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Invited Review Article

Stents with specialized functions: drug-eluting stents and stents with antireflux devices

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A B S T R A C T

Biliary drainage in malignant biliary obstruction improves patient survival and quality of life. Although bypass surgery was historically the main method of treating malignant biliary obstruction, stent insertion using endoscopy or interventional radiology is currently recognized as the first-line of treatment. Biliary stents have undergone various modifications in terms of material and structure, with the aim of increasing stent patency. One such modification is the antitumor-agent-eluting stent, which is intended to suppress tumor ingrowth through chemical changes in the membrane. Another modified stent is the antireflux stent, which physically prevents the reflux of food by using an antireflux valve. Although the safety of these modified stents has been demonstrated in both animal and human studies, their efficacy, compared with conventional stents, remains unknown. Although the development of these functional stents is challenging, their potential is promising. Effort is necessary to increase stent patency, which requires much modification and development, to prolong patient survival.

Keywords: antireflux stent, drug-eluting stent, functional stent, malignant biliary obstruction

Introduction

Biliary stents have undergone various modifications, with the goal of improving the management of both malignant biliary obstruction and benign stenosis. New stent materials include plastic stents and self-expanding metal stents (SEMSs); SEMSs can be uncovered or covered. Moreover, various functional stents are being developed to serve a diverse range of purposes, including antimigratory stents, easily removable or shape-modifying stents, antihyperplasia stents, drug-eluting stents (DESs), radioactive stents, and bioabsorbable stents.[1] These stents have been developed with the goal of improving stent patency through modifications. This paper discusses DESs, which prevent tumor ingrowth into the stent, and antireflux stents (ARSs), which suppress food reflux.

Drug-eluting stents

SEMSs can become obstructed by tumor ingrowth through the stent mesh, tumor overgrowth at the proximal or distal end of the stent, the compaction of biliary sludge or food, or mucosal hyperplasia due to stent-induced chronic inflammation.[2,3] The use of covered SEMSs cannot prevent tumor ingrowth completely, although these stents were designed to suppress such ingrowth. This is because the polyurethane used in the covered SEMSs is biodegraded *in vivo* by hydrolysis, oxidation,[4] and continuous contact with bile flow.[5,6] Degraded membranes form microcracks and holes in the stent can result in tumor ingrowth and stent occlusion.[6,7] Given the limitations associated with the use of covered SEMSs in the physical suppression of ingrowth, there have been efforts to coat similar stents with antitumor drugs, to prevent tumor invasion into the membrane and to prolong stent patency. The results of animal and human studies of DESs are summarized in Table 1.[2,8–13] Antitumor agents used in drug-eluting stents include hydrophobic paclitaxel and hydrophilic gemcitabine.

Paclitaxel-eluting stent

The antitumor agent paclitaxel interferes with cell proliferation in the G0/G1 and G2/M phases of the cell cycle, and triggers molecular signaling, via the mitochondrial pathway, causing cell apoptosis.[14–16] Paclitaxel causes the dose-dependent inhibition of cell proliferation by human epithelial gallbladder cells, human fibroblasts, and pancreatic carcinoma cells.[14] This inhibitory effect, observed in cell lines, has become the theoretical foundation for the development of drug-eluting stents for use in malignant biliary strictures.[14] Lee et al[8] developed a metallic stent covered with a paclitaxel-incorporated membrane (MSCPM-I), i.e., a paclitaxel-eluting SEMS, and the safety of this device was proven in the porcine bile duct. Polyurethane membranes were eluted with three

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Table 1 Outcomes of Drug-eluting Metal Stent in Animal and Human Studies

Author (y)	Type of study		Comparison groups (*N*)	Stent patency (mean ± SD)	Patient survival	Stent occlusion (*N*, %)			Complications (*N*, %)		
						Ingrowth	Overgrowth	Sludge	Cholangitis	Pancreatitis	Migration
Lee et al[8] (2005)	Animal	Paclitaxel (MSCPM-I)	Animal (Porcine)	NA	NA	Histology: epithelial denudation, mucin hypersecretion, epithelial metaplasia			No transmural necrosis and perforation		
Suk et al[10] (2007)	Human (P)	Paclitaxel (MSCPM-I)	Single arm ($n = 21$)	429 d (range, 68–810)	350 d (range, 68–811)	2 (9.5)	3 (1.6)	4 (1.9)	3 (1.4)	0	1 (0.4)
Lee et al[9] (2009)	Animal	Paclitaxel (PECMS)	Animal (Canine)	NA	NA	Histology: minimal mucosal hyperplasia in PECMS			No perforation		
Song et al[11] (2011)	Human (RCT)	Paclitaxel (PECMS)	PECMS ($n = 26$)	Not different* ($P = 0.307$)	Not different* ($P = 0.596$)	5 (19.2)	0	0	3 (11.5)	1 (3.8)	0
			CCMS ($n = 26$)			4 (15.3)	0	0	0	1 (3.8)	4 (15.3)
Jang et al[2] (2013)	Human (RCT)	Paclitaxel (MSCPM-I)	MSCPM-I ($n = 60$)	199.1 ± 235.4 d	269.5 ± 260.3 d	13 (22.4)	5 (8.6)	1 (1.7)	5 (8.6)	2 (3.5)	1 (1.7)
			CCMS ($n = 46$)	148.7 ± 98.8 d	181.9 ± 116.8 d	9 (21.4)	2 (4.8)	2 (4.8)	1 (2.4)	4 (9.5)	0
Jang et al[12] (2012)	Animal	Paclitaxel (MSCPM-II)	Animal	NA	NA	Histology: mucosal atrophy, decreased wall thickness, intestinal metaplasia			No transmural necrosis and perforation		
Chung et al[13] (2012)	Animal	Gemcitabine	Animal	NA	NA	Histology: Moderate to severe inflammation, fibrous reaction			No transmural necrosis and perforation		

CCMS, conventional covered metal stent; MSCPM, metallic stent covered with a paclitaxel-incorporated membrane; NA, not available; P, prospective; PECMS, paclitaxel-eluting covered metallic stent; RCT, randomized controlled trial; SD, standard deviation.

* Stent patency and survival time were not significantly different between the two groups (PECMS and CCMS).

concentrations of paclitaxel (0%, 10%, and 20% weight/volume) in three groups and then, surgically inserted into porcine bile ducts. After 4 weeks, the segment of bile duct containing the stent was examined histologically. Epithelial denudation, mucin hypersecretion, and epithelial metaplasia were present in the bile ducts, but transmural necrosis and perforation were not observed in any animal. Another animal study also demonstrated the safety of paclitaxel-eluting SEMSs.[9] In that study, endoscopically inserted paclitaxel-eluting covered metallic stents (PECMSs) and conventionally covered metal stents (CMSs) were compared in canine bile ducts. The PECMS group had mucosal hyperplasia and the stented segments were significantly thicker, these changes were not observed in the CMS group. The histological changes associated with the use of a paclitaxel-eluting stent are considered secondary to mechanical irritation arising from the radial force of the stent because the stent lumen is larger than the canine bile duct, and local irritation due to paclitaxel itself. There were no cases of perforation or necrosis of the bile duct. Through these animal studies, paclitaxel-eluting SEMSs were established as the foundation for developing a safe, new treatment modality for malignant biliary obstruction.

Several human studies have followed these animal studies. A multicenter single-arm pilot study using an MSCPM-I was the first such human study, enrolling 21 patients.[10] The mean patency of an MSCPM-I was 429 (median 270, range 68–810) days and the cumulative patency rate at 3 months, 6 months, and 12 months was 100%, 71%, and 36%, respectively. This mean patency is longer than that of other metal stents, and demonstrates the feasibility and efficacy of a MSCPM-I. Moreover, when the patients' serum paclitaxel concentration was measured, the highest concentration was seen between 1 and 10 days after stent insertion. Although a low level of paclitaxel ($0.015–0.20 \times 10^{-1}$ mg/mL) was detected in the blood samples of patients for over 50 days, the values were lower than the therapeutic range of paclitaxel ($0.9 \times 10^{-4}–1.1 \times 10^{-1}$ mg/mL). The presence of paclitaxel in the serum demonstrates that the MSCPM-I provided a high local paclitaxel concentration at the target tissue, including the bile duct and tumor, after which the paclitaxel was released slowly into the systemic circulation. These results provide evidence of the safety of such stents, from the perspective of the local application of an antitumor agent in DESs. The MSCPM-I appeared to maximize the drug concentration in the immediate tumor environment, while minimizing systemic exposure and nontarget organ toxicity.

A prospective comparative study using an MSCPM-I found no significant differences between an MSCPM-I and a conventional CMS, in terms of stent patency or patient survival.[2] However, the mean patency of the MSCPM-I might have been underestimated in this study, because a substantial number of patients who received an MSCPM-I died from disease progression before the stent was blocked. Furthermore, the membranes of the stents (MSCPM-I and CMS) used in the study consisted of a single polyurethane layer. Polyurethane membranes can be biodegraded by bile flow resulting in the formation of microcracks and holes in the stent. Consequently, if the membrane is damaged by bile, it can be assumed that the paclitaxel eluted in the membrane lacks sufficient local antitumoral effect to suppress tumor ingrowth. It is likely that this limitation in the polyurethane membranes led to the lack of a difference in stent patency between the groups. A prospective pilot study comparing PECMSs and CMSs, conducted by another group, found no statistical differences in the duration of stent patency or patient survival between the two groups.[11] Although the two prospective studies did not demonstrate superiority in terms of the efficacy of the paclitaxel-eluting stent, they did show its safety, and reported acceptable complication rates in the human bile duct.

The MSCPM-II was developed to overcome the limitations of the MSCPM-I and improve drug release.[12] It is a double-layer drug-eluting metal stent developed to overcome the limitations associated with polyurethane membranes. The inner polytetrafluoroethylene (PTFE) layer is resistant to degradation by bile and the outer polyurethane layer contains paclitaxel.[12] In addition, the MSCPM-II incorporated the surfactant Pluronic F-127 and polyurethane in the outer layer, to promote the steady release of paclitaxel.[12,17] In an animal study using the MSCPM-II, the histological changes in the porcine biliary epithelium consisted of an inflammatory cell infiltrate and fibrotic reaction, and were considered acceptable in terms of safety.[12] In the porcine serum analysis, released paclitaxel was detected for 28 days with the 10% Pluronic F-127 concentration.