Autologous hCTPs

Study design

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Institute of Advanced Biomedical Engineering and Science

Tokyo Women’s Medical University
Today’s presentation consists of two main topics

- **Main topics**

- **Autologous epithelial cell sheet products** for esophageal regeneration

- **Clinical study design** for cell tissue products (compared with drugs) in Japan / Sweden
Current clinical issue

- Endoscopic submucosal dissection (ESD) involves *en bloc* removal of superficial esophageal squamous cell carcinoma (SCC).
- However, luminal stricture often occurs after ESD when the lesion involves more than three-fourth of the circumference. Frequent sessions of balloon dilatation by endoscopy is required in such situation, compromising the quality of life.
**Issue 1: High frequency of complication**

Resected more than 75% circumference

Post-operative constriction 68-92% \(^{1-3}\)

**Issue 2: Refractory complication**

Standard treatment for constriction: Endoscopic balloon Dilatation (EBD)

Expensive medical treatment fee
K522-3  12480 (¥124,800)

**Refractory esophageal constricture**

- Full-Circumferential ESD (100%) 32.7 times EBD
- Semi-circumferential ESD (>75%) 11.0 times EBD

Quantum TTC®
Esophageal Balloon Dilator

Nagasaki Univ. Hospital
Cell Sheet Engineering

Cell Sheet formation
On Culture Dishes

Enzyme Treatment

Desruption of structure
and Functions

Temp. Responsive Polymer
Poly(N-isopropylacrylamide)
(PIPAAm)

Hydrophobic Surfaces

20 nm

T Changes
(37 → 20°C)

Maitain structure and
Functions

Our Invention

Oral epithelial cell sheet

Hydrophophilic Surfaces
First in Human study (2008~2010)


UMIN ID: UMIN000000473

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<th>Title of the study</th>
<th>Treatment of artificial esophageal ulcerations after EMR by endoscopic transplantation of autologous oral mucosal epithelial cell sheets</th>
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<td>Target sample size</td>
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Clinical study: 10 cases (2013~2014)

Nagasaki Univ. Hosp.

Biopsy

5~6mmΦ

Seeding to dishes

Isolation

CPC

TWIns

● Tissue

● Blood serum

● Cell sheets

Cell sheet transplantation

Nagasaki

Tokyo

Tissue

Blood serum

Isolation

CPC

TWIns

1,200 km

Biopsy

Cell sheet transplantation

20℃
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| Primary outcome | Morbidity  
Stricture |
| Secondary outcome | Adverse event |
| Study design | Single arm  
Histrical control |
| Target sample size | 10 |
| Progress | Completed  
2013-2014 |
Conventional transplantation (with support membrane)
Cell sheets transplantation with dedicated device

6 cell sheets transplanted using a new dedicated device
Dedicated delivery device
Endoscopic cell sheet transplantation device developed by using a 3-dimensional printer and its feasibility evaluation in a porcine model

Masanori Maeda, PhD,a Nobuo Kanai, MD, PhD,a Shinshiro Kobayashi, MD,b,c Takahiro Hosoi, MSc,a,d Ryosuke Takagii, PhD,a Takashi Okhi, MD, PhD,a,b,c Kohji Muragaki, MD, PhD,a,d Masayuki Yamato, PhD,a,d Sesshu Eguchi, MD, PhD,a Fumio Fukai, PhD,a, and Teruo Okama, PhD
Nagasaki, Tokyo, Japan

Background: To prevent severe esophageal stenosis after aggressive endoscopic submucosal dissection (ESD), our group previously reported an efficient treatment using cell sheets that had been fabricated from patient cells. However, this transplantation procedure had not been easy for every endoscopist and needed to be improved to derive the full effect of epithelial cell sheets.

Objective: To develop an endoscopic device that enables easy and effective cell sheet transplantation and to evaluate its performance and clinical feasibility.

Design: An animal study.

Setting: Animal experimentation laboratory.

Intervention: Three pigs underwent circumferential esophageal ESD while under general anesthesia. A total of 12 cell sheets were endoscopically transplanted to the ESD site. Six cell sheets were transplanted by using an endoscopic device that we developed, and six cell sheets were transplanted by using the conventional method.

Main Outcome Measurements: Procedure time, transplanted area on the ESD site, transplantation success rate, and monitoring of adverse events or incidents.

Results: The device allowed successful transplantation of all cell sheets with a shorter procedure time than with the conventional method (4.8 ± 0.8 minutes vs 13.3 ± 5.7 minutes, respectively) and on a larger area (41.8 ± 4.2 mm², respectively). No adverse events were monitored in each method.

Limitations: Animal study, small sample.

Conclusion: A newly designed endoscopic cell sheet transplantation device would be useful.

BACKGROUND

Esophageal stenosis is one of the major adverse events after aggressive endoscopic submucosal dissection (ESD) for early-stage esophageal cancer. For treating stenosis, endoscopic balloon dilation has been widely used, although repeated stenosis is still an issue. Clinical research involving steroid therapies and stent treatments have been studied to overcome esophageal stenosis after aggressive ESD.
Tissue-engineered Epithelial cell sheet

Dedicated delivery device

Specialized Cell Sheet Delivery Technique
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<th>No</th>
<th>Age</th>
<th>Gender</th>
<th>Circum. (%)</th>
<th>Resected Size</th>
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<th>Cell Sheets</th>
<th>Stenosis</th>
<th>Balloon (times)</th>
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Results(1+2)

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No treatment
More than 75% cir. ESD → Constriction rate 68～92%
→ Refractory stenosis

Cell sheets transplantation
More than 75% cir. ESD → Constriction rate 34%
→ Refractory stenosis ↓
Clinical trial
Clinical development of epithelial cell sheet for esophageal regeneration

Clinical research in academia

**Tokyo Women’s Medical University**

Company sponsored clinical trial

- **Japan**: Tokyo Women’s Medical University
  - 20 patients
- **Sweden**: Karolinska University Hospital
  - 10 patients

**CellSeed**

- **Japan**
- **Europe**
Treatments for avoiding constriction

✔ Triamcinolone injection

Hashimoto, et al. GIE 2011

✔ Oral prednisolone administration

Yamaguchi. Isomoto, et al. GIE 2011
**JCOG 1217**

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Triamcinolone injection group

Day 0: treatment

12 weeks: Adverse event

Less than 5cm ESD

Oral prednisolone administration group

Day 0: treatment

12 weeks: Adverse event

Less than 5cm ESD

PSL: 30mg 25mg 20mg 15mg 10mg 5mg
Autologous epithelial cell sheet (in Japan)

Biopsy

Day 0: treatment

Cell culture for 14 days

CPF

12 weeks: Esophageal stenosis rate

More than 75% circumference ESD

Single arm study design

No treatment

- Biopsy...
- Hard end point...

No treatment

High frequency of stenosis

More than 75% circumference ESD
In conclusion

Cell sheet product has an uniquely potential.

Clinical study of hCTPs should be designed to compare the status of each disease case-by-case.