Cellular therapies in Japan

Yuji Heike, MD, Ph. D.
National Cancer Center

Akihiro Shimosaka, Ph. D.
Senior Research Adviser
Institute of Medical Science, Tokyo University

Director, Division of Research and Development
Research Foundation for Community Medicine
Development and Regulatory Steps for regenerative therapy in Japan
1. Basic and developmental research by Academy/Company
2. Pre-clinical research needed for clinical study
3. Pre-meeting with Pharmaceutical and Medical Devices Agent(PMDA) for IND application
4. Confirmation by PMDA for next step
5. Filing for clinical study
   Pre-Meeting with PMDA for final study if needed and license application
6. Approval
   Price listing for insurance reimbursement
   Some cases, without reimbursement price listing, marketing start for limited market
7. Marketing
Approved/ ongoing clinical application

1. Regenerative therapy
2. DC therapy
3. Activated T-cell therapy
Approved product

Autologus cultured skin for severe burn
Japan Tissue Engineering Co., Ltd. (J-Tec)
obtained approval and reimbursed by insurance.
306,000 J Yen/Seat (Seat: 8 × 10cm)
Price listed in January, 2009
Process

Patients

Harvest skin

Normal skin cell

isolation of cell

transplant

form seat

culture

3T3-J2細胞
Japanese Insurance System

Therapy must be 100% insurance coverage
Or 100 % private coverage ➔ no mixed treatment
Not allowed to combine insurance and private coverage. Even only one drug is not reimbursed, patient must cover all the expense for the whole treatment.

➔ To overcome this problems, certain hospital can apply for advanced therapy which is not be covered by insurance but allowed to combine private and insurance covered therapy
Therapies approved as advanced therapy
Hospital basis approval

1. MNC injection for neovascularization for atherosclerosis/ limb ischemia
2. Treatment of systemic sclerosis with purified autologous CD34+ stem cell
On going study

1. Cardio vascular regenerative therapy
   both company and investigator sponsored
2. Studies on other auto immune disease
3. Study on cultured cornea, not in Japan, in France sponsored by Japanese company
4. Regenerative therapy for cartilage/bone
5. Regenerative therapy for teeth
6. others
DC Study
Majority are Investigator IND study
Who should take responsibility when more than two not approved elements are involved.
Like such case
PB apheresis->CD14+ separation (device)-> DC maturation (medium, growth factor)-> autologous tumor derived antigen (processing)-> electroporation(device) => Need paradigm change

Regulate as not a drug, not a device but combined therapy like surgery
Neovascularization Study

Animal study and pioneer study were reported by Japanese researchers but only approved as advanced therapy which is not covered by insurance yet.
Kamihata H, Matsubara H, Nishiue T et al.,

Model: Swine
LAD occlusion
Interval 60 min

BM MN cells vs. endothelial cells

Angiogenesis

Global LV function

Myocardial Perfusion
Hamano K, Li TS, Kobayashi T, Hirata K, Yano M, Kohno M, Matsuzaki M. 
Therapeutic Angiogenesis Induced by Local Autologous Bone Marrow Cell Implantation

Model: Dog
LAD occlusion
Interval 30 d

BM MN cells

Regional LV function

Angiogenesis

border zone

A

B

C

Vessel Count

Normal area  Marginal area  Infarction area

Model: Pig, LAD occlusion interval 2 wks
5-azacytidine-treated stromal cells

Global LV function (MIBI)
A. Stroke volume
B. Ejection fraction
Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial

Eiko Takeda-Yukawa, Hiroaki Matsumoto, Taroaki Munemoto, Uchi Ikeda, Satoshi Shintani, Katsuya Mimasu, Katsuya Aronao

before 8 weeks after

before 24 weeks after before 2 weeks after
Cardiac study

There are few groups who are studying neovascularization using bone marrow derived purified CD34+ cells using Isolex 300 and CliniMACS.

Isolex was approved for autologous CD34+ separation but not indicated.

CliniMACS is not approved yet but investigators can use under doctor decision.
Possible benefit of cardiac regenerative application

Dilated cardiac dysfunction
Patient need organ transplant for cure
14 yr. old patient with dilated, non/ischemic cardiomyopathy
LVAD implantation
14 yr. old patient with DCM
Berlin Heart EXCOR LVAD
Implantation of hematopoietic stem cells – 72 sites
14 yr. old patient with DCM

Berlin Heart EXCOR LVAD

04/14/05  Resuscitation, Centrifugal pump in another Hospital
04/18       Transport to DHZB
04/27       Implant BerlinHeart EXCOR LVAD and autologous
            bone marrow stem cell transplanation
June       Repeat pump rate reduction trials show
July       improvement of cardiac function
08/16       Pump stop under Dobutamine shows normal function
08/29       Explant LVAD
09/19       Discharge home
            Stable normal cardiac dimensions and function since
Post-LVAD
after LVAD-Explant
Radial Strain (%) at LVAD Implant vs. after LVAD Explant
Autoimmune disease HSCT
EBMT Information from Dr. Tyndal

Reports 420
  – allogeneic 11
  – autologous 409

HSCT = haematopoietic stem cell transplant
Autologous: patients

»Patients mobilised 405*

- Patients transplanted 394
- Team / country 94 / 21
- Sex, females (%) 271 (67%)
- Age, median years (range) 35 (2–69)
- Interval diagnosis-ASCT, median months 6 (1–28)
- Follow-up, median months (range) 20 (1–81)

*Reports = 409; double-transplant = 4
ASCT = autologous stem cell transplant
<table>
<thead>
<tr>
<th>Disease</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>122</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>1</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>ALS</td>
<td>2</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>63</td>
</tr>
<tr>
<td>Systemic lupus erythematous</td>
<td>51</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>69</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Juvenile chron. Arthritis</td>
<td>43</td>
</tr>
<tr>
<td>Ankylosing spondilitis</td>
<td>2</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>7</td>
</tr>
<tr>
<td>MCTD</td>
<td>4</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>3</td>
</tr>
<tr>
<td>Behcet</td>
<td>3</td>
</tr>
<tr>
<td>Wegener’s</td>
<td>3</td>
</tr>
<tr>
<td>Polychondritis</td>
<td>1</td>
</tr>
<tr>
<td>ITP</td>
<td>10</td>
</tr>
<tr>
<td>AIHA</td>
<td>3</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>4</td>
</tr>
<tr>
<td>Evans</td>
<td>1</td>
</tr>
<tr>
<td>TTP</td>
<td>2</td>
</tr>
<tr>
<td>Bowel disease</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

ALS = amyotrophic lateral sclerosis; AIHA = autoimmune haemolytic anaemia; MCTD = mixed connective tissue disease; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura
Stem cell source

Number of patients

Graft type

Auto BM  Auto PB

Auto = autologous; BM = bone marrow; SCT = stem cell transplant
Priming

Number of patients

Cy = cyclophosphamide; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor
Tdep = T-cell depletion; CD34\(^+\) = CD34\(^+\) selection
Conditioning

BEAM = carmustine, etoposide, ara-C and melphalan; ATG = antithymocyte globulin; Rad = radiotherapy; Bu = busulphan; Oth = other
Outcome

- Patients not transplanted
  - dead:
    (toxicity / progressive disease / other)
  - alive:
    (response / flare / withdrawal / transplant pending)

- Patients transplanted
  - alive
  - death by progressive disease
  - death by infectious complications / toxicity

Transplant-related mortality at 1 year (range) 7% (4–10 %)
Response in SSc – 63 patients

• Skin score > 25% improved 69%

• Lung function trend to stabilisation

• TRM - first 45 patients 17%
  – first 65 patients 12.5%
  – with new exclusion criteria 7.5%

• Pulmonary hypertension > 50 mmHg outcome poor

• Cardiac toxicity and cyclophosphamide?

TRM = treatment related mortality
Response in MS – 85 patients

- Primary progressive MS 22%
- Secondary progressive MS 55%
- Three-year progression free survival (non primary progressive MS) 78%
  NB: IFN beta = 60%
- Improved by 1 EDSS = 11 patients (6 worse later)
- Deaths:
  - TRM = 5 patients, progressive disease = 2 patients
- MRI
  - inactive stayed inactive
  - active – 85% became inactive

MRI = magnetic resonance imaging;
EDSS = expanded disability scale score;
MS = multiple sclerosis

Japanese Advanced Therapy approval
Cy + G-CSF mobilized PB cells
CliniMACS CD34+ selection
For SS at Kyushu University
Activated T-Cell Therapy

Autologous activated T-Cell Therapy
Doctor’s own protocol, cell culture is made by hospital or contract cell processing center.

Not approved.
Private cover only but popular among end stage cancer patients
Business Model

Contracted Medical Institution

Services Offered:
1. Technology and know-how in Cell Culturing and Processing
2. Rights for Exclusive Use of the Cell Processing Center, and its Facilities and Equipment
3. Know-how in Quality Assurance
4. Custom-Made Medical Practice Management System, and others
ISCT Mission

ISCT is a global association driving the translation of scientific research to deliver innovative cellular therapies to patients

• Foster international translational research
• Inform national and global regulatory framework development and harmonization
• Drive commercialization strategies
• Educate principal investigators, lab directors, technologists, regulators and commercial stakeholders
Medical Tourism

• Medical tourism: Travel across international borders to acquire healthcare, often on a temporary basis

• Estimates vary

• 1.5 million per year US in 2008 (Toucan Capital)
• 750,000 Americans traveled abroad in 2007 (Deloitte quoting Baliga/Horowitz, 2008)
• Projected to be 1.6 million patients by 2010 (Deloitte, 2008)
Stem Cell Research Forges Ahead in Latin America: Positive results have been noted in a variety of medical conditions utilizing stem cell therapies, including Parkinson’s, multiple sclerosis, diabetes, vision problems, and other neurological disease…..

StemCellsChina.Com: If you are interested in receiving stem cell therapy, please fill out this short form. A qualified stem cell doctor will be glad to contact you with helpful treatment information….

Cell Medicine arranges stem cell therapy for patients with the following conditions: Autoimmune diseases, cerebral palsy, critical limb ischemia, degenerative joint disease, diabetes, heart failure, multiple sclerosis, osteoarthritis, rheumatoid arthritis & spinal injury…Treatment is only available outside the US and Canada and is not covered by most insurance…..
Korean Company in Japan

Therapy is regulated as drug in Korea and is difficult for the company to run the study. In Japan, autologous cell therapy can be regulated as clinical treatment under doctor own decision and can make business.

Japan is thought to be a easy country to run clinical application without regulatory control.

Reported on news paper.
Korean Company in Japan

• クリニックを韓国でなく日本に設立したのは、韓国では自己幹細胞の治療を薬事法で「医薬品」として管理しており、複雑な臨床試験など厳しい規制を設けているため。日本では、自己幹細胞の治療を「高度先進医療技術」と定め、医師の判断の下で自由に治療が可能だ。
Cell Therapy Medical Tourism

• Medical tourism for terminal diseases: a long and inglorious tradition
• Significant risks to
  – Patients
  – The field of Cellular Therapy
• Mainstream medicine has not responded to protect patients
Clinical Trials vs Experimental Therapies/Medical Innovation

• Field will never progress without well controlled clinical trials

• Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated therapies, if truthfully and ethically informed

• Patients’ need to understand the difference between the two paradigms
Bedrock of Ethical Principles

- Declaration of Helsinki
- WHO
- Belmont report
- Clinical trials directive of the European Commission
- Professional societies
- Others
Patients’ Rights

1. **Right to Seek Treatments**

2. **Right to Information**
   - Accurate representation to regarding safety and efficacy record of treatment
   - Likely side effects
   - Need for centralized repository of therapies

3. **Right to Informed Consent**
   - Clinical trials
   - Unproven therapies
Role of Local Regulatory Authority

- ISCT acknowledges jurisdiction of local regulatory authorities
- However the degree of regulation and safeguards vary markedly and are often not enforced
- Key roles for independent ethics committees
- Need for international harmonization
  - International Conference on Harmonization (ICH)
  - International industry/professional organizations
Responsibility of Investigators

- Regulatory compliance
- Publication/dissemination of results
- Following GCPs/clinical standards established by local regulatory authorities
- Responsibility in advertising
- Reporting adverse events
- Patient supportive care and follow up
What Can ISCT Do?

• Ensure
  – Mitigation of patient risks
  – Promotion of scientific development
  – Compassionate and early access to promising therapy
  – Promotion of full financial disclosure

• Simple warnings are not enough!
Proposal

1. Cell Therapy Consumer’s Guide
   – To differentiate among
     • Approved/standard therapies (eg, HSC transplant)
     • Controlled clinical trials
     • Valid compassionate use of unapproved therapies
     • Treatments not subject to independent scientific and ethical review
   – Provide an unbiased review of claims made for unapproved therapies
Proposal

2. Leverage ISCT expertise in regulatory affairs and international presence to work toward global regulatory harmonization
   – Working through ICH
   – Partnership with other societies
   – Beneficiaries
     • Patients (safety & efficacy)
     • Field of cell therapy (scientific advancement)
Proposal

3. Partnership with patient advocacy groups and professional societies
   - A personalized and empathetic connection to patients searching for support
   - Access to experts, assessment of emerging technology/treatments & professional recommendations
Conclusions

• Cellular therapy medical tourism is here to stay
• Legitimate cell therapy opportunities for medical tourists: appropriately regulated by local authorities
• However there are many more unethical and potentially dangerous cell therapies
• Proposals for ISCT
  1. Consumers’ guide
  2. International harmonization
  3. Partnership with patient advocacy groups
     – Will organize Asian Pacific Activity
Thank You very much