporating drugs on metal stents: direct attachment of the drug to the metal stent; loading the drug into pores in a porous metal stent; and incorporating the drug into a polymer that coats the stent [14]. In some studies, the stents were dipped in a solution of drug-incorporated polymer to promote drug incorporation [7, 10, 12]. MSCPM-1 was mounted on a glass tube and dipped in a container filled with medical-grade polyurethane-paclitaxel liquid (PPL) made from a mixture of polyurethane, paclitaxel, and tetrahydrofuran (THF) solution, which was used as a solvent for the polyurethane. The glass tube with the stent was removed shortly after it was dipped in the container. The PPL was heat-dried and the glass tube was removed from the stent, leaving the PPL coating on the stent surface [7]. MSCPM-1 was susceptible to biodegradation and tumor ingrowth was more likely due to its single-layer structure. To overcome these weaknesses in MSCPM-1, MSCPM-2 was comprised of a double-layer structure with addition of the surfactant Pluronic F-127. Paclitaxel can be incorporated into the core of polymeric micelles formed by Pluronic F-127 to facilitate the steady release of paclitaxel [10]. The MSCPM-2 coating solution was composed of a mixture of paclitaxel-polyurethane-Pluronic polymer and THF. The coating process was conducted using the dip-coating technique [10]. GEM-eluting membranes were also manufactured using the dip-coating method [12].

The long-term, continuous release of high concentrations of antitumor agents is necessary to maintain stent patency and suppress tumor ingrowth and progression. The surfactant Pluronic F-127 was added to MSCMP-2 to promote steady release, and resulted in more-effective drug release from the membrane compared with MSCPM-1 (Fig. 1). Prolonged GEM release for more than 2 weeks is difficult to attain due to its high water-solubility. A mixture of THF and ethanol was used as a dipping solution since it maintains GEM in crystal form in the solution. Nano-granulated GEM was used to generate more favorable release profiles. Release from nano-granulated GEM is slower than free GEM due to its smaller surface area (Fig. 2).

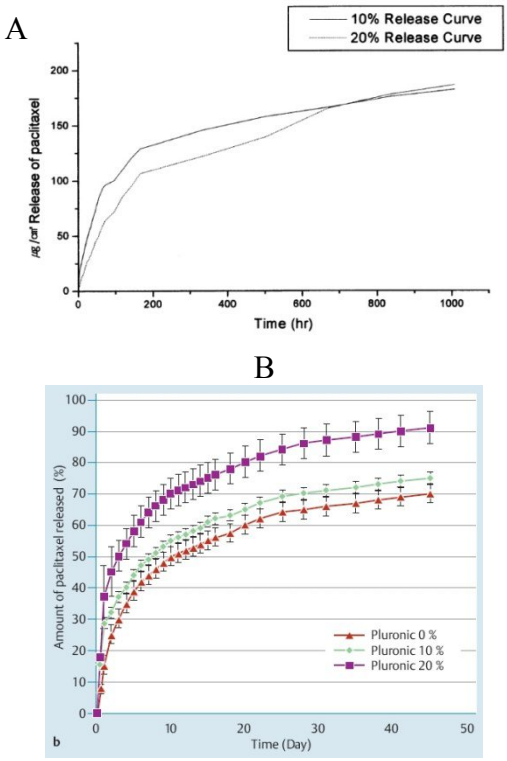

Figure 1. **A**. Release rates of 10% and 20% wt/v paclitaxel stents in MSCPM-1 in phosphate-buffered saline (adapted from [7]). **B**. *In vitro* cumulative release of paclitaxel measured by HPLC for experimental stents with varying concentrations of Pluronic, showing the initial release profiles over the first 50 days in MSCPM-2 (adapted from [10]).

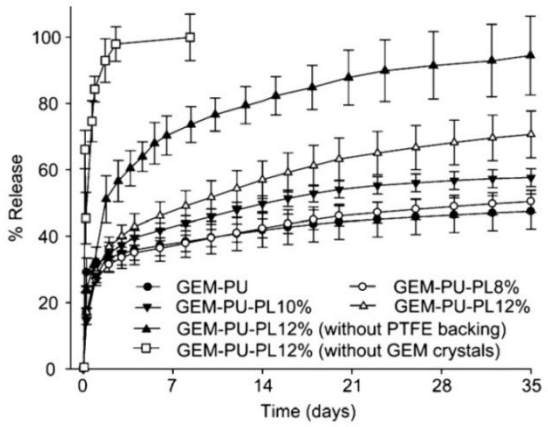

Figure 2. Release of GEM from polyurethane (PU) and polyurethane-Lutrol® F127 (PU-PL) membrane. Lutrol® F127 was applied as a weight percentage of PU. GEMPU-PL12% showed the most controlled release of GEM, with an initial burst release of 35% of the total GEM loaded, followed by the sustained release of an additional 35% (adapted from [12]).

The serum concentration of paclitaxel released from paclitaxel-incorporated DES *in vivo* was evaluated to examine continuous drug release and systemic effects. Low levels of paclitaxel released from MSCPM-1 were detected in blood samples of patients after 50 days [15]. With MSCPM-2, paclitaxel released into porcine serum was detected after 28 days [10].

2.4 DES and animal safety studies

Studies of DES would be facilitated by a large animal model of pancreatic or bile duct cancer; however, no such model exists. Therefore, animal models of DES focus on their safety in the normal bile duct.

In animal bile duct models, DES caused no severe complications and was safe. An inflammatory cell infiltrate and fibrous reaction were noted in the segments of bile duct that were in contact with the MSCPM-1. Epithelial denudation, mucin hypersecretion, and epithelial metaplasia also were seen in pig bile ducts [7]. No stent occlusion was observed in any animal. In another animal study of paclitaxel-eluting stents [8], mucosal hyperplasia resulting from fibrous reaction and inflammation was more prominent in the paclitaxel-eluting stent group. These findings are comparable to the results in a porcine biliary model [7]. The areas that had been stented with the MSCPM-2 showed histological findings similar to those with the MSCPM-1, including a dilated lumen, mucosal atrophy, and decreased wall thickness [10]. No transmural necrosis or perforation was observed in any animal

studies using paclitaxel-eluting stents [7, 8, 10]. When GEM-eluting stents were inserted in porcine bile ducts, only mild inflammatory cell infiltration in the mucosal layer and fibrous reactions in the submucosal layer of the bile ducts were detected, while no perforation, necrosis, or stent occlusion was observed in any animal [11].

2.5 DES and human studies

Human studies indicate little progress in the treatment of malignant biliary obstruction. Although studies have not demonstrated superior survival or stent patency, the safety of DES has been proved. In a pilot study of 21 patients with unresectable malignant biliary obstructions [15], occlusion of the MSCPM-1 was observed in nine patients and was caused by bile sludge or clogs in four, tumor overgrowth in three, and tumor ingrowth in two. The mean patency of MSCPM-1 was 429 days and the mean patient survival was 350 days. Although this study shown that the use of MSCPM-1 was safe, feasible and effective, it had limitations, including the small number of patients and its nature as a one-arm study. The efficacy and safety of MSCPM-1 were compared prospectively with those of CMS in patients with malignant biliary obstructions (unpublished data). Although the use of the MSCPM-1 produced no significant differences in stent patency or survival in patients with malignant biliary obstructions compared with the use of the CMS, this study demonstrated that the MSCPM-1 can be used safely in humans. Song *et al*. [9] reported that PECMS did not achieve better stent patency or survival time than CMS in patients with unresectable distal malignant biliary obstructions. Although results were similar, no information regarding the *in vitro* drug-release profiles of the drug-integrated membranes was gathered. Moreover, the evaluation of the antitumor effects of PECMS was limited. A recent multicenter, randomized, double-blind, comparative clinical human study using the MSCPM-2 has been initiated.

2.6 Theoretical background for use of DES

The DES used to treat malignant biliary obstructions should possess the following characteristics for optimal therapeutic effect: continuous drug release, adequate penetration of the surrounding tissue to achieve effective tissue concentrations, and no adverse systemic effects [15]. In a rodent experiment to assess the local anti-tumor effect, tumor reduction was observed after implantation of MSCPM-2 discs with various paclitaxel concentrations (unpublished data). After 27 days, results using films coated with 800 μg of 10% paclitaxel were significant compared with the control (non-treated) group (Fig. 3).

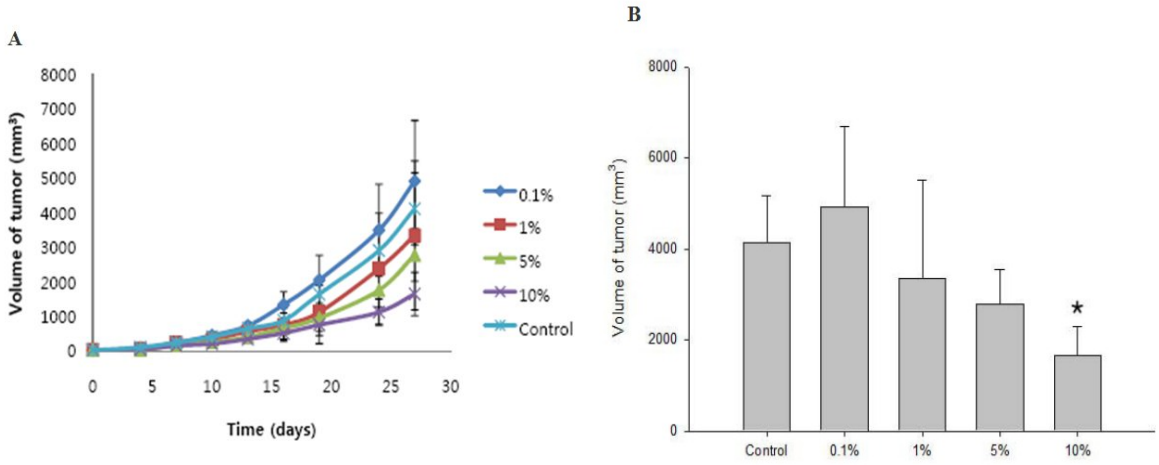

Figure 3. (**A**) Mean tumor volumes in five groups. The group treated with 10% paclitaxel/Pluronic-polyurethane films exhibited significant tumor suppression after 27 days. (**B**) After 27 days, the tumor volume in the group treated with 10% paclitaxel/Pluronic-polyurethane films had regressed significantly compared with the other groups.

2.7 Future of DES

To develop more effective DES, active research into stent materials, metal surface treatments, drug-coating techniques, and polymer types is ongoing. Several coating techniques have been developed, in which a pure drug or polymer-drug matrix coating is most commonly applied to the surface of the stent (Table 1).

Table 1. Potential candidates for drug elution (adapted from[14]).

Antineoplastic	Paclitaxel (Taxol™) Taxol derivative (QP-2) Actinomycin D Vincristine
Antithrombin	Hirudin and iloprost Heparin
Immunosuppressants	Sirolimus (Rapamycin™) Tranilast Dexamethasone Tacrolimus (FK506)
Collagen synthetase inhibitor	Halofuginone Propyl hydroxylase C-proteinase inhibitor Metalloproteinase inhibitor

Angiopeptin V
Vascular endothelial growth factor

Although there are reports of the safety and efficacy of DES in malignant biliary obstruction, no study has investigated the underlying mechanism. Studies to clarify the mode of action with regards to local drug delivery to tumors and the anti-tumor effect are needed and will accelerate the research and development of DES. Moreover, the processes and mechanisms of local drug delivery systems at the cellular level and in mouse models of cancer with various anticancer drug-eluting films should be explored. The membrane covering the DES might be damaged due to contact with continuous bile flow. To overcome this problem, effort is being made to produce a double-layer DES with an inner layer of polytetrafluoroethylene (PTFE), which is resistant to bile degradation, and a drug-containing polyurethane outer layer.

3. CONCLUSION

Investigations of the use of nonvascular DES for malignant biliary obstruction are currently insufficient. Nevertheless, trials have led to advances in DES and have demonstrated both their safety and doubts regarding their clinical efficacy. We hope that DES will be effective against tumors through diverse mechanism and, more importantly, will prolong stent patency and patient survival. Further investigations and clinical studies of DES are required to achieve these goals.

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