[15:50 - 16:30]

The Present Situation of Pharmacogenomics in Japan and a Pharmacogenomic Study of Irinotecan

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One of the important missions of pharmaceutical companies is to promote the proper use of pharmaceutical product, in other words, to place as much effort as possible to maximize the effectiveness of drug and to minimize adverse events. The completion of the human genome sequence represents an important milestone in scientific achievement that will eventually lead to a greater understanding of biology and disease of human. Along with such rapid evolution of recent genomic research and genome related analysis technology, Personalized Medicine, sometimes called Taylor-Made Medicine or Made-to-Order Medicine, which is to administer the most appropriate medicine with the most appropriate dosage based upon the use of a diagnostic test to understand the genetic characteristics of each patient, has been developed. As Pharmacogenomics (PGx) is the one of the most effective approach to materialize Personalized Medicine, which is nothing other than ultimate of proper use of drug, pharmaceutical companies should work actively on PGx.

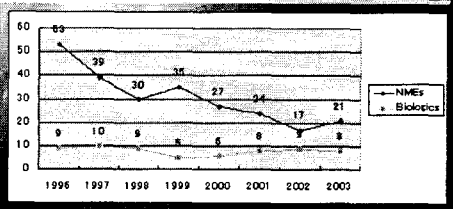
In Japan, however, although the number of PGx studies is increasing along with the spread of recognition of their importance and necessity, quality and amount of the studies are significantly low compared to those of Western developed countries. Still now most pharmaceutical companies in Japan except subsidiaries of Western mega-pharmaceutical companies are in the situation of exploring the solutions to many issues they are facing such as difficulty in designing the study, lack of public acceptance, complicated ethical concerns and so many issues related to regulations etc.

Irinotecan is the cancer chemotherapeutic agent discovered and initially developed in

Japan. With its high efficacy, Irinotecan currently plays an important role in worldwide cancer chemotherapy, however, for some patients, it causes a serious diarrhea or bone marrow depression that are sometimes life-threatening. Therefore, Irinotecan is one of the typical drugs that need promotion of proper use with PGx approach.

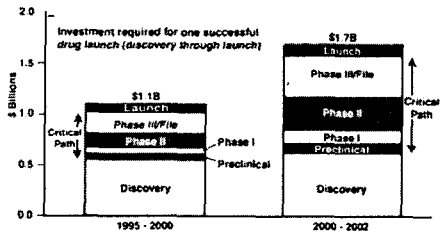
In this presentation, I would like to review the current situation of the Japanese PGx studies and the progress of PGx study of Irinotecan. Also from perspective of pharmaceutical company, efficacy and necessity of PGx, and conditions needed to improve environment for its implementation in each country will be discussed taking the PGx study of Irinotecan as an example.

Decrease of NMEs



- During the last decade the number of NME (that of the US PhRMA member companies) has been tended to decrease.
- In 2003 only 21 products were given official approval in the US.

Investment Escalation per Compound



PGx Regulations in the US

- Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers (2003/02)
- Guidance for Industry: PGx Data Submissions - Draft (2003/11)
- Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping Systems (2005/08)
- Guidance for Industry: PGx Data Submissions - Final (2005/03)
- Drug-Diagnostic Co-Development Concept Paper - Draft (2005/04)
- Guidance for Industry and FDA Staff: PGt Tests and Genetic Tests for Heritable Markers - Draft (2006/02)
- EC, EMEA and FDA Agree on Guiding Principles for Joint FDA EMEA VGDS Briefing Meetings (2006/05)

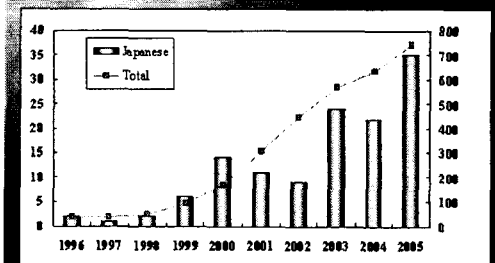
PGx Regulations in Japan

- **Submission of Information for Use in the Preparation of a Guideline of PGx in Clinical Studies of Drugs - Draft (2004/06)**
- **Request for Public Comments to above Draft (2004/06-07)**
- **Revised Ethical Guideline for Research on Human Genome/Gene Analysis (2004/12)**
- **Submission of Information for Use in the Preparation of a Guideline of PGx in Clinical Studies of Drugs - Final (2005/03)**

Submission of Information for Use in the Preparation of a Guideline of PGx in Clinical Studies of Drugs

- **Published on 2005/03/18**
- **Major Requests for submission by MHLW are**
  1. **A List of Clinical Studies Conducted or being Conducted by Genome Testing**
  2. **A List of Planned Clinical Studies *Designed to be Conducted by Genome* Testing**
  3. **A List of Completed Clinical Studies Subject to Post-factum Analysis**

Increase of PGx/PGt Articles



Tackling of JHSF for PGx

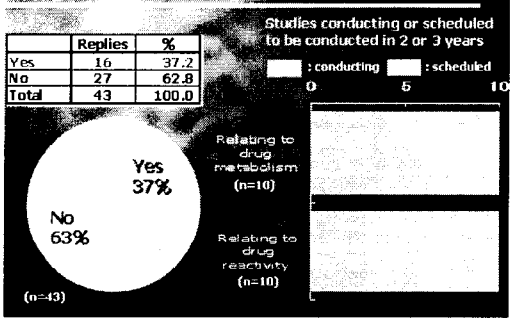
- JHSF (Japan Health Sciences Foundation) was established by 128 companies in April, 1986, under the support of the MHLW (MHW at that time)
- The mission of JHSF is promoting of basic and advanced technologies related to medicine, drugs and of contributing to human health and welfare
- Since 1998, JHSF has continuously performed the investigation of the tendencies and future views of genome sciences including PGx and has offered reports every year
- In 2002 JHSF performed a questionnaire survey in order to grasp the present situation of PGx in Japan
- In 2004 JHSF performed another survey and the result showed overall expectations of PGx in Japan
- This year JHSF has published PGx related reports that revealed some remained issues for PGx in Japan

JHSF Questionnaire Survey

- **Purpose: Grasp of the PGx Present Situation in Japan**
- **Term: September 27 - November 1, 2002**
- **Target: 91 JHSF Member Companies**
- **Method: Questionnaire Survey by Mail**
- **Recovery: 53 Companies(44 valid)**
- **Breakdown of the 44 companies: 37 Pharmaceuticals and 7 Others**

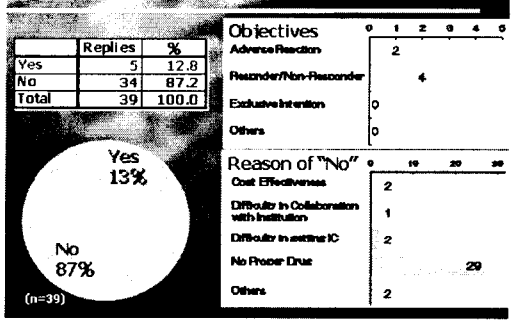
1. Do you have any plans to conduct PGx study with developing drugs ?

	Replies	%
Yes	16	37.2
No	27	62.8
Total	43	100.0



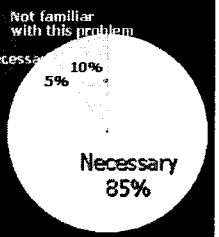
2. Do you have any plans to conduct PGx study with post-marketing drugs ?

	Replies	%
Yes	5	12.8
No	34	87.2
Total	39	100.0

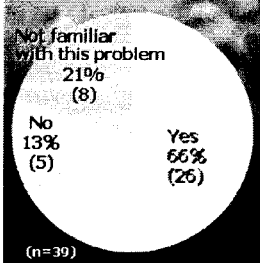


3. What do you think about the necessity of 'guidelines' for conducting PGx studies ?

	Replies	%
Necessary	35	85.4
Not necessary	2	4.9
Not familiar with this problem	4	9.8
Total	41	100.0



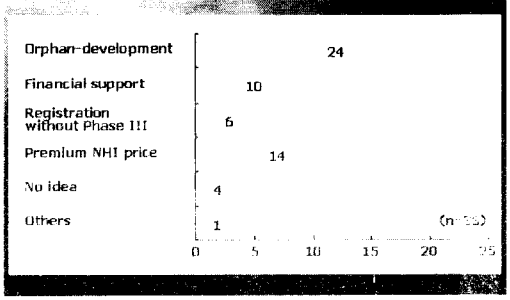
4. Are you concerned about decreases in the patients number by PGx study ?



	Replies	%
A higher price, which compensate the decrease in the number of patients, may not be accepted.	14	58.3
Patients may prefer less effective drugs prescribed without gene testing.	8	33.3
Objection from the sales division.	14	58.3
Patients may not accept gene testing.	20	83.3
Other	2	8.3

Replies from 24 companies

5. What do you expect for MHLW if you will develop drugs for the non-responders ?



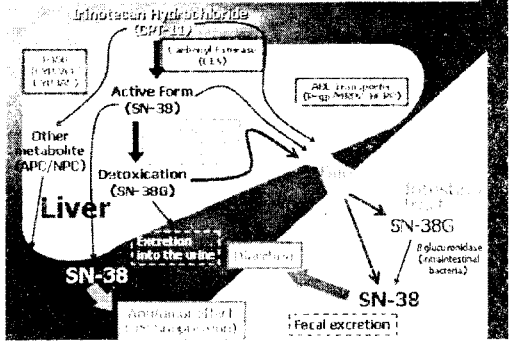
Summary of the Survey

- In Japan research/study case and understanding of PGx are increasing
- Most pharmaceutical companies are expecting the potency of PGx but simultaneously looking for the solutions to remained subjects and issues
- In order to promote PGx study both government and companies should create more clear vision and better condition
- FDA PGx Data Submission Guidance has strongly affected Japanese situation

Irinotecan Hydrochloride (CPT-11)

- Exhibits anticancer effect by inhibiting topoisomerase I
- Put on the market in April, 1994, in Japan
- Indications at present: 9 types of cancer
- Its usefulness is recognized worldwide:
  - In Europe and America, irinotecan/5-FU/leucovorin is one of the first choice treatment for metastatic colon/rectum cancers
  - In Japan, irinotecan/cisplatin shows better results than those of conventional therapies against small cell/non-small cell lung cancers
- However, serious bone marrow suppression and diarrhea may develop, which sometimes becomes fatal

Metabolism and Excretion of Irinotecan



Research in Nagoya University

-Retorospective study- Ando Y, Cancer Res (2000)

UGT1A1*28 (Tajima)	Case	Frequency	Ratio of Critical Side Effect 1)
6/6	93	0.79	15% (14)
6/7	18	0.15	44% (8)
7/7	7	0.06	57% (4)

1) Leukopenia (Grade 4) / Neutrophil reduction or watery diarrhea continued more than 5 days

	odds ratio	95% significant range	P
UGT1 A1*28	7.29	2.52~22.3	0.0003

Research in Chicago University

-Prospective study- Iyer L, Pharmacogenomics J (2002)

UGT1A1*28 (Tajima)	Case	Frequency	Ratio of Critical Side Effect
6/6	9	0.45	0 (0%)
6/7	7	0.35	1[1] (14%)
7/7	4	0.20	2[2] (50%)

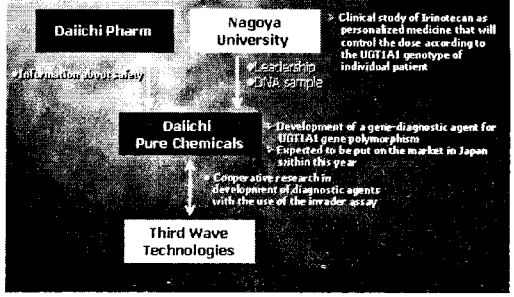
1) Diarrhea (Grade 4)
2) Diarrhea (Grade 3) / Neutrophil reduction (Grade 4) for one / Neutrophil reduction (Grade 3) for the other

- SN-38G/SN-38 ratio: 6/6>6/7>7/7
- Worst Case in neutrophil reduction: 6/6>6/7>7/7

Tackling the PGx Study of Irinotecan in Daiichi

- Focus to Safety
- 2 Major Approaches:
  1. Development of a diagnostic agent for UGT1A1 gene polymorphism
  2. Participation in the Millennium Genome Project

Development of Diagnostic Agent for UGT1A1 Gene Polymorphism



Millennium Genome Project (1)

- Anticancer drugs are mainly targeted drugs in the "Drug-Reactive Gene Analysis Project" which forms a part of the "Millennium Project"
  - Purpose: to clarify gene polymorphism including single nucleotide polymorphism (SNP), which has effects on efficacy of drugs and development of adverse reactions, further to apply the information to personalized medicine
- Irinotecan has been selected as one of the drugs targeted for examination

Millennium Genome Project (2)

"Study on Identification of Gene Polymorphism Which Has Correlation with Adverse Events by Anticancer Drug (Irinotecan hydrochloride)"
Purpose: To clarify the molecular mechanism of development of adverse events by the present drug, further to establish method for avoiding serious adverse events by the gene polymorphism analysis before administration

Medical Information:
Medical information on patients to whom the present drug has been administered at The National Cancer Center Hospital/ The National Cancer Center Hospital East and to whom observations on the situation at the onset of adverse reactions have been completed

Gene Information:
Information on gene polymorphism obtained from DNA which has been extracted from the stored tissues kept by the National Cancer Center

Yakult/Daiichi
A part of clinical information of PMS study on all cases (April,1995~Jan., 2000)

Recent Topics of Irinotecan

- MHLW permitted to revise the label of Topotecin and Campto (Irinotecam HCl) (2003/12)
- FDA permitted to revise the label of Camptosar (Irinotecam HCl) (2005/06)
  http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf
- FDA Clears Genetic Test (The Invader UGT1A1 Molecular Assay) That Advances Personalized Medicine (2005/08)
  http://www.fda.gov/bbs/topics/NEWS/2005/NEW01220.html

Conclusion

- PGx is no longer new approach, it's already real practice
- The present situation of PGx in Japan is belated from the US but understanding of PGx are certainly spreading
- In order to promote PGx study/research any related parties should cooperate closely
- Based upon the experience on Irinotecan we, Daiichi, would like to lead to create infrastructure for realization of personalized medicine