第 4 回 PMDA 国際バイオロジクスシンポジウム

PMDA 4th International Symposium on Biologics

再生医療/細胞･組織加工製品の臨床評価

The clinical evaluation of the cell/tissue-based products

平成 21 年 10 月 9 日　灘尾ホール　東京

9th October, 2009
Nadao Hall, Tokyo, Japan

独立行政法人　医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency (PMDA)

AGENDA

Opening Remarks & Keynote Speech Chair: Dr. Toyoshima, PMDA

13:30-13:35 Opening Remarks
近藤達也 独立行政法人医薬品医療機器総合機構 理事長: Dr. Tatsuya Kondo, Chief Executive, PMDA

13:35-13:50 Keynote Speech
平山佳伸、独立行政法人医薬品医療機器総合機構 上席審議役: Dr. Yoshinobu Hirayama, Associate Executive Director, PMDA

Session I Chair：Mr. Takayama, PMDA & Dr. Tominaga, PMDA

13:50-14:25 Clinical evaluation of cell based medicinal products – Europeans' perspective
Dr. Bettina Klug, Paul-Ehrlich-Institut

14:25-14:55 PMDA's perspective on the clinical evaluation of cell/tissue-based products
柳 健一 独立行政法人医薬品医療機器総合機構 生物系審査第2部 審査役代理: Dr. Kenichi Yanagi, Deputy Review Director, Office of Biologics II, PMDA

14:55-15:05 Break

Session II Chair：Dr. Klug, PEI & Dr. Shikano, PMDA

15:05-15:35 J-TEC's perspective: The clinical development of the autologous cell/tissue-based medicinal products
畠賢一郎 株式会社ジャパン・ティッシュ・エンジニアリング常務取締役研究開発部長: Dr. Kenichiro Hata, Managing Director, R&D Department, Japan Tissue Engineering Co.,LTD.

15:35-16:05 Contribution of biostatistics to designing clinical trials
森田智視 横浜市立大学大学院医学研究科／附属市民総合医療センター 臨床統計学・疫学 教授: Prof. Satoshi Morita, Yokohama City University Medical Center

16:05-16:20 Break

Panel Discussions Chair：Dr. Hirayama, PMDA

16:20-17:25 Dr. Bettina Klug、Dr. Yanagi、Dr. Hata、Prof. Morita
(Specific comment：松山晃文 財団法人 先端医療振興財団 先端医療センター研究所 チームリーダー： Dr. Akifumi Matsuyama, Director, Department of somatic stem cell therapy, Institution of biomedical research and innovation laboratory, Foundation for Biomedical Research and Innovation)

Closing Remarks Chair; Dr. Hirayama, PMDA

17:25-17:30 Summary Report
豊島聰 独立行政法人医薬品医療機器総合機構 理事・審査センター長: Dr. Satoshi Toyoshima, Executive Director and Director, Center for Product Evaluation, PMDA

Overall Chair: Dr. Tadano, PMDA

Speakers

(Abstract & Curriculum Vitae)

Opening Remarks

近藤達也　独立行政法人医薬品医療機器総合機構　理事長
Dr. Tatsuya Kondo, Chief Executive, PMDA

Curriculum Vitae

He has a lot of clinical experiences as a neurosurgeon since he graduated from Medical Department of the University of Tokyo in 1968. He worked for the department of neurosurgery in the 1st national hospital (1972 ~ 1974) and the department of Neurosurgery, Faculty of Medicine, The University of Tokyo (1974 ~ 1978).

He studied the biology of brain tumor as a visiting researcher with Max-Planck scholarship at Max-Planck Institute, West Germany from March to December of 1977.

He served as a neurosurgeon at International Medical Center of Japan from 1978 to 2003 and he contributed to hospital management and clinical discipline as the Director of the hospital, International Medical Center of Japan from April, 2003 to March, 2008.

Keynote Speech

平山佳伸　独立行政法人医薬品医療機器総合機構　上席審議役
Dr. Yoshinobu Hirayama, Associate Executive Director, PMDA

Abstract

Pharmaceuticals and Medical Devices Agency (PMDA) is a youthful organization, which has been launched and come into service on April 2004, as a consolidation of three regulatory organizations. PMDA is responsible for the general administration of pharmaceuticals and medical devices, such as consultation (planning and implementation of clinical trials and preparation of NDA dossiers, etc.), scientific reviews for marketing authorization, post-marketing safety, and relief services for adverse health effects etc., based on the pharmaceutical affairs law of Japan. To improve the drug/devise lag problem and to strengthen the post-marketing safety measures in Japan, we are now reinforcing our organization. To review the biologics (pharmaceuticals and medical devices originating in biological source) such as blood products, vaccine, gene therapy, and cell/tissue-based products, we have two offices.

Cell/Tissue-based products are one of the most expected products of their use in medical practices, gathering wide range of attention, not only by the healthcare professionals, but also by the nation. However, most of them are still in a primitive stage and under the translational process from academia to venture companies. Currently, Japan has only one approved cell/tissue-based product. To facilitate the development on this field, PMDA participates for the development of guidance, provides seminars to lecture the pharmaceutical regulations on biologics, and consultations for industries and venture companies, in addition to the usual review process including “Kakunin-shinsei” to confirm the minimum quality and safety of cell/tissue-based products in advance of their clinical trials, aiming at the realization of efficient R&D.

On this symposium with specialists of from inside and outside of Japan, we want to discuss “The clinical evaluation of the cell/tissue-based products”, which might be a tough problem on the development, to proceed the objective and the medically rewarding evaluations. We hope this symposium is supportive for the development of the cell/tissue-based products.

Curriculum Vitae

Dr. Yoshinobu Hirayama is currently the Associate Executive Director of Pharmaceuticals and Medical Devices Agency (PMDA). He is responsible for the evaluation of the Biologics.
He received a Ph. D. from Kyoto University. He is a pharmacist and his specialized field was pharmaceutical sciences. He has been in governmental service since 1980 and worked on food chemistry in MHW, life science research coordination in Science and Technology Agency, and medical insurance and evaluation of new drug application in MHW. He has served as the Director of Clinical Trial Advice Division, Organization for Pharmaceutical Safety and Research (1996-2000), the Director of 1st Bureau of Evaluation, Pharmaceuticals and Medical Devices Evaluation Center (2000-2003), and the Director of Safety Division, MHLW (2003-2005). He served as a Professor of Osaka City University, Graduate School of Medicine (2005-2009).

Session I

Clinical evaluation of cell based medicinal products – Europeans' perspective

Dr. Bettina Klug, Paul-Ehrlich-Institut, Langen Germany

Abstract

Advanced therapy medicinal products (ATMPs), as all other biotechnology medicinal products, are subject to a centralised authorisation procedure, involving one single scientific evaluation of the quality, safety and efficacy of the product, carried out by the European Medicines Agency (EMEA). Overall, the same regulatory principles apply as for all other types of biotechnology medicinal products. However, as technical requirements, in particular the type and amount of quality, non-clinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific.

For cell-based medicinal products, a multidisciplinary guideline is available, addressing the products development, manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products (CBMP). Although the guideline is intended for products entering the Marketing Authorisation (MA) procedure, the principles laid down in this guideline should be considered by applicants entering into clinical trials

The presentation will highlight some specific thoughts which are relevant for the clinical studies for cell based medicinal products.

Due to the specific biologic characteristics of the cell-based medicinal products, the classical phase I to phase III approach in the clinical development might not me applicable. Alternative approaches, if justified might be acceptable.

The relevant non-clinical studies, previous clinical experience of the treated pathology, and initial clinical studies could be applied for demonstration of the "proof of principle" and the choice of clinically meaningful endpoints for safety and efficacy evaluation.

A key element of the ATMP Regulation is the requirement for long-term follow up of patients enrolled in clinical trials with ATMPs to detect signals of early or delayed adverse reactions, to prevent clinical consequences of such reactions and to ensure timely treatment as well as to gain information on the long-term safety and efficacy of the intervention.

Curriculum Vitae

Bettina Klug graduated in Medicine in 1985 at the Johannes Gutenberg University, Mainz (Germany). After completion of the thesis she joined the Institute Pasteur as a research fellow.

In 1988, she joined the Department of Bacteriology at Paul-Ehrlich-Institute and held the position as a deputy Head of Sector section "toxoid vaccines". She was responsible assessor for the clinical and non-clinical aspects of all anti-bacterial and toxoid vaccines, and participated in the quality assessment of these products. Her research focused on Hapten-carrier vaccines.

In 1996 she jointed the newly established department of Haematology and Transfusion Medicines as deputy head of sector "coagulation factor II". Her responsibilities included clinical assessment of blood and plasma derived products.

After holding for 5 years a position as scientific administrator at the EMEA, London, she recently joined the department of medical biotechnology at the Paul-Ehrlich-Institut. Her responsibilities include the assessment of the clinical dossiers for marketing applications of advanced therapy medicinal products.

Bettina Klug holds a degree in Immunology from the Pasteur Institute and a Master Degree in Infectious diseases. Her major interests are infectious diseases, with special emphasis to vaccine development.

PMDA's perspective on the clinical evaluation of cell/tissue-based products

柳健一　独立行政法人医薬品医療機器総合機構　生物系審査第 2 部　審査役代理
Dr. Kenichi Yanagi, Deputy Review Director, Office of Biologics II, PMDA

Abstract

Rapid advancement in the field of tissue engineering has led to the development of innovative medical products, including various types of cell/tissue-based products. These products are expected to have a high potential in the treatment of various diseases for which standard therapies are not established. In Japanese regulatory framework, sponsors who develop cells/tissue-based products are required to apply for the confirmation prior to the first clinical trial in Japan, so-called "Kakunin-Shinsei," for assuring the quality and safety of these products. After completing evaluation of quality and safety in "Kakunin-Shinsei", these products are subjected to clinical trials. Here PMDA's perspective on clinical evaluation of cell/tissue-based products is introduced. The purpose of clinical trials is to scientifically evaluate the safety and efficacy of the products for target diseases. At present, there is no public guideline on the clinical evaluation for cell/tissue-based products in Japan, however in the general principle for the handling and use of cell/tissue-based products (Notification No. 1314, 2000), "The use of cell/tissue-based products should be confined to the medical treatments where the clinical advantage over the other products/treatment is expected, because the potential risk of the transmission of infectious agents derived from the products is not completely ruled out." In line with this principle, developers are expected to design scientifically appropriate clinical trial protocols with considering characteristics of the developing products, target diseases of the products, existing therapy for the diseases and so on. PMDA would like to support to ensure faster accessibility to more effective and safer cell/tissue-based products for the public in Japan through consultations and reviews.

Curriculum Vitae

Education

He received his MD degree from the University of Tsukuba.

He received his PhD degree from the Graduate School of Medicine, the University of Tsukuba.

Experience

He joined PMDA on April 2006 as a reviewer in the Office of Biologics.

Prior to PMDA he was a deputy director for nanotechnology and materials, Bureau of Science and Technology Policy (CSTP), Cabinet Office, Japan.

Including that, he has experience as an officer of the Japanese government

He has experience as an assistant professor on biomedical engineering including development of a bioartificial liver at the Basic Medical Sciences, the University of Tsukuba.

He has experience as residency in surgery at the University Hospital, the University of Tsukuba.

Session II

J-TEC's perspective:
The clinical development of the autologous cell/tissue-based medicinal products

畠賢一郎　株式会社ジャパン・ティッシュ・エンジニアリング常務取締役研究開発部長
Dr. Kenichiro Hata, Managing Director, R&D Department, Japan Tissue Engineering Co.,LTD

Abstract

Japan Tissue Engineering Co., Ltd. (J-TEC) was established in 1999, to make industrialization for autologous cultured epidermis as a tissue engineering product. Around that time, there are few guidelines for making medical product using living cells/tissues and for its clinical trial in Japan. As we obtained a big support (approximately 1 billion yen) from The Organization for Pharmaceutical Safety and Research for the establishment, we strongly felt responsibility as a pioneer in the field of regenerative medicine in Japan.

Our autologous cultured epidermis, called JACE, the first tissue-engineered product using human cells/tissues in Japan, was approved for manufacturing and sales in 2007, and listed as item covered by the national health insurance in January, 2009. As we have problems and troubles because of poor experiences in this field, the business is not going well until now. With regard to autologous cultured cartilage, we applied for pre-clinical approval in 2001, started clinical trial in 2004 and finally submitted application for manufacturing and sales in August, 2009. We hope the good business by autologous cultured cartilage in the near future.

In this condition, we consider the protocol for clinical trial with the product using cells from patients. Unfortunately, there is no clear guideline for this in Japan. In clinical trial, safety and effect should be shown with concreteness, reality, uniformity and consistency. It is not good situation for the group or company trying to clinical trial without suitable guideline.

Many problems should be solved to establish protocol for clinical trial; for example what is the endpoint? Should control experiment be done? How do we estimate the results? As the purpose of regenerative medicine is to treat incurable disease, clinical trial using autologous cultured products may be required to compare with the best method. Moreover, there is no definite method of estimation due to small number of facility for the trial.

In this meeting, I will present the summary of our protocol for autologous cultured products and above written problems. Furthermore, I would like to show the ideal product in the future.

Curriculum Vitae

Ken-ichiro Hata is currently Managing director, Japan Tissue Engineering Co., Ltd. (J-TEC). He is responsible for the R&D activity in the company.

He graduated from Hiroshima University, School of Dentistry in 1991. He received his Ph.D. from Nagoya University Graduate School of Medicine in 1995. His specialized field was Oral and Maxillofacial Surgery (surgical treatment for jaw deformity and cleft lip palate), and Tissue Engineering for clinical applications.

He was a clinical staff at Nagoya University Hospital (1995-1996), and Meijo Hospital (1996-1997). His academic carrier include an Assistant Professor at Nagoya University Graduate School of Medicine, Department of Oral Surgery (1996-2000), an Associate Professor at Nagoya University School of Medicine, Department of Tissue Engineering (2000-2002), an Associate Professor at Nagoya University Hospital, Center for Genetic and Regenerative Medicine(2002-2004), before joining J-TEC in 2004.

Contribution of Biostatistics to Designing Clinical Trials

森田智視　横浜市立大学大学院医学研究科／附属市民総合医療センター　臨床統計学・疫学　教授
Dr. Satoshi Morita, Professor, Department of Biostatistics and Epidemiology, Yokohama City University

Abstract

It can be difficult to conduct clinical trials for diseases including pediatric cancer and sarcoma because they are uncommon. That is, low incidence in these populations makes it infeasible to complete the patient accrual within a reasonable study period and achieve adequate statistical power. Using clinical trials for those diseases as examples, this paper presents how biostatistics can contribute to designing and analyzing clinical trials in such uncommon diseases and what biostatisticians have done and are doing for it. Bayesian approach may be one of the possible solutions to address the issue. Since pediatric physicians are accustomed to relying on evidence from adult studies, it may be natural to consider “borrowing strength” from adult trials. Because sarcoma has many subtypes, it may be useful to construct a design that allows the efficacy of therapy to be evaluated in the multiple subtypes. Bayesian approaches allow borrowing strength from previous or simultaneous trials. Next, we discuss development of a new endpoint for a disease for which there is no universally accepted measure to assess response to therapy. As an example, we use malignant ascites secondary to gastric cancer. Although ascitic volume can be objectively measured by 3D-CT, which was originally used to estimate the volume of organs before and after transplantation, such a measurement may not be fully sufficient. The development of malignant ascites brings a rapid deterioration accompanied by increasing abdominal distention with associated pain, loss of appetite, etc., all of which have a significant negative impact on performance status and quality of life for these patients. Thus, we need to establish a new endpoint accounting for patient-centered changes.

Curriculum Vitae

Satoshi Morita is Professor of Biostatistics and Epidemiology in both Yokohama City University Graduate School of Medicine and Yokohama City University Medical Center. Prior to coming to Yokohama City University, Dr. Morita was an associate professor in Kyoto University Hospital Translational Research Center. He has served as a director for Biometric Society of Japan, a biostatistical advisor for Japan Surgical Society, an associate editor for Surgery Today, an editorial board member for the Journal Gastric Cancer, and a reviewer board member for Japanese Journal of Clinical Oncology. His research interests include Bayesian statistics, clinical trial design, and patient-reported outcome research. Over the course of his career, he has designed over 100 clinical trials in oncology and other areas. He has served as the head biostatistician on program project grants in pediatric cancer, cancer vaccine, diabetes mellitus, and acute coronary syndrome.

Closing Remarks

Summary Report

豊島聰　独立行政法人医薬品医療機器総合機構　理事･審査センター長
Dr. Satoshi Toyoshima, Executive Director and Director, Center for Product Evaluation, PMDA

Curriculum Vitae

Dr. Satoshi Toyoshima is currently Executive Director, Director of Center for Product Evaluation at the Pharmaceuticals and Medical Devices Agency (PMDA). He is responsible for the review and evaluation of NDA, Biologics, OTC/Generic Drugs, Medical Devices and Conformity Audit.
He received his Ph.D. from University of Tokyo in 1975. His Specialized Field was Biochemistry, Immunology, and Regulatory Science.

His career includes a post doctoral fellow at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), USA (1977-1979), an Associate Professor at University of Tokyo, Faculty of Pharmaceutical Sciences (Xenobiotics Immunochemistry) (1980-1992), Deputy Director-General of Pharmaceutical Basic Institute of Japan Tobacco Co. Ltd. (1992-1995), and a Professor at Hoshi University (Biochemistry) (1995-2000), before joining Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), the predecessor of PMDA, as the Center Director in 2000.