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PULMONARY PROCEDURES

Biodegradable Cisplatin-Eluting Tracheal Stent for Malignant Airway Obstruction

In Vivo and In Vitro Studies

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Background: **Self-expandable metallic stents (SEMSs) are effective in the palliation of malignant airway obstruction. Tumor ingrowth, however, frequently occurs because of a shortage of effective local therapy. Additionally, SEMSs are frequently associated with problems of fracture, migration, and difficult removals. Our goal was to develop a novel bioabsorbable stent with cisplatin elution to circumvent such problems.**

Methods: **Biodegradable stents made of polycaprolactone were fabricated by a laboratory-made, microinjection molding machine. In vitro mechanical strength of the stents was compared with the strength of Ultraflex SEMSs. Polylactide-polyglycolide copolymer and cisplatin were coated onto the surfaces of the stents. Elution method and high-performance liquid chromatography (HPLC) analysis were used to examine the in vitro cisplatin release characteristics. In vivo, the stents were surgically implanted into the cervical trachea of 15 New Zealand white rabbits. Bronchoscopic examination was performed weekly (1 to approximately 5 weeks) before killing. Cisplatin concentrations in trachea, lung, and blood were analyzed by HPLC. Histologic examination was also performed.**

Results: **The biodegradable stent exhibited mechanical strength comparable to the strength of Ultraflex SEMSs and provided a steady release of cisplatin for > 4 weeks in vitro. The in vivo study showed sustained cisplatin levels in rabbit trachea for > 5 weeks with a minimum drug level in blood. Histologic examination showed an intact ciliated epithelium and marked leukocyte infiltration in the submucosa of the stented area.**

Conclusions: **Our study demonstrated that the biodegradable stents provided physical properties comparable to the properties of SEMSs and a sustained release of cisplatin for > 5 weeks, which showed great potential in the treatment of malignant airway obstruction.**

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Abbreviations: EITC = endobronchial intratumoral chemotherapy; HPLC = high-performance liquid chromatography; PCL = polycaprolactone; PLGA = poly (D,L)-lactide-co-glycolide; SEMS = self-expandable metallic stent

Approximately 30% of patients with lung cancer have central airway obstruction.[1] Self-expandable metallic stents (SEMSs) are commonly used in these patients for the palliation of the symptom.[2] Stent tumor regrowth, however, commonly occurs because there is no effective in situ therapy.[3,4] Despite external radiation after airway stenting providing borderline survival benefits, it was reported that 37% of the patients were not able to complete radiation therapy, and more than one-third of patients still died because of tumor growth-related asphyxia.[3,5]

On the other hand, SEMs are also notorious for various troublesome complications, including stent fracture, migration, impaired mucociliary clearance, and increased bacterial infection.[4,6,7] Additionally, the embedded nature of the stent makes subsequent bronchoscopic removal difficult and risky. We believe that an ideal airway stent should (1) possess sufficient strength to perform its mechanical function, (2) be biodegradable (no need for removal after serving its purpose), (3) be biocompatible so that the material breakdown process will not cause any tissue irritation, and/or (4) provide effective pharmaceuticals for a sustained period of time.

Endobronchial intratumoral chemotherapy (EITC) (ie, the injection of conventional cytotoxic drugs

directly into the tumor tissue through a flexible bronchoscope) has been described in several clinical studies with encouraging results.[8-10] Local high doses of cytotoxic action can reduce large local tumor cell burdens, with rapid alleviation of endobronchial obstruction.[8-10] Furthermore, unlike conventional IV chemotherapy, EITC exhibits no significant systemic toxicity. However, such drug delivery was transient and could be prolonged for only a few hours to days in the gel-form or oil-form injection.[11] Hence, the clinical indication was only limited to cases of asymptomatic endobronchial tumors with $<50\%$ obstruction.[8]

In our laboratory, we had successfully designed and fabricated a mesh-type, biodegradable stent with a backbone of polycaprolactone (PCL)[12] that permitted airway remodeling in rabbits.[13] In this report, following our previous work, we aimed to develop biodegradable drug-eluting stents that can provide a sustainable release of cisplatin, which is the most commonly used antitumor medication in lung cancer for the treatment of malignant tracheal obstruction. An elution method and a high-performance liquid chromatography (HPLC) analysis were used to determine the in vitro release of cisplatin from the biodegradable stents. In addition, the stents were surgically implanted into the cervical trachea of 15 rabbits. The level of cisplatin by in vivo release in the trachea, lung, and blood were analyzed weekly. Histologic examination was also performed.

Materials and Methods

Composition of Biodegradable Stents

The biodegradable polymers used were poly(ε-caprolactone), with a molecular weight of 80,000 Da (Sigma-Aldrich Co LLC). A DuPont model TA-2000 differential scanning calorimeter (TA Instruments) was used to characterize the thermal properties of the polymer. The measured results suggested that the melting temperature of the polymer was approximately 60.7°C.

Fabrication of Bare PCL Stents

To fabricate a biodegradable stent, a stent element design, as shown in Figure 1A, was first developed. The stent elements were fabricated by a laboratory-made, microinjection molding machine. The machine was used for transporting, melting, and pressurizing the polymeric materials, which were fed into the machine in granular form. It mainly consists of two parts: the injection unit and the clamping unit. The function of the injection unit is to melt the polymer and inject it into the mold, whereas the clamping unit holds the mold, opens and closes it, and ejects the finished product. The plasticization of the polymers inside the barrel was completed by the energy provided by the surrounding heater, which was controlled by a temperature moderator. The melt temperature used was 100°C. This is followed by injection, wherein the pneumatically actuated plunger pushes downward to force the polymer melt into the relatively cold, empty cavity of the already closed mold. The temperature of the mold was maintained at room temperature. When the stent element is cooled to a state of sufficient rigidity, which occurs when all regions of the part have cooled down to below the melting temperature of the polymer, the mold opens and the stent element is obtained.

After molding, each stent element was interconnected with another stent element (Fig 1B). By interconnecting six and 10 elements, respectively, the assembly was rolled into mesh tubes, and the final connecting points were welded by a hot spot welding. During the hot welding process, the thermoplastic PCL was melted and used as glue in its molten state to join the components. No other agents were used. Biodegradable stents of two different external diameters (6 mm and 10 mm) were obtained (Fig 1C).

Spray Coating of Cisplatin

After the assembly process, the PCL stents were coated with cisplatin by a spray coating device, which was designed and built in our laboratory. Poly (D,L)-lactide-co-glycolide (PLGA) (75:25, Resomer RG 756; Boehringer Ingelheim GmbH) and cisplatin (Sigma-Aldrich Co LLC) were first dissolved in acetonitrile at predetermined ratios (90/10, 80/20, 70/30, 50/50, weight/weight) and were then delivered by the spray coater with a volumetric flow rate of 4 mL/h. All spray coating experiments were carried out at room temperature.

Mechanical Properties of PCL Stents

To compare the PCL stents manufactured in this study with the commercial 10-mm-covered Ultraflex SEMSs (Boston Scientific), both PCL (10 mm in diameter) and Ultraflex stents were compressed by a 1-N force, and the deformation rates were recorded. Area load was applied over the full length of the stents with a 1,500-mm^2 plate mounted on a LLOYD tensiometer (AMETEK, Inc). The cross-head speed was 1 mm/min.

In Vitro Elution of Cisplatin From the Stents

An in vitro elution method was used to determine the release characteristics of cisplatin from the stents. A phosphate buffer, 0.15 mol/L (pH 7.4), was used as the dissolution medium. The stents' elements were placed in glass test tubes with 1 mL of phosphate buffer. All tubes were incubated at 37°C. The dissolution medium was collected daily for subsequent HPLC analyses. Fresh phosphate buffer (1 mL) was then added for the next 24-h period, and this procedure was repeated for 6 weeks.

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