THE APPLICATION OF INDICATION BASED PRICING TO REGENERATIVE MEDICINE THERAPIES: AN INTERACTIVE WORKSHOP

DISCUSSION LEADER: DIANA I. BRIXNER, RPH, PHD

PROFESSOR, DEPARTMENT OF PHARMACOTHERAPY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES, DIANA.BRIXNER@UTAH.EDU.
PANELISTS

• Masayuki Yamato, PhD, Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan

• Michael Drummond, PhD; Professor, Center for Health Economics, University of York, York, United Kingdom

• Mime Egami, BA, Adjunct Professor, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, United States; Executive Director, Cell Sheet Tissue Engineering Regenerative Medicine Initiatives, Tokyo, Japan

• Diana Brixner, RPh, PhD, FAMCP, Executive Director, Pharmacotherapy Outcomes Research Center; Professor, College of Pharmacy, University of Utah, Salt Lake City, United States
PRESENTATION OVERVIEW

• Understand production, treatment and evidence generation for regenerative therapy (Yamoto)

• Pricing challenges in regenerative medicine under newly established Regenerative Medicine Promotion Act in Japan (Egami)

• Describe how indication pricing has been used in other disease areas and indications (Drummond)

• Discuss the application of indication based pricing to the application of regenerative medicine in the heart and knee. (Panel)
MEETING THE NEEDS

• Value-engineered translation of regenerative therapies is necessary to set regulatory frameworks, policy, and tie investment decisions to value-based criteria of health systems.

• Attention needs to be paid to applying novel economic modeling methods to better inform investment decisions.

THE FUTURE FOR REGULATION AND REIMBURSEMENT

Therapies that receive conditional approval are eligible for reimbursement by the Japanese health system, but Japan’s universal health insurance system requires up to 30% copayment from patients depending on age and type of condition (unpublished observations).

THE FUTURE FOR REGULATION AND REIMBURSEMENT\(^1\) 
CONT’D

• The scheme transfers the economic and health risks of experimental regenerative medicine technologies to the Japanese health system.

• The scheme may negatively impact the ability to collect meaningful efficacy data for final regulatory and reimbursement decisions, because patients with access to therapies have no incentive to enroll in well-designed clinical.

• Conditional licensing and reimbursement regimes are being discussed cautiously on both sides of the Atlantic.

---

PRODUCTION, TREATMENT AND EVIDENCE GENERATION FOR REGENERATIVE MEDICINE

MASAYUKI YAMATO, PHD;
PROFESSOR, INSTITUTE OF ADVANCED BIOMEDICAL ENGINEERING AND SCIENCE, TOKYO WOMEN’S MEDICAL UNIVERSITY, TOKYO, JAPAN, YAMATO.MASAYUKI@TWMU.AC.JP.
REGULATORY APPROVAL AND NHI PRICING OF REGENERATIVE MEDICINE PRODUCTS IN JAPAN

Mime Egami, BA:

ADJUNCT PROFESSOR, DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES / EXECUTIVE DIRECTOR, CELL SHEET TISSUE ENGINEERING REGENERATIVE MEDICINE INITIATIVES, TOKYO, JAPAN MIME.EGAMI@UTAH.EDU.
New category “Regenerative Medicine Products”

New category is created to regulate Regenerative Medicine Product (incl. gene therapy products), while reimbursement system does not reflect this change – Pricing committee of either drug or medical device is appointed by each regulatory profile (major mode of action).

Expedited approval system and provisional reimbursement pricing

After the safety is confirmed by small size clinical trial and its efficacy is scientifically predicted, conditional and term-limited (provisional) marketing authorization (5-7 years) with reimbursement is provided for timely access to the patients (full outcome report is required)

Regenerative Medicine product will be re-approved after provisional period with the updated reimbursement price
EXPEDITED APPROVAL SYSTEM UNDER PMD ACT

[Conventional approval process before PMD Act]

Clinical study ➔ Phased clinical trials (confirmation of efficacy and safety) ➔ Marketing Authorization ➔ Marketing

[Current regulatory scheme for regenerative medicine products under PMD Act]

Clinical study ➔ Clinical trials (likely to predict efficacy, confirming safety) ➔ Conditional / term-limited authorization ➔ Marketing (Further confirmation of efficacy and safety during 5-7 years) ➔ Marketing authorization or Revocation ➔ Marketing continues

Post-marketing data collection is required for safety and efficacy
BASIC STRUCTURE OF NHI PRICING IN JAPAN

• Newly listed (approved) NHI drug prices are investigated by specific committee and officially determined by Chuikyo.

  • “Comparative Method” for new drugs/devices that have listed product(s) in the comparative category
    • NHI pricing will be:
      Current comparative NHI price + “premium”

  • “Cost Calculation Method” for innovative drugs/devices with no comparative products on the list
    • NHI price is determined by cost data provided by company and industry average margin (incl. orphan)
“COST CALCULATION METHOD”

- Sum of product costs & margins

Price adjustment is applied to the profit as "premium", depending on novelty, efficacy & safety, versus existing standard treatment; this premium assessment is judged by "clinical trial" data.

Premium evaluation for RM product is not feasible as small trial case to judge efficacy, impact of training period for physicians until standard therapy (technology) is established.
If constant large scale production is available for 10 years, GMP man. Cost of cell-sheet may be reduced from $40,000(60/yr) to $22,000(500/yr).
Manual or Partial automation cannot realize scale merit. (as a sample case, 3 week culture is assumed)

Data provided by FIRST project at Tokyo Women’s Medical University TWIn
REGENERATIVE MEDICINE PRODUCT LAUNCHED AND INSURED IN JAPAN BY NOW

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Type</th>
<th>Company</th>
<th>Listing date (regulatory approval date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Sheet</td>
<td>Autologous Skeletal Myoblast Sheets</td>
<td>Terumo Co.</td>
<td>Nov.2015 (Sep.2015)</td>
</tr>
<tr>
<td>TEMCELL HS</td>
<td>Mesenchymal Stem cells for GVHD (allogeneic)</td>
<td>JCR Pharmaceuticals</td>
<td>Nov.2015 (Sep.2015)</td>
</tr>
</tbody>
</table>

Time lag between regulatory approval and listing is significantly improved
HEART SHEET PRODUCT OUTLINE

Kit A: for biopsy of skeletal myoblast tissue and serum at hospital, send back to Terumo to subculture and expand

Kit B: ship frozen cell to hospital + cell sheet preparation kit + culture media pack per sheet

Order Flow

Terumo

Hospital
## NHI: ORIGINAL REIMBURSEMENT PRICING

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>NHI Price</th>
<th>Pricing method</th>
<th>Profit Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Profit Margin</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Industry average</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>A kit: Biopsy/Culture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>B kit: Man./Transplant.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JACE</td>
<td>¥ 306,000 per sheet 2016/4 pricing revised</td>
<td>Not Announced</td>
<td></td>
</tr>
<tr>
<td>JACC</td>
<td>¥ 2,080,000 2016/4 pricing revised</td>
<td>Cost Calculation Method</td>
<td>5.8% (Medical device)</td>
</tr>
<tr>
<td>Heart Sheet (Cond. A)</td>
<td>A kit ¥ 6,360,000 B Kit ¥ 1,680,000</td>
<td>Cost Calculation Method</td>
<td>5.8% (Medical device industry margin)</td>
</tr>
<tr>
<td>TEMCELL HS</td>
<td>¥868,680 per bag (10.8ml)</td>
<td>Cost Calculation Method</td>
<td>15.9% (Pharmaceutical industry margin)</td>
</tr>
</tbody>
</table>

“*Heart Sheet*” is under expedited approval, while other 3 products received full approval.
# NHI: REVISED REIMBURSEMENT PRICING

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>NHI current price</th>
<th>Comparison to Original Pricing</th>
<th>Budget Impact per treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>A kit: Biopsy/Culture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JACE</td>
<td>A kit ¥ 4,380,000</td>
<td>¥ 306,000 x max. 40 sheets</td>
<td>25→200+ hospital</td>
</tr>
<tr>
<td></td>
<td>B kit ¥ 151,000 ps</td>
<td>¥ 12,240,000</td>
<td>20→40 sheets</td>
</tr>
<tr>
<td></td>
<td>¥10,420,000(40sts)</td>
<td></td>
<td>△ ¥1,820,000</td>
</tr>
<tr>
<td>JACC</td>
<td>A kit ¥ 879,000</td>
<td>¥ 2,080,000 per treatment</td>
<td>240+ hospital</td>
</tr>
<tr>
<td></td>
<td>B kit ¥ 1,250,000</td>
<td></td>
<td>+ ¥49,000</td>
</tr>
<tr>
<td></td>
<td>¥ 2,190,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Sheet</td>
<td>A kit ¥ 6,360,000</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B kit ¥ 1,680,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>¥14,760,000( 5sts)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In case of autologous RM, reimbursement by the process is becoming standard pricing.
ISSUES ON NHI SYSTEM FOR RM PRODUCTS

• Japan applies its own HTA by Government, not QALY/ICER.
• All approved drugs are “automatically” covered and reimbursed by NHI system. “Budget Impact” is the top consideration point.
  • No “Threshold” argument even on “mediocre” products
  • Conditions of 1) Regulatory + 2) Reimbursement = modified budget impact acceptable for NHI system.
  • Companies hesitate to touch other than NHI pricing.
• Weak information asymmetry between “NHI pricing” and “Outcome evaluation”, previous PMS data was mainly for safety issue.
HTA CHALLENGE FOR UPCOMING RM PRODUCTS

• What is the transparent pricing to encourage patient and industry for “Initial pricing” (CCM now) and “Repricing” (outcome data based ? Up/Down ? Budget impact ?)
  • How to reflect “established values” into Repricing ?
    • Value by physician’s view point (clinical benefit/cure)
    • Value by patients’ viewpoint (Improved QOL)
    • Composed Value for society (innovation appreciation and decrease in social costs)

• When global convergence and communication available ?
  • How to link with global debate on “indication-based pricing” or “differential pricing” ?

• Shall we make special evaluation if RM provides cure treatment ?
IS INDICATION-BASED PRICING AN OPTION FOR REGENERATIVE MEDICINE THERAPIES?

MICHAEL DRUMMOND, PHD

PROFESSOR, CENTER FOR HEALTH ECONOMICS, UNIVERSITY OF YORK, YORK, UNITED KINGDOM, MIKE.DRUMMOND@YORK.AC.UK.
## VARIATION IN COST-EFFECTIVENESS BY INDICATION – BEVACIZUMAB

<table>
<thead>
<tr>
<th>NICE Technology Appraisal</th>
<th>Indication</th>
<th>ICER (£/Quality-adjusted life-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA118 (Jan 2012)</td>
<td>Metastatic colorectal cancer</td>
<td>60,430-88,400</td>
</tr>
<tr>
<td>TA263 (Aug 2012)</td>
<td>First-line metastatic breast cancer</td>
<td>82,000-182,000</td>
</tr>
<tr>
<td>TA284 (May 2013)</td>
<td>First-line advanced ovarian cancer</td>
<td>128,000-161,000</td>
</tr>
</tbody>
</table>
VALUE-BASED PRICING BY INDICATION

• A number of countries in Europe based the price of a drug on its ‘added value’, either based on a clinical assessment or an assessment of the QALYs gained.

• In the UK, ‘patient access schemes’, involving confidential discounts, are often negotiated to ensure that a drug meets NICE’s value for money criterion in a particular indication.

• However, the implications for these discounts when a drug has multiple indications is not clear.

• In Italy, separate registries are created by indication, and sometimes by line of therapy, to support pricing agreements.
Main objective was to explore the methodological issues in undertaking appraisals of regenerative therapies.

An exploratory study estimated the costs and effects (QALYs) of CAR-T (in relapsed or refractory B-cell acute lymphoblastic leukaemia in children and young adults), as compared with current care.

Two indications assessed: bridge to hematopoietic stem cell transplantation; curative intent.

Large amount of uncertainty in all estimations, based on current level of knowledge.

An Expert Panel with a strong understanding of NICE Technology Appraisals was then convened to discuss a range of scenarios for price discounts and payment models.
## BENEFITS AND COSTS OF CAR-T IN THE TWO INDICATIONS

<table>
<thead>
<tr>
<th></th>
<th>Bridge to HSCT</th>
<th>Curative Intent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed incremental QALY gain per patient</td>
<td>7.46</td>
<td>10.07</td>
</tr>
<tr>
<td>Assumed price (acquisition cost) to be close to NICE’s threshold for end-of-life therapies</td>
<td>£356,100</td>
<td>£528,600</td>
</tr>
<tr>
<td>Scenario</td>
<td>Expert Panel ‘Decision’</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>One-off acquisition cost</td>
<td>Reject</td>
<td></td>
</tr>
<tr>
<td>One-off acquisition cost with 20% discount</td>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td>Lifetime leasing (£2,756 per month)</td>
<td>Reject</td>
<td></td>
</tr>
<tr>
<td>Payment for patients with remission only (approx. reduction of 35% in average cost)</td>
<td>Accept</td>
<td></td>
</tr>
</tbody>
</table>
CHALLENGES IN IMPLEMENTING INDICATION-BASED PRICING

• Flume et al identify barriers in terms of legal feasibility, data collection, billing arrangements and other factors in 6 European countries

• Tracking the number of patients treated in each indication can be difficult in some settings

• The need to maintain a single published price (per unit) of the drug implies the use of differential rebates by indication

• Understanding the nature of the rebates given and to whom (e.g., the treatment center, the health ministry/insurer, the general government budget) is important for giving appropriate incentives

DIANA I. BRIXNER, RPH, PHD;

PROFESSOR, DEPARTMENT OF PHARMACOTHERAPY, UNIVERSITY OF UTAH, SALT LAKE CITY, UNITED STATES, DIANA.BRIXNER@UTAH.EDU.
PRICING MODELS FOR REGENERATIVE MEDICINE

• How premium is transparently reflected in CCM and Should CCM based premium vary for heart vs. knee?

• What evidence would be needed to justify differences:
  • Values to different stakeholders
    • Patient
    • Physician
    • Payer
    • Public society

• If regenerative medicine provides cure, how does the model change?
INPUTS FOR INDICATION BASED PRICING IN REGENERATIVE MEDICINE

• Cost:
  • Time relatively equal (2~3 weeks) or linear by manual manufacturing process
  • Quantity needed has minimal impact to price
  • Training and distribution service required by regulatory approval

• Outcomes: QoL (heart - life threatening, Knee – Patient QOL)
  • Knees: $/QALY
  • Heart: $/QALY

• Safety: procedure risk of each
  • Heart higher risk
  • Knee lower risk
ACKNOWLEDGEMENT

• Tianze Jiao, PhD, Postdoctoral fellow, McGill University, Montreal, Canada